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Interaction of Cardiovascular Nonmodifiable Risk Factors, Comorbidities and Comedications With Ischemia/Reperfusion Injury and Cardioprotection by Pharmacological Treatments and Ischemic Conditioning

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ABBREVIATIONS: ACE, angiotensin II converting enzyme; Akt, protein kinase B; AMI, acute myocardial infarction; ATP, adenosine triphosphate; CABG, coronary artery bypass grafting; CsA, cyclosporine A; DPP-IV, dipeptidyl peptidase IV; ECG, electrocardiogram; ERK, extracellular signal related kinase; GSK-3 β , glycogen synthase kinase-3 β ; HF, heart failure; IL, interleukin; I/R, ischemia/reperfusion; IRI, ischemia/reperfusion injury; IS, infarct size; KATP, ATP-dependent potassium channel; LDL-C, LDL-cholesterol; LV, left ventricle; LVH, left ventricular hypertrophy; MACE, major adverse coronary events; MI, myocardial infarction; miR, micro-RNA; MMP, matrix metalloproteinases; mPTP, mitochondrial permeability transition pore; MRI, magnetic resonance imaging; MVO, microvascular obstruction; NAD, nicotinamide adenine dinucleotide; NLRP3, nucleotide-binding and oligomerization domain (NOD)-like receptor domain-containing protein 3; NO, nitric oxide; NOS, nitric oxide synthase; PCSK9, proprotein convertase subtilisin/kexin type 9; PI3K, phosphoinositide-3-kinase; PPCI, primary percutaneous coronary interventions; PreC, preconditioning; PostC, post-conditioning; RCT, randomized controlled trial; RIC, remote ischemic conditioning; RISK, reperfusion injury salvage kinase; PKC, protein kinase C; ROS, reactive oxygen species; SHR, spontaneously hypertensive rat; SGLT2, sodium-glucose cotransporter 2; STEMI, ST-segment elevation myocardial infarction; SAFE, survivor activating factor enhancement; STAT, signal transducers and activators of transcription; TIMI, thrombolysis in myocardial infarction; TNF, tumor necrosis factor.

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Abstract—Preconditioning, postconditioning, and remote conditioning of the myocardium enhance the ability of the heart to withstand a prolonged ischemia/reperfusion insult and the potential to provide novel therapeutic paradigms for cardioprotection. While many signaling pathways leading to endogenous cardioprotection have been elucidated in experimental studies over the past 30 years, no cardioprotective drug is on the market yet for that indication. One likely major reason for this failure to translate cardioprotection into patient benefit is the lack of rigorous and systematic preclinical evaluation of promising cardioprotective therapies prior to their clinical evaluation, since ischemic heart disease in humans is a complex disorder caused by or associated with cardiovascular risk factors and comorbidities. These risk factors and comorbidities induce fundamental alterations in cellular signaling cascades that affect the development of ischemia/reperfusion injury and responses to cardioprotective interventions. Moreover, some of the medications used to treat these comorbidities may impact on cardioprotection by again modifying cellular signaling pathways. The aim of this article is to review the recent evidence that cardiovascular risk

factors as well as comorbidities and their medications may modify the response to cardioprotective interventions. We emphasize the critical need for taking into account the presence of cardiovascular risk factors as well as comorbidities and their concomitant medications when designing preclinical studies for the identification and validation of cardioprotective drug targets and clinical studies. This will hopefully maximize the success rate of developing rational approaches to effective cardioprotective therapies for the majority of patients with multiple comorbidities.

Significance Statement—Ischemic heart disease is a major cause of mortality; however, there are still no cardioprotective drugs on the market. Most studies on cardioprotection have been undertaken in animal models of ischemia/reperfusion in the absence of comorbidities; however, ischemic heart disease develops with other systemic disorders (e.g., hypertension, hyperlipidemia, diabetes, atherosclerosis). Here we focus on the preclinical and clinical evidence showing how these comorbidities and their routine medications affect ischemia/reperfusion injury and interfere with cardioprotective strategies.

I. Introduction

Acute myocardial infarction (AMI) and subsequent heart failure (HF) remain the leading causes of death

and disability worldwide. Effective treatment of AMI is based on procedures that promote the return of blood flow to the ischemic zone of the myocardium (i.e., reperfusion therapy). The achievement of prompt and successful

reperfusion to the infarct-related artery has revolutionized the management of ST-segment elevation myocardial infarction (STEMI), which is mostly equivalent to AMI arising from epicardial coronary artery plaque rupture [type I myocardial infarction (MI)] and complete acute coronary artery occlusion and is associated with acute ST-segment elevation on the electrocardiogram (ECG). Nonetheless, there is considerable room for further improvement. Reperfusion, however, may lead to further myocardial cell death, termed lethal myocardial reperfusion injury. Currently, there is no effective drug therapy for ischemia/reperfusion (I/R) injury (IRI) on the market, and routinely used pharmacological agents for ischemic heart disease do not salvage the I/R myocardium when applied at reperfusion. As such, new therapeutic targets are needed to protect the myocardium against the detrimental effects of acute IRI to reduce myocardial infarct size (IS), preserve left ventricular (LV) function and prevent the onset of HF (Heusch et al., 2014; Hausenloy et al., 2017; Heusch and Gersh, 2017; Heusch, 2020).

The heart possesses a remarkable ability to adapt to I/R stress, and this molecular plasticity of the heart in I/R has been the focus of intense research. Over the past 35 years, many cardioprotective strategies against myocardial IRI have been proposed. The cardioprotective strategies can be categorized based on the specific protective modality, time of application,

and cellular or intracellular targets. The cardioprotective strategies that have been studied most are based on either (i) the controlled application of episodes of brief I/R (ischemic conditioning by mechanical occlusion and reperfusion of heart and other tissues), (ii) the application of physical measures (e.g., exercise), or (iii) the administration of chemical substances (pharmacological agents) (see Section II) (Fig. 1).

Established pharmacological treatments administered to patients with cardiovascular disease potentially affect the outcome from IRI and the possibility to protect the heart. Additionally, new pharmacological treatments—derived through the better understanding of the underlying signaling cascades involved in endogenous cardioprotection—could be administered either prior to a sustained episode of I/R (i.e., prior to cardiovascular surgery) or as early as possible during reperfusion [in case of patients with STEMI undergoing primary percutaneous coronary interventions (PPCI)] to potentially protect further from IRI.

Ischemic heart disease results from coronary atherosclerosis, which, in turn, develops as a consequence of a number of comorbidities predisposing to atherosclerosis development; it always coexists with other systemic disease states. These comorbidities include systemic arterial hypertension with related LV hypertrophy and metabolic diseases such as hyperlipidemia or diabetes mellitus. In addition, age

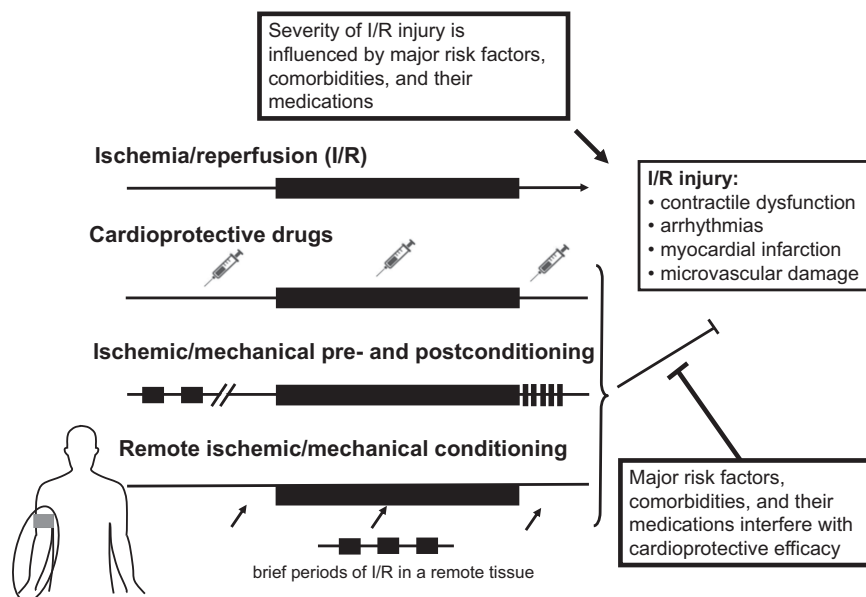


Fig. 1. The concept of ischemia/reperfusion injury and cardioprotection by pre-, post-, and remote conditioning as well as by drugs is expressed graphically (black areas denote periods of ischemia). Myocardial ischemia and reperfusion lead to I/R injury characterized by the development of contractile dysfunction, arrhythmias, tissue necrosis (infarction), and microvascular damage. Ischemic preconditioning is a well-described acute and subacute adaptive response in which brief exposure to I/R by mechanical occlusion of coronary arteries markedly enhances the ability of the heart to withstand a subsequent ischemia/reperfusion injury. In this diagram, 2 brief periods of ischemia are used to precondition the myocardium against a subsequent period of ischemia that is longer than the preconditioning periods. Brief cycles of I/R applied following a longer period of ischemia also confer cardioprotection against the consequences of I/R, a phenomenon termed "ischemic postconditioning." Brief cycles of I/R applied in a remote cardiac tissue or remote organ (in this diagram the upper limb by a pressure cuff) before, during, or right after a longer period of cardiac ischemia also provides cardioprotection, a phenomenon termed "remote conditioning." The cardioprotective effect of conditioning strategies results in attenuation of I/R injury. Major cardiovascular risk factors and their medications influence the severity of ischemia/reperfusion injury and interferes with cardioprotective efficacy.

and sex are major nonmodifiable risk factors affecting the development of ischemic heart disease. These risk factors and comorbidities exert multiple biochemical effects on the heart that affect the development of IRI and interfere with responses to cardioprotective interventions (Figs. 2 and 3).

The aim of this article is to update our previous reviews (Ferdinandy et al., 1998; Ferdinandy et al., 2014; Ferdinandy et al., 2007) on the effect of cardiovascular risk factors and comorbidities on IRI and cardioprotection and to show the ongoing critical need for preclinical studies that model the presence of risk factors and comorbidities and their pharmacological treatments. Such studies are required for the proper validation of molecular targets for cardioprotection as well as the efficacy and safety of potential cardiovascular drugs (Heusch, 2015, 2020), thereby maximizing the chances of success for translation of cardioprotection into the clinical arena and for the benefit of the majority of ischemic heart disease patients who have multiple comorbidities and associated medications.

II. Experimental Approaches to Cardioprotection

An orchestrated communication between the various cell types of the heart is vital for the maintenance of myocardial homeostasis. The human heart contains billions of cardiomyocytes; their activity needs to be coordinated to facilitate contractile activity, supported by fibroblasts, endothelial, and smooth muscle cells

(Hausenloy, Chilian, et al., 2019), immune cells, and sympathetic and parasympathetic neurons (Hausenloy, Bøtker, et al., 2019). Intercellular communication in the heart can occur directly through cell–cell contacts, including gap junctions and tunneling nanotubes, or at longer distances involving the release of soluble factors or vesicle-enclosed mediators (for review see Martins-Marques et al., 2021). In stress conditions, such as acute I/R and developing AMI, a finely tuned crosstalk between the different types of cardiac cells assumes particular importance to sustain efficient responses in wound healing and extracellular matrix remodeling (Daiber et al., 2021). Crosstalk between cardiac and inflammatory cell-types also facilitates endogenous adaptive protection against IRI, the so-called conditioning phenomena (Fig. 2).

A. Conditioning Phenomena

1. Ischemia-Related. The “conditioning” phenomena describe the IS reduction after sustained I/R by brief non-lethal periods of I/R, which are performed either before (pre), during (per), or after (post) the sustained ischemia followed by reperfusion. Whereas in ischemic preconditioning (PreC) or ischemic postconditioning (PostC) the heart itself is subjected to the conditioning I/R, in remote ischemic conditioning (RIC) organs or tissues other than the heart (e.g., skeletal muscle) undergo I/R, and this “conditioning at a distance” reduces myocardial IS (for review see Hausenloy et al., 2017; Heusch et al., 2015). As with ischemic PreC, the benefits of RIC appear to be biphasic with a short initial window of protection during the first 12 hours, followed by a period of loss of protection and finally a longer “delayed” or “second” window of

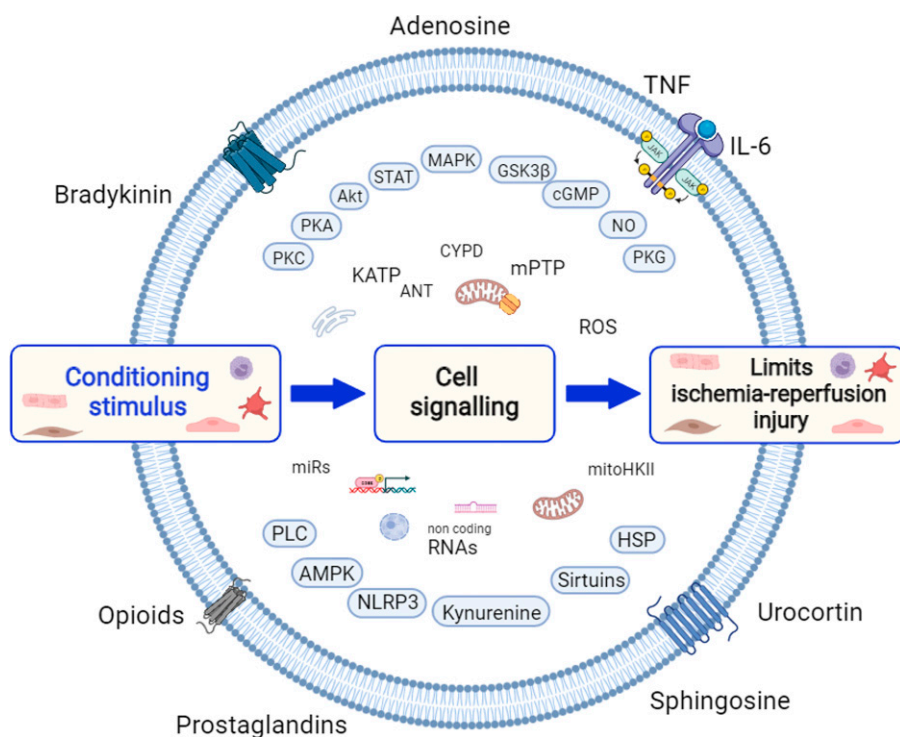


Fig. 2. This diagram shows some of the major cellular mechanisms suspected to contribute to cardioprotection induced by either mechanical or drug-induced conditioning stimulus of different cells of the heart tissue that leads to attenuation of I/R injury of the heart. Most of the cellular mechanisms of cardioprotection seems to be unexplored so far, as conditioning stimuli of cardioprotection is associated with extensive changes in cellular signaling that also includes global cardiac gene expression profile at the coding and noncoding RNA, proteome, and metabolome levels. AMPK, adenosine 5'-monophosphate activated protein kinase; ANT, adenine nucleotide translocase; cGMP, cyclic guanosine monophosphate; CYPD, cyclophilin D; NO, nitric oxide; GSK-3β, glycogen synthase kinase-3β; HSP, heat shock proteins; KATP, ATP-dependent potassium channel; MAPK, mitogen-activated protein kinase; miR, micro-RNA; mitoHKII, mitochondrial hexokinase II; mPTP, mitochondrial permeability transition pore; NLRP3, nucleotide-binding and oligomerization domain (NOD)-like receptor domain-containing protein 3; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; ROS, reactive oxygen species; STAT, signal transducers and activators of transcription; TNF, tumor necrosis factor.

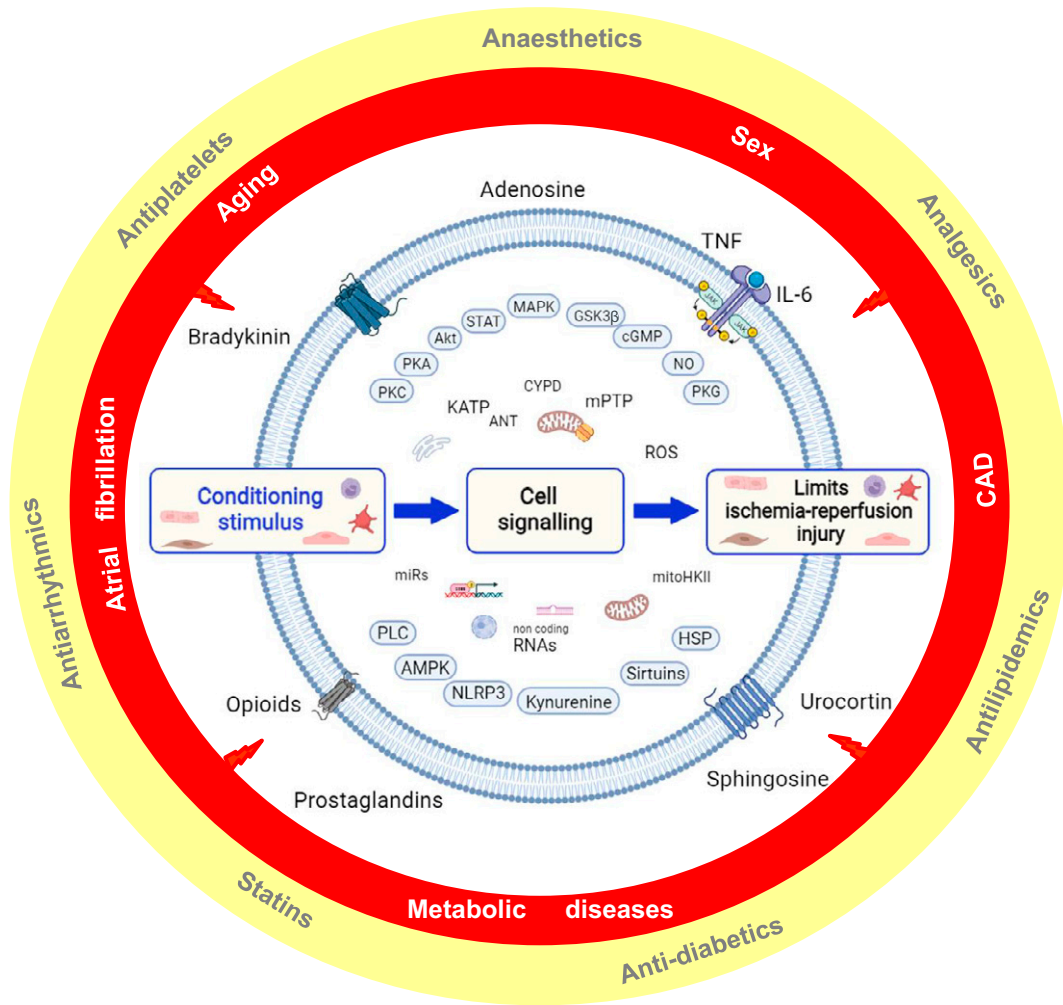


Fig. 3. This diagram shows that different cardiovascular risk factors and comorbidities as well as their routine medications dramatically alter cardiac cellular signaling thereby interfering with cardioprotective mechanisms explored in drug-naive young healthy hearts used in the majority of preclinical studies.

protection lasting as long as 72 hours after RIC exposure (Madias, 2015). When using leg ischemia to induce RIC in mice, leg temperature is decisive for cardioprotection, and leg hypothermia abrogates protection (Penna et al., 2022). The importance of different conditioning strategies to improve patients’ outcome is highlighted in Section III.

Repeated administration of RIC over weeks or months (long-term RIC), has been investigated for improving several aspects of cardiovascular health (for review see Epps et al., 2016; Chong et al., 2019). A seminal experimental study demonstrated that RIC repeated daily for 28 days after MI protected against adverse LV remodeling and increased survival in a rat model even though IS was not reduced compared with the single RIC treatment (Wei et al., 2011). This was further supported by a rat study showing survival benefit even when RIC treatment was commenced 4 weeks after MI (Yamaguchi et al., 2015). In a lipopolysaccharide-induced mouse model mimicking bacterial sepsis, RIC reduced circulating and myocardial inflammatory

mediators and led to improved LV function, cardiac output, and survival (Honda et al., 2019). Moreover, repeated RIC provided an additional 7 days survival benefit beyond a single-occasion treatment (Honda et al., 2019).

2. Drug-Related. Elucidation of some mechanisms involved in cardioprotection induced by ischemic conditioning strategies has identified a number of signaling pathways, many of which have been targeted by pharmacological agents applied either before the sustained ischemia (pharmacological PreC) or just at the onset of reperfusion (pharmacological PostC) to reduce myocardial IRI (for review see Heusch, 2015, 2020; Calabrese, 2016b; Torregroza et al., 2020). While results from experimental studies were encouraging, translation to the clinical setting again failed to meet the expectations (for review see Heusch, 2017; Roth et al., 2021 and Sections III and V for details).

Apart from ischemic and pharmacological PreC and PostC, another clinically applicable possibility to

precondition the heart against IRI is exercise (for review see Wojcik et al., 2018). Recent clinical investigations confirm that exercise may precondition the human heart (for review see Quindry and Franklin, 2021). Low-load blood flow restricted resistance exercise (Bøtker, Lassen, et al., 2018) improved functional capacity, quality of life, and muscle mitochondrial function in patients (Groennebaek et al., 2019). The mechanisms responsible for exercise-induced cardioprotection include maintenance of endothelial nitric oxide synthase (NOS) coupling (Santana et al., 2018), increased release of circulating hormones (Lu and Pan, 2017; Otaka et al., 2018; Bo et al., 2021), as well as extracellular vesicles (Görgens et al., 2015; Bei et al., 2017), finally leading to preserved mitochondrial dynamics (Ghahremani et al., 2018; Yuan et al., 2018) in cardiomyocytes.

B. Endpoints

As outlined earlier, the heart consists of many different cell types. Therefore, endogenous protection can be directed not only to cardiomyocytes but also to the coronary circulation (including effects on endothelial cells, vascular smooth muscle cells, vessel innervation) (Heusch, 2016, 2019a; Hausenloy, Chilian, et al., 2019) and circulating blood cells, to name a few.

1. Cardiomyocyte Death. To develop strategies to protect the heart from IRI, it is important to define the precise mechanisms by which cardiomyocytes die. Necrosis is known to play a major role in myocardial IRI. Apoptosis is a form of programmed cell death mediated by caspases and characterized by cell shrinkage, chromatin condensation, and blebbing (budding) of the plasma membrane. Despite early studies showing evidence of apoptosis in the heart following I/R, its contribution remains controversial. The protein machinery required for apoptosis is expressed at very low levels in the healthy adult heart, which suggests that the signs of apoptosis that can be detected may be due to cardiac cells other than cardiomyocytes (e.g., fibroblasts, endothelium, leukocytes) (reviewed in Davidson et al., 2020).

Mitochondria play a central role in both of these pathways of cell death, as either a causal mechanism in the case of mitochondrial permeability transition pore (mPTP) opening leading to necrosis or as part of the signaling pathway in mitochondrial cytochrome *c* release and apoptosis. Autophagy may impact this process by removing dysfunctional proteins or even entire mitochondria through a process called mitophagy (for in-depth review see Gatica et al., 2022). More recently, roles for other programmed mechanisms of cell death such as necroptosis and pyroptosis have been described (for review see Davidson et al., 2020).

Necrosis was previously believed to always be an uncontrolled pathway of cell death. However, it is now evident that there are controlled forms of

necrosis, of which necroptosis and pyroptosis are of particular relevance in the heart. Necroptosis involves the recruitment of cytosolic adaptor proteins to complex I, an increase in plasma membrane permeability, re-localization of phosphorylated mixed-lineage kinase domain-like pseudokinase to the plasma membrane, and receptor-interacting-protein 3 activation (Zhang et al., 2016). In the heart, receptor-interacting-protein 3 also causes activation of calmodulin-dependent protein kinase II (Zhang et al., 2016). Necroptotic proteins are also present in the human failing heart due to MI (Szobi et al., 2017). Necroptosis clearly contributes to IRI, because either pharmacological inhibition or deletion of key proteins is cardioprotective (Smith et al., 2007; Newton et al., 2016). Limited evidence suggests that conditioning strategies can reduce necroptosis. For example, ischemic PreC is associated with inhibition of translocation of mixed-lineage kinase domain-like pseudokinase within the plasma membrane, and ischemic PreC is ineffective in hearts where necroptosis is already inhibited (Szobi et al., 2018).

Pyroptosis is a type of programmed necrosis that can be activated in the heart in response to injury. One major difference between pyroptosis and other forms of necrosis is that the proteins involved in pyroptosis are expressed at low levels in the healthy heart, and, as such, in healthy hearts, the contribution of pyroptosis to infarction occurring in the first few hours of reperfusion following ischemia may be limited. However, damage-associated molecular patterns such as interleukin (IL)-1 β increase the expression of proteins of the inflammatory and innate immune systems including nucleotide-binding and oligomerization domain-like receptor domain-containing protein 3 (NLRP3), apoptosis-associated speck-like protein containing caspase recruitment domains, and caspase-1, which make up a complex called the NLRP3 inflammasome (Kawaguchi et al., 2011). Following this “priming” stimulus, a stress such as I/R causes rapid assembly and activation of the NLRP3 inflammasome, leading to cleavage and activation of IL-1 β and IL-18. Activated caspase-1 also cleaves the protein gasdermin D, which forms cytosolic membrane pores, the lethal and defining feature of pyroptotic cell death (Shi et al., 2015).

Most acute I/R experiments use IS (relative to ischemic area at risk) as a hard endpoint, measured using either tetrazolium staining (postmortem) or late gadolinium cardiac magnetic resonance imaging (MRI) (Bøtker, Hausenloy, et al., 2018). The levels of cardiac proteins such as troponin released by necrotic cells into the blood or perfusate may be used as a supporting measurement. Cardiac contractile function is sometimes used as endpoint but is less robust and less meaningful in the acute period since cardioprotective strategies such as ischemic PreC may have inconsistent effects on ventricular function (Kloner and Jennings, 2001; Gelpi et al., 2002). Since

ventricular fibrillation contributes to deaths following MI, another relevant endpoint measurement, which is a target for ischemic PreC, is cardiac arrhythmia (Hagar et al., 1991).

2. Coronary Microvascular Obstruction. Another target for cardioprotection that has been somewhat overlooked in acute myocardial IRI is the coronary circulation (Heusch, 2016, 2019a; Hausenloy, Chilian, et al., 2019). The function in health and disease of the coronary circulation including the microvasculature is pivotal to our understanding of the complex processes and interactions among myocardial ischemic injury, reperfusion injury, and cardioprotection (Kaski et al., 2018). The putative initiating mechanism in approximately 97% of patients who experience an acute coronary syndrome is plaque erosion or rupture (type I MI), and there is abundant evidence that the response of the microvasculature plays a crucial role in determining the clinical course and final outcome. Moreover, type II MI, which results from changes in systemic hemodynamics and their impact on the matching of coronary blood flow and myocardial metabolism, occurs usually in the presence of significant epicardial coronary atherosclerosis (Ibanez et al., 2018; Thygesen et al., 2018). Finally, MI in the absence of obstructive (<50% diameter reduction on angiography) coronary artery disease still involves in most cases structural or functional alterations of the epicardial or more distal coronary microcirculation (Ibanez et al., 2018; Thygesen et al., 2018). Whereas obstruction of the coronary circulation and reduction of coronary blood flow causes myocardial ischemia (Heusch, 2019b), it is the reopening of the coronary circulation and restoration of coronary blood flow that induces reperfusion and salvages the dependent myocardium from infarction, but this comes at the price of reperfusion injury (Heusch and Gersh, 2017). Type IV MI is defined as any infarction related to interventional reperfusion (Thygesen et al., 2018) including notably microembolization (Heusch, 2016; Kleinbongard and Heusch, 2022). Thus, the coronary circulation in one form or the other is an integral component of the process of myocardial ischemia, microvascular dysfunction, reperfusion, reperfusion injury, and healing.

The coronary microcirculation is as much a victim of myocardial IRI as the cardiomyocytes. The most extreme form of coronary vascular injury following myocardial I/R is no-reflow as recognized in dogs more than 5 decades ago (Krug et al., 1966; Kloner et al., 1974). Such no-reflow, more specifically microvascular obstruction (MVO) (de Waha et al., 2017) and intramyocardial hemorrhage (Reinstadler et al., 2019), determines the prognosis of patients with reperfused AMI independently of IS (Stone et al., 2016). Because morphologic alterations of the coronary microvasculature are difficult to assess in the absence of reperfusion,

it is not clear to what extent MVO is a direct consequence of ischemic injury or is caused by the process of reperfusion. Furthermore, since regions of coronary vascular injury typically occur within the infarcted myocardium, the causal relationship and relative contribution of cardiomyocyte and coronary microvascular injury from I/R is not clear. However, multiple mechanisms contribute to coronary microvascular injury from myocardial I/R: endothelial and interstitial edema (Garcia-Dorado et al., 2012; Fernández-Jiménez et al., 2015; Zhou et al., 2017), impaired vasomotion (Ehring et al., 1995; Kleinbongard et al., 2011), leukocyte adherence (Kupatt et al., 2002), erythrocyte stasis (Driesen et al., 2012), platelet aggregation (Pearson et al., 1990; Folts, 1999), extravascular compression by the interstitial edema (Manciet et al., 1994), and ultimately capillary destruction with consequent intramyocardial hemorrhage (Kloner et al., 1974; Higginson et al., 1982; Bulluck et al., 2016). Clinically, coronary microvascular injury is assessed using various imaging modalities, notably in angiography by decreased thrombolysis in MI (TIMI) flow grade and myocardial blush grade, and in cardiac MRI as edema by T2 weighted mapping and lack of contrast medium in gadolinium-hypercontrasted infarcted myocardium or intramyocardial hemorrhage (Heusch, 2016, 2019a; Hausenloy, Chilian, et al., 2019).

What is fortunate is that coronary microvascular injury is not an all-or-none phenomenon but a process subject to modification and damage limitation (Hausenloy, Chilian, et al., 2019; Heusch, 2019a). In the experimental model, mechanical interventions of ischemic conditioning reduced not only IS but also the area of no-reflow (Skyschally et al., 2017). Ischemic PreC reduced endothelial dysfunction (DeFily and Chilian, 1993; Kaeffer et al., 1996), leukocyte adherence (Kurzelewski et al., 1999), edema formation (Zhao et al., 2003), and MVO (Posa et al., 2010) and improved coronary vasodilator responses to adenosine, nitric oxide (NO), and reactive hyperemia (Gattullo et al., 1999), although not all studies have been consistent in demonstrating such benefit (Bauer et al., 1993). Moreover, delayed ischemic PreC provided endothelial protection and improved coronary vasodilation 24 hours later (Kaeffer et al., 1997; Kim et al., 2007). Ischemic PostC improved endothelial function and vasodilator response to acetylcholine and reduced leukocyte adherence, edema, and no-reflow in dogs and pigs (Zhao et al., 2003; Zhao et al., 2007), but again not all studies were positive (Bodi et al., 2014). RIC reduced IS and area of no-reflow in pigs (Skyschally et al., 2017), again with some studies lacking such effects (Baranyai et al., 2017). Hypothermia in rabbits reduced IS and area of no-reflow, and no-reflow was even reduced when hypothermia was delayed later into reperfusion (Hale et al., 2013). Some drugs, when given at reperfusion, reduced IS and no-reflow [e.g., cyclosporine A (CsA)] (Zalewski et al., 2015) and angiotensin-like peptide 4 (Galaup et al., 2012).

Nitroglycerine can protect both the myocardium and the coronary vasculature but also interferes with RIC (Heusch, 2001; Hauerslev et al., 2018).

The experimental agenda surrounding the reduction of reperfusion injury in the microvasculature has been extensive, but for reasons not clearly understood much has been “lost in clinical translation,” and definitive clinical trials demonstrating benefit are conspicuous by their absence (Heusch, 2017; Heusch and Gersh, 2020). More specifically, there is still debate on the role of coronary microvascular dysfunction as cause or consequence of MI and reperfusion injury (Lerman et al., 2007; Heusch, 2019a). Clinical studies evaluating ischemic PreC’s effect on coronary MVO do not exist. However, several clinical studies notably using MRI looked not only at IS but also at coronary microvascular injury, including edema, MVO, and intramyocardial hemorrhage, in patients with acute STEMI undergoing either ischemic PostC (Thuny et al., 2012; Dwyer et al., 2013; Mewton et al., 2013; Bodi et al., 2014; Eitel et al., 2015; Kim et al., 2015; Traverse et al., 2019), RIC (Crimi et al., 2013; White et al., 2015; Liu et al., 2016), or both in combination (Eitel et al., 2015). The effects on IS and MVO differed and were partly concordant but partly not, leaving the issue of causality between the 2 manifestations of myocardial IRI open and a challenge for further studies (Heusch, 2019a). The effects of hypothermia on IS and MVO in patients demonstrated modest benefits at best, and the most recent trial actually pointed in the wrong direction in terms of safety signals (Noc et al., 2021). Metoprolol is 1 exception and demonstrated a modest benefit on the reduction of both IS and MVO in patients with AMI (García-Prieto et al., 2017).

In conclusion, the coronary circulation is both a culprit and a victim of myocardial IRI. Cardioprotection notably reduces cardiomyocyte injury, as reflected by IS, but also coronary microvascular injury, as reflected by the area of no-reflow. The targets are clear, but identifying clinical approaches that favorably influence coronary microvascular obstruction and thereby induce cardioprotection have been difficult and remain the “last frontier” of reperfusion therapy (Heusch, 2019a).

C. Chronic Endpoints

Importantly, the primary endpoints in experimental and clinical studies differ (Bochaton et al., 2019). The most robust primary endpoint in experimental studies on cardioprotection is IS (Bøtker, Hausenloy, et al., 2018), and coronary microvascular injury is also increasingly recognized as a manifestation of IRI and thus a target of cardioprotection (Heusch, 2016, 2019a; Hausenloy, Chilian, et al., 2019) (see previous discussion). However, in clinical studies IS and coronary MVO are major determinants of LV remodeling and prognosis (Stone et al., 2016; de Waha et al., 2017; van der Bijl et al., 2020) but still only

surrogate endpoints whereas the primary clinical endpoint is mortality and/or hospitalization for HF (Bøtker, Hausenloy, et al., 2018). In smaller clinical trials, however, adverse LV remodeling, as characterized by an increase in LV end-diastolic volume of 15% to 20% between baseline and follow-up measures, or circulating levels of NH₂-terminal pro-B-type natriuretic peptide, have been used as clinical endpoints (Pryds et al., 2017; Ikonomidis et al., 2021). Thus, when comparing experimental and clinical studies, not only the endpoints per se but also the time frame over which these endpoints are assessed differ (Heusch, 2018; Lecour et al., 2021).

D. Signaling Mechanisms Involved in Cardioprotection

1. Classic Pathways. Timewise, there are 3 key steps in the mechanism of cardioprotection: the trigger step, the mediator step, and the end-effector step, which may or may not involve different signaling pathways. These steps can be clearly distinguished only in ischemic PreC but are more difficult to discern in ischemic PostC and RIC (Heusch, 2015; 2020) (Fig. 2). These have been extensively characterized over the past 35 years and are well established, although some controversies still remain (reviewed in Heusch, 2015; Hausenloy et al., 2016). Moreover, given the fact that none of these pathways have resulted in clinically validated cardioprotective drug targets in the last 30 years suggests the possibility that more systematic research approaches will uncover novel, more druggable targets (Varga et al., 2015; Hausenloy et al., 2017; Perrino et al., 2017). Ischemic PreC causes a localized increase in the extracellular concentration of the autacoid mediators adenosine (Liu et al., 1991), bradykinin (Schulz et al., 1998), opioids (Schulz et al., 2001), and sphingosine (Keul et al., 2016), which bind to receptors on the cardiomyocyte plasma membrane and act additively to initiate the trigger pathway. Ligand-receptor signaling leads to the activation of a sequence of cytosolic kinase pathways that ultimately cause opening of mitochondrial ATP-sensitive potassium channels (K_{ATP}) and allow potassium entry into mitochondria (Liu et al., 1996). Connexin 43 located at the inner mitochondrial membrane forms hemichannels that are also believed to be involved in the passage of potassium into mitochondria and required for cardioprotection by ischemic PreC (Boengler et al., 2005; Heinzl et al., 2005; Miro-Casas et al., 2009; Boengler, Ungefug, Heusch, Leybaert, et al., 2013; Gadicherla et al., 2017; Hirschhäuser et al., 2021). The reperfusion phase of ischemic PreC is crucial for the trigger pathway of cardioprotection, because reoxygenation allows mitochondrial respiration to recommence, which is associated with a small burst of reactive oxygen species (ROS) that activates protein kinase C (PKC) (Liu et al., 1994); the role of PKC in ischemic PreC of larger mammals such as the pig is still contentious (Vahlhaus et al., 1996).

The reperfusion injury salvage kinase (RISK) pathway describes a group of prosurvival kinases that must be

activated at the time of reperfusion for ischemic PreC to protect against IRI (Schulman et al., 2002). The relative importance of different signaling pathways appears to vary between species. In rodents, the ischemic PreC signaling pathway is dependent on both the phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) 1 and mitogen-activated protein kinase/extracellular signal related kinase (ERK)1/2 signaling pathways (Hausenloy and Yellon, 2004; Kunuthur et al., 2012; Rossello et al., 2017). In pigs and humans, the salvage activating factor enhancement (SAFE) pathway, consisting of gp 130/tumor necrosis factor (TNF) receptor-mediated activation of janus kinase/signal transducers and activators of transcription (STAT) factors, appears to play a more important role (Lecour, 2009; Heusch et al., 2012; Kleinbongard, Skyschally, Heusch., 2017; Hadebe et al., 2018). Evidence suggests that the RISK and/or SAFE pathways are also involved in ischemic PostC and RIC, although the RISK pathway might not be essential to achieve cardioprotection (Skyschally et al., 2009; Inserte et al., 2013). Similarly, ischemic PreC may activate the RISK and SAFE pathways to limit mPTP opening and reduce IS (Davidson et al., 2006; Hausenloy et al., 2004; Lecour, 2009), but it remains unclear whether cardioprotective kinases protect directly via phosphorylation of end-effector proteins, or indirectly via improved mitochondrial respiration, suppression of mitochondrial calcium overload and oxidative stress (Clarke et al., 2008; Heusch et al., 2011; Skyschally et al., 2018). The NOS/NO-cyclic guanosine monophosphate signaling pathway is also necessary for ischemic PreC (Talukder et al., 2010). NO, being a gaseous molecule, can diffuse between organelles and cells to protect mitochondria from I/R by nitrosylating and inhibit mitochondrial complex I, suppressing the production of damaging ROS during early reperfusion (Chouchani et al., 2013; Rassaf et al., 2014).

Since ischemic PostC is applied at reperfusion, the trigger step is obviously different from ischemic PreC and may or may not involve different signaling pathways. By preventing complete reperfusion, ischemic PostC is believed to maintain an acidic myocardial pH, thereby acting at several cell targets involved in cardioprotection (i.e., preventing hypercontraction, calpain-mediated proteolysis, mPTP opening, and gap junction-mediated spread of injury during the first minutes of reflow) (Cohen et al., 2008; Inserte et al., 2011). However, aspects of the signal transduction and end-effector appear to be similar between ischemic PostC and ischemic PreC (e.g., protein kinases and ROS) (Penna et al., 2006; Barsukevich et al., 2015).

The signaling mechanism for RIC necessitates an additional step to enable communication between the triggering pathway in the remote organ and the end-effector pathway in the heart. A wide range of humoral factors have been proposed to mediate this communication, but there is no consensus on the

critical molecule/s, and there may be multiple redundant factors (for review see Kleinbongard, Skyschally A, Gent, et al., 2017; Tsibulnikov et al., 2019). The parasympathetic nervous system is also required for transmission of the cardioprotective signal (Donato et al., 2013), meaning that both neural and hormonal signals are required (Lim et al., 2010). The spleen is an important relay organ between the neuronal and humoral signals of RIC (Lieder, Kleinbongard, et al., 2018; Heusch, 2019c). Interestingly, the various forms of ischemic conditioning (ischemic PreC, ischemic PostC, RIC) may all lead ultimately to the same cellular end-effectors to mediate cardioprotection (Heusch, 2015, 2020; Wolfrum et al., 2002). In this respect, the reduction in myocardial IS by RIC also involves activation of the PI3K/Akt pathway (thereby enhancing autophagy) (Gao et al., 2022), activation of STAT3 (Kleinbongard et al., 2018), and adenosine 5'-monophosphate activated protein kinase (Xu et al., 2022).

2. Mitochondria. Mitochondria are at the crossroads of cell death and survival through a plethora of functions that make them not only triggers but also mediators and end-effectors of cardioprotection due to their multifaceted participation in the pathophysiology of IRI, as extensively reviewed elsewhere (Davidson, Ferdinandy, et al., 2019). During ischemia, the interruption in the generation of mitochondrial adenosine triphosphate by oxidative phosphorylation is the triggering mechanism for the profound ionic and biochemical disturbances of cardiomyocytes (see previous discussion), the duration of which determines the fate of the cells (Piper et al., 1998). Upon reperfusion, the abnormal resumption of mitochondrial respiration (leading to an excessive and unregulated ROS production) and mitochondrial matrix calcium accumulation can synergistically exacerbate energy collapse through the activation of irreversible mPTP, a pathologic disruption of the inner membrane that induces massive matrix swelling and culminates in cell death (Halestrap and Richardson, 2015). In support of this, mice in which mitochondrial calcium overload was inhibited by cardiomyocyte-specific deletion of the mitochondrial calcium uniporter were protected against IRI (Luongo et al., 2015).

However, despite the enormous interest aroused by mPTP as a therapeutic target to prevent mitochondrial failure, its molecular entity remains controversial. Either a change in the dimerization of the FoF1-ATP synthase or a structural alteration within the enzyme holocomplex constitute some of the proposed models of the energy-dissipating channel that have received the most experimental support (Giorgio et al., 2013; Alavian et al., 2014; Bonora et al., 2017). Nevertheless, attempts to prevent mPTP by pharmacological inhibition of cyclophilin D (a regulatory protein known to interact with FoF1-ATP synthase; Giorgio et al., 2013) to desensitize mPTP against calcium resulted in inconsistent effects on cardiomyocyte survival during I/R and failed to confer clinical benefit in

patients (Lim et al., 2012; Cung et al., 2015; Rahman et al., 2018). Of note, the failure of clinical trials to demonstrate cardioprotection using mPTP inhibitors does not negate its role in human heart but is more likely due to incomplete understanding of required dose/target in humans (Shanmuganathan et al., 2005; see Section IIIa3). In contrast, the attenuation of the complex 1-mediated mitochondrial ROS generation by different interventions, including either pharmacological or genetic inhibition of the reverse electron transport from complex II to complex I reduces mPTP opening and limits IS in mice (Chouchani et al., 2014; Valls-Lacalle et al., 2016; Yin et al., 2021) and in the in vivo pig model (Valls-Lacalle et al., 2018). Malonate—as one example—only reduced infarct size in the isolated mouse heart when administered at reperfusion, whereas an acidic malonate formulation was required to affect infarct size with administration before ischemia (Prag et al., 2022; Schulz and Heusch, 2022). However, malonate turned out not to have additive cardioprotective effects on IS reduction in pigs when combined with RIC (Consegal et al., 2021), despite the fact that conditioning strategies had been previously shown to modulate mPTP susceptibility (Heusch et al., 2011).

In a pig model of IRI with or without ischemic PostC, mitochondrial proteome analysis revealed a dual role for ischemic PostC promoting metabolic reprogramming of the myocardium and a protective response mediated by the voltage-dependent anion channel 2 and DJ-1 in the mitochondria (Gallinat et al., 2022). Cardiac mitochondria are dynamic organelles and organize into differentiated populations. As a general rule, interventions capable of decreasing mitochondrial fission (or increasing mitochondrial fusion) reduce IRI (Hernandez-Resendiz et al., 2020). Hence, genetic or pharmacological inhibition of the fission protein dynamin-related protein 1 mitigated cardiac injury in murine models of I/R, although this treatment failed to protect the heart in the more clinically relevant closed-chest pig model of AMI (Ong et al., 2019). Similarly, the beneficial effects of both aerobic exercise conditioning (Ghahremani et al., 2018) and RIC (Cellier et al., 2016) on IS have been attributed to a better maintenance of the elongated mitochondrial morphology in rat models of in vivo I/R. As for their subcellular location, subsarcolemmal mitochondria have a greater contribution to ROS production (Crochemore et al., 2015) and IRI (Lesnefsky et al., 1997) and are more sensitive toward pharmacological and ischemic conditioning than interfibrillar mitochondria (Holmuhamedov et al., 2012; Sun et al., 2015). Moreover, only subsarcolemmal mitochondria contain connexin 43 at their inner membrane (Boengler, Stahlhofen, et al., 2009), a protein involved in the ischemic PreC cardioprotection (Rodriguez-Sinovas et al., 2006; Ruiz-Meana et al., 2014) that has recently been identified as one of the interactors of the FoF1-ATP synthase (Boengler et al., 2018). Also, STAT 3 activation impacts on mitochondrial function; it increases respiration, ATP formation, and

calcium retention capacity and decreases ROS formation in rat and mouse mitochondria of myocardium undergoing IRI with ischemic PreC or PostC (Boengler et al., 2008; Boengler et al., 2010; Heusch et al., 2011; Boengler, Ungefug, Heusch, and Schulz, 2013; Skyschally et al., 2018). Taken together, there are multiple available lines of evidence that link the cardioprotective effect of conditioning strategies with better mitochondrial function and integrity, yet the causality between both phenomena is difficult to establish. In part, a more preserved mitochondrial function and network could simply be the consequence of the otherwise well-known beneficial effects of these maneuvers on cellular ionic homeostasis (Inserte et al., 2014; Hausenloy et al., 2016). Furthermore, the effects on mitochondria can vary depending on the conditioning algorithm, the animal species, and the subtype of mitochondria.

3. Metabolism and Metabolomics. It has long been known that cardiac substrate metabolism is a main determinant of the severity of IRI. This is not surprising considering that I/R is in principle a metabolic pathology, with abruptly altered metabolism and thus energy production during the nonhomeostatic transitions from normoxia to ischemia and from ischemia to reperfusion (Guth et al., 1987). One of the first cardioprotective strategies examined against IRI was a metabolic treatment, employing glucose-insulin-potassium infusions to attenuate electrographic disturbances during MI (Sodi-Pallares et al., 1962). It is now known that almost every specific metabolic substrate pathway can affect cardiac IRI (Zuurbier et al., 2020). However, the complex interactions between these metabolic pathways have likely hindered the development of a singular metabolic treatment providing robust cardioprotection against IRI in the clinical condition. Nevertheless, in terms of metabolic approaches, it seems that activation of glycolysis, glucose, and ketone oxidation and inhibition of fatty acid metabolism and oxygen consumption holds the most promise for protecting the heart against IRI (Zuurbier et al., 2020).

Increases in glucose uptake and glycolysis in rodent hearts are mandatory for protecting the heart during low-flow ischemia (Lochner et al., 1996) and for various cardioprotective interventions such as ischemic PreC (Ji et al., 2013), ischemic PostC (Correa et al., 2008), and nicotinamide adenine dinucleotide (NAD) supplementation (Nadtochiy et al., 2018) to be effective.

The coenzyme NAD⁺ is critical for many biochemical pathways and the cellular stress response, and it is decreased in aging and many pathologies including cardiovascular diseases (Fang et al., 2017). During cardiac I/R, NAD⁺ is acutely decreased in rat heart (Di Lisa et al., 2001), partly due to mPTP opening. NAD⁺ is also used by sirtuins, a group of lysine de-acetylation enzymes controlling metabolism (Anderson et al., 2014). Metabolic overloading such as that present in the

metabolic syndrome results in increased acetylation (due to increases in acetyl-coenzyme A) and thereby inhibition of, for example, glucose uptake pathways in rat hearts (Renguet et al., 2017), interfering with cardioprotection. Sirtuins can de-acetylate these pathways and restore cardioprotection. In several studies NAD precursors protected against cardiac IRI (Yamamoto et al., 2014; Nadtochiy et al., 2018; Xiao et al., 2021).

That an activated glucose metabolism is needed for protection is commensurate with the finding that many of the critical signaling molecules (ROS, NO, PKC) triggering and mediating protection (see Fig. 2) are also known activators of glucose metabolism (Tada et al., 2000; Nishino et al., 2004). Metabolomic studies in rat hearts also indicated that protection through PKC ϵ is associated with changes in glucose metabolism (Mayr et al., 2009). It seems that ischemic PreC-activated glucose metabolism (e.g., glycolysis) slows down mitochondrial reactivation following reperfusion (Zuurbier and Ince, 2002), possibly through increased binding of the glycolytic enzyme hexokinase II to mitochondria (Gurel et al., 2009; Nederlof et al., 2017). Glucose and mitochondrially bound hexokinase II are both needed for effective ischemic PreC and reductions in IS and cell death in rodent hearts (Pasdois et al., 2012; Smeele et al., 2011; Sun et al., 2008). Slowing down mitochondrial activity results in decreased oxygen consumption during reperfusion, which has been suggested to contribute to cardioprotection (Burwell et al., 2009). However, the role of mitochondrial function for cardioprotection during reperfusion is somewhat contentious, since STAT3 activation has been shown to mediate cardioprotection by ischemic PostC and RIC through improved mitochondrial function (see previous discussion).

Increased fatty acid uptake and incomplete fatty acid metabolism during ischemia aggravate IRI through the build-up of long-chain acylcarnitines within the mitochondria, resulting in an increase of mitochondrial ROS production (Dambrova et al., 2021). However, although ischemic PreC efficacy is often decreased in conditions of elevated fatty acid metabolism, this is not always observed (Dalgas et al., 2012). Metabolomics studies have suggested that (i) exercise-induced cardioprotection is associated with changes in rat heart ammonia recycling, protein biosynthesis, and pantothenate and coenzyme A biosynthesis (Parry et al., 2018) and (ii) RIC in rats and humans with decreases in plasma ornithine and increases in kynurenine and glycine (Chao de la Barca et al., 2016; Kouassi Nzoughet et al., 2017; Bakhta et al., 2020). Previous work in murine hearts had already indicated the possible important role of alpha-ketoglutarate induced kynurenic acid synthesis in mediating RIC (Olenchock et al., 2016).

Oeing et al. (2021) recently confirmed the importance of glucose metabolism in cardioprotection and ischemic PreC by demonstrating that mechanistic target

of rapamycin c1-activated glycolysis at the expense of fatty acid oxidation offers protection of the murine heart against IRI and mediated ischemic PreC protective effects. Lochner et al. (2020) confirmed the mandatory role of glucose in ischemic PreC and that high fatty acid levels prevented ischemic PreC in rat heart.

4. Circulating Cells. Circulating cells can strongly impact on IRI through various mechanisms (for a review, see Davidson, Andreadou, et al., 2019). Among the different circulatory cells, platelets play an important role in myocardial I/R. Platelets, beyond hemostasis and thrombosis, are characterized as versatile cells directly involved in various physiologic and pathophysiological processes (Russo et al., 2017). Several imaging studies have provided evidence that platelets contribute to IRI in in vivo rodent models of cardiac IRI; they are activated early during reperfusion and localized within the ischemic and necrotic areas (von Elverfeldt et al., 2014; Ziegler et al., 2016; Ziegler et al., 2019). Additionally, circulating platelets change their characteristics due to IRI (Eicher et al., 2016; Kaudewitz et al., 2016) as has been shown by proteomic studies in STEMI patients (Ruggeri, 2002).

Platelets also carry and release multiple factors with the potential to reduce IRI (Hjortbak et al., 2021; Kleinbongard et al., 2021), although the role of circulating platelets as signal mediators of cardioprotection is far from being understood. In recent studies, RIC exerted its cardioprotective effect through modulating platelet function by reducing the formation of monocyte-platelet conjugates and thrombus formation (Lanza et al., 2016) and was associated with a reduction in platelet reactivity within the first 48-hour post STEMI (Gorog et al., 2021) (for review see Kleinbongard et al., 2021). More studies are necessary to understand the role of platelets in IRI and their importance for conditioning strategies.

Erythrocyte dysfunction contributes to a reduced NO bioavailability and thereby to increased IS and mortality from IRI in mice (Wischmann et al., 2020); also, erythrocyte stasis contributes to the no-reflow phenomenon (Kyrou et al., 2011).

Neutrophil (polymorphonuclear leukocyte) recruitment to ischemic, and more particularly reperfused, myocardium has been recognized as a pathologic hallmark of AMI for nearly a century. As described earlier, neutrophil adherence and plugging may play a key role in MVO supply and no-reflow. However, a direct causal role of neutrophils in the evolution of myocyte death, at least in the early stages of AMI, has been contentious (Baxter, 2002; Lefer, 2002). There is evidence that effective IS-limiting interventions including ischemic PreC and ischemic PostC result in reduced neutrophil accumulation. One study suggests that neutrophil inhibition is causally related to IS limitation by ischemic PostC (Granfeldt et al., 2012). There is also limited evidence from human

RIC studies to suggest that rapid and long-lasting systemic neutrophil inhibition occurs in response to the RIC stimulus (Kharbanda et al., 2001; Shimizu et al., 2010; Saxena et al., 2013). The extent to which these observations are mechanistically important in cardioprotection is unknown.

5. Innate Immunity and the NLRP3 Inflammasome.

Neither circulating monocytes nor cardiac-resident macrophages contribute to acute IRI, although they are crucial for longer term infarct and LV remodeling (Bajpai et al., 2019).

During I/R, resident cardiac mast cells degranulate, releasing their proteolytic and damaging contents. Consequently, mast cell stabilizing compounds are cardioprotective (Wang et al., 1996; Rork et al., 2008; Bajpai et al., 2019). However, mast cell degranulation does not appear to contribute to ischemic PreC (Wang et al., 1996).

Necrosis or pyroptosis of cardiac cells during I/R releases their contents into the extracellular milieu, where they are recognized by the innate immune system as damage-associated molecular patterns. Some damage-associated molecular patterns particularly relevant to cardiac I/R injury include proteins of the extracellular matrix, heat shock proteins, S100 proteins, ATP, histones, high-mobility group box 1 (HMGB1), IL-1 α , and mitochondrial deoxyribonucleic acid (Vilahur and Badimon, 2014). For example, heat shock protein 60 can induce apoptosis in cardiomyocytes (Kim et al., 2009). Damage-associated molecular patterns are recognized by toll-like receptors, particularly toll-like receptors 2 and 4, and are targets for reducing IRI. Histones released during I/R damage cardiomyocytes by toll-like receptor 4 related mechanism (Shah et al., 2022). Inhibition of toll-like receptor 2 reduces IS in both mouse and pig models (Arslan et al., 2010; Arslan et al., 2012). Knockout of toll-like receptor 3 (Lu et al., 2014) or 4 (Oyama et al., 2004) reduces IS in mice after I/R. Mitochondria are fundamentally involved in innate immunity and sterile inflammation. After exposure to NLRP3 activators, damaged mitochondria accumulate, leading to increased production of oxidized mtDNA fragments. These associate with the NLRP3 inflammasome in the cytosol and are required for its activation (Zhou et al., 2011; Zhong et al., 2018). The complement system forms an important aspect of the innate immune system. Blocking of either the classic, antibody-activated, complement pathway with a C1 esterase inhibitor or of complement factor C5a in the alternative pathway reduces IS in animals subject to I/R (Buerke et al., 1995; van der Pals et al., 2010) (reviewed in Yasuda et al., 1990).

The NLRP3 inflammasome and innate immunity are potential targets for acute cardioprotection. However, Zuurbier et al. showed that NLRP3 is barely expressed in healthy murine hearts, and deletion of NLRP3 had no effect on IS following I/R either in perfused mouse

hearts or in vivo (Zuurbier et al., 2012; Jong et al., 2014). In contrast, Sandanger et al. (2013) reported that isolated mouse hearts lacking NLRP3 had smaller IS following global I/R. Generally, it seems that approximately 24 hours reperfusion time is required for priming (expression) of the NLRP3 inflammasome for pyroptosis to make a significant contribution to IS in wildtype hearts (Merkle et al., 2007; Kawaguchi et al., 2011; Sandanger et al., 2013; Jong et al., 2014; Sandanger et al., 2016). In line with this, an NLRP3 inflammasome inhibitor was able to reduce IS even when administered to mice after 1 hour of reperfusion but only when IS was measured 24 hours following infarction (and not after only 3 hours) (Toldo et al., 2016). The selective NLRP3-inflammasome inhibitor MCC950 reduced IS measured 7 days following I/R in pigs (van Hout et al., 2017). A recent study has implicated an NLRP3-independent, oxidative stress-dependent pathway of caspase-11 mediated cleavage of gasdermin D within cardiomyocytes, and release of IL-18 in IRI, and showed that IS was reduced in gasdermin D knockout mice 24 hours after I/R (Shi et al., 2021).

There is some evidence that the NLRP3 inflammasome may be involved in ischemic PreC, although more studies are required to investigate the role of priming. The benefit of ischemic PreC was lost in NLRP3 knockout but not apoptosis-associated speck-like protein containing caspase recruitment domains knockout hearts in the ex vivo Langendorff model (Zuurbier et al., 2012). Pharmacological preconditioning with a toll-like receptor 2 agonist was also lost in NLRP3 knockout hearts (Sandanger et al., 2016). There is limited evidence that RIC might also affect innate inflammation, as recently reviewed (Pearce et al., 2021). Notably, it has been reported that expression of the NLRP3 inflammasome is higher in infiltrating inflammatory cells and murine cardiac fibroblasts (Kawaguchi et al., 2011; Sandanger et al., 2013), so these may be a target for cardioprotection in addition to cardiomyocytes. An important question remains whether comorbidities can prime expression of NLRP3 inflammasome and gasdermin D, which would increase their relevance to the I/R process in diseased hearts.

Indeed, sterile inflammation has been described in other inflammatory conditions such as gout, pseudogout, type 2 diabetes mellitus, metabolic syndrome, atherosclerosis, asbestosis, silicosis, and Alzheimer's disease (for review see Algoet et al., 2022). There is a growing understanding that these disorders are pathophysiologically linked to and can modulate the course of IRI and its response to treatment. The term "metaflammation" describes a metabolically triggered chronic enhanced systemic inflammatory status that is associated with these conditions (Itoh et al., 2022), and such a chronic inflammatory status is also observed in the elderly population without comorbidities (termed "inflammaging") (Liberale et al., 2022).

6. Exosomes. Since our last substantial review of this topic, there has been an explosion of interest in cell-derived nanoparticles called exosomes (Prakash et al., 2020). These extracellular vesicles are released from all types of cells and are found in the blood of all species. Although they are derived mainly from erythrocytes and platelets, some are derived from the vasculature and some from cardiomyocytes (Hegyesi et al., 2022), and they play a role in cardioprotection (Sluijter et al., 2018). Ischemic PreC increases the release of exosomes from endothelial cells or from the heart, and these exosomes are cardioprotective via a signaling pathway involving ERK1/2 (Davidson, Riquelme, et al., 2018). The potential for exosomes to be involved in RIC was first suggested in 2014 (Yellon and Davidson, 2014), and at the same time the first evidence for this was provided by the demonstration that exosomes could transfer cardioprotection from 1 isolated heart to another (Giricz et al., 2014). RIC was shown in both humans and rats to increase the number of exosomes in the blood, although in this study no additional protection was seen with exosomes after RIC (Vicencio et al., 2015). Another study measured elevated levels of microRNA (miR)144 in the blood of mice and humans following RIC, which they proposed was circulated via exosomes to the heart to induce cardioprotection in mice (Li et al., 2014). In patients undergoing coronary artery bypass grafting (CABG), prior RIC increased the number of circulating exosomes and notably their miR 20 content along with reduced postoperative troponin release (Frey et al., 2019). It was recently proposed that IPost increases the release of miR 423-3p-containing exosomes from cardiac fibroblasts and that these participate in the cardioprotective effects of ischemic PostC, via the downstream effector RAP2C (member of RAS oncogene family) (Luo et al., 2019). In healthy volunteers undergoing RIC, protection was transferred to isolated rat hearts and mediated by extracellular vesicles and their miR cargo of miR 16-5p, 144-3p and 451a (Lassen, Just, et al., 2021). It remains unclear how miRs are able to act rapidly enough on their target transcripts to affect a rapidly developing AMI. Interestingly, diabetes impairs cardioprotection by exosomes (Davidson, Andreadou, et al., 2018; Wider et al., 2018).

7. Cardiac Transcriptome. Rapid development of ‘omics technologies in the last 2 decades especially with transcriptomics have enabled the measurement of expression of all known coding and noncoding RNAs. Noncoding RNAs exhibit highly organized spatial and temporal expression patterns and are emerging as critical regulators of differentiation, homeostasis, and pathologic states, including in the cardiovascular system (Abbas et al., 2020; Shah et al., 2022). Unbiased bioinformatics evaluation of such data has led to the discovery of novel mechanisms and promising drug targets for cardioprotection (for reviews see Perrino et al., 2017; Parini et al., 2020). It was shown in the early

2000s that ischemic PreC dramatically altered cardiac gene expression pattern at the mRNA level in rats (Onody et al., 2003) (for review see Perrino et al., 2017). Global cardiac miR expression changes are also observed in pig models of ischemic PreC and ischemic PostC (Spannbauer et al., 2019). In 2013, the first evidence was provided that the expression profile of noncoding miR (fine-tune regulators of mRNA expression) in preconditioned and postconditioned hearts are also altered and several miRs expression changes are associated with cardioprotection—these miRs have been termed protectomiRs (Varga et al., 2014). In particular, a mimic of miR 125b has been shown by several groups to play an important role in ischemic PreC in different models (Wang et al., 2014; Bayoumi et al., 2018; Varga et al., 2018). To date, several miRs have been proposed to be involved in cardioprotective signaling, such as miR 1, miR 144, and miR 221. By unbiased molecular network analysis of miR-mRNA interactions, novel gene targets can be explored (for review see Makkos et al., 2021). Other noncoding RNAs such as circular and long-noncoding are also involved in cardioprotective signaling; however, little is known about their function and possible therapeutic relevance (Wu et al., 2017; Cai et al., 2019; Jusic et al., 2020; Lou et al., 2021).

III. Clinical Approaches to Cardioprotection

A large number of clinical studies have evaluated the cardioprotective effects of ischemic PreC, ischemic PostC, and RIC in patients experiencing acute myocardial IRI during AMI or in cardiac surgery patients. Unfortunately, the results have been variable and overall disappointing (Heusch and Rassaf, 2016) with large multicenter phase 3 studies failing to show any benefit on “hard” clinical outcomes with these cardioprotective interventions and treatments in AMI or cardiac surgery patients (Hausenloy et al., 2015; Meybohm et al., 2015; Hausenloy, Kharbanda, et al., 2019) (see Tables 1 and 2). Apart from providing an overview of recent clinical cardioprotection studies, the challenges facing the translation of cardioprotection for patient benefit will be discussed (Heusch, 2017, 2020), and future opportunities for realizing the clinical potential of cardioprotection will be highlighted.

A. Cardioprotective Strategies

Cardioprotective strategies include mechanical interventions to change blood flow with different clinically approved or novel medical devices as well as with repositioning of drugs on the market and novel drug candidates (Fig. 1). Regulatory and ethical requirements for such clinical studies are not covered in this review.

1. Ischemic Preconditioning and Postconditioning. Clinically, the use of ischemic PreC has been largely restricted to patients undergoing cardiac surgery (for review see Buja, 2022). In this setting, early studies

demonstrated that intermittent cross-clamping of the aorta reduced myocardial injury (assessed by serum cardiac biomarkers such as creatine kinase-MB or troponin T) (Jenkins et al., 1997), and a meta-analysis found potential benefits with RIC with reduced arrhythmias, less inotrope support requirement, and reduced intensive care unit stay (Walsh et al., 2008). However, given the invasive nature of the ischemic PreC stimulus and the potential risk of cerebral thromboembolism from cross-clamping of an atherosclerotic aorta, ischemic PreC has been largely abandoned in cardiac surgery.

In contrast to ischemic PreC, ischemic PostC could be applied at the time of reperfusion in AMI patients undergoing balloon angioplasty at the time of PPCI (Staat et al., 2005). Although shown to be initially promising, with ischemic PostC reducing myocardial IS and preserving cardiac function in a number of small clinical studies (Staat et al., 2005; Thibault et al., 2008), these were followed by several neutral and even negative studies (Freixa et al., 2012; Heusch, 2012; Tarantini et al., 2012). Unfortunately, the large DANAMI-3 trial, which evaluated the effects of ischemic PostC in 1234 STEMI patients undergoing PPCI, failed to report any beneficial effects on clinical outcomes (Engström et al., 2017). The reasons for this failure are not clear but may relate to the ischemic PostC protocol used in the study with the ischemic PostC protocol being delivered within the stent and/or the low-risk patient population (making the study underpowered). Of note, in a post hoc study patients without thrombectomy had reduced risk of all-cause mortality and hospitalization for HF with ischemic PostC (Nepper-Christensen et al., 2020). Ischemic PostC has also been shown to reduce perioperative myocardial injury in the setting of CABG using intermittent cross-clamping of the aorta once the patient has come off cardiopulmonary bypass (Luo et al., 2008; Candilio and Hausenloy, 2017), but, as for ischemic PreC, the invasiveness of the procedure has limited its application. In a recent multicenter trial, ischemic PostC by 3 cycles of normothermic antegrade blood cardioplegia before release of the aortic clamp did not improve cardiac index (primary endpoint) or reduce troponin T or creatine kinase release but reduced a combined secondary endpoint of intraoperative ventricular fibrillation and postoperative atrial fibrillation and suggested hemodynamic differences in the response to PostC between male and female patients undergoing aortic valve replacement (see Kaljusto et al., 2022 and accompanying editorial Podesser and Kiss, 2022). Both ischemic PreC and ischemic PostC require the cardioprotective intervention to be applied directly to the heart, making the procedure invasive and more challenging to apply in the clinical setting. In this regard, RIC, which allows the cardioprotective stimulus to be applied to an organ or tissue away from the heart, has

been intensively investigated as a cardioprotective intervention in the clinical setting.

2. Remote Ischemic Conditioning. The ability to apply the cardioprotective stimulus to the arm or leg by simply inflating and deflating a pneumatic cuff on the upper arm/leg or thigh to induce brief nonlethal episodes of I/R, has greatly facilitated the testing of limb RIC in patients at risk of acute myocardial IRI (Heusch et al., 2015). Single-occasion RIC reduces arterial stiffness and LV remodeling after AMI (Ikonomidis et al., 2021) beyond IS reduction alone, but the effect does not unequivocally translate into a reduction of HF admission in patients (Sloth et al., 2014). Several smaller clinical studies have demonstrated that limb RIC (applying 3 to 4 5-minute cycles of cuff inflation and deflation) prior to CABG surgery reduced perioperative myocardial injury (quantified by serum troponin levels) (Hausenloy et al., 2007; Thielmann et al., 2013), although not all studies have been positive (Rahman et al., 2010). Unfortunately, 3 large, multicenter studies in cardiac surgery patients failed to show any improvement in clinical outcomes with limb RIC applied to cardiac surgery patients (Hong et al., 2014; Hausenloy et al., 2015; Meybohm et al., 2015). The reasons for this failure are not clear but have been attributed to the potential confounding effects of certain comedications such as propofol anesthesia (Kottenberg et al., 2012), nitrates (Candilio et al., 2015), or beta-blockers (Cho et al., 2019) (see Section V). Furthermore, the causes of myocardial injury during CABG are not only due to acute myocardial IRI as coronary embolization, direct handling of the heart, and inflammatory injury associated with cardiopulmonary bypass may be etiological and not amenable to RIC cardioprotection. In contrast, an acute STEMI patient treated by reperfusion using PPCI represents a “purer” setting of acute myocardial IRI, which should be more amenable to the cardioprotective effects of limb RIC.

The first study to demonstrate this in STEMI patients was by Bøtker et al. (2010), who showed applying limb RIC patients in the ambulance on the way to the PPCI center, improved myocardial salvage (assessed by myocardial single-photon-emissions-tomography imaging) but did not reduce myocardial IS. Subsequent studies confirmed the cardioprotective effect of limb RIC administered on arrival at the hospital quantified by cardiac MRI (White et al., 2015) and even at the onset of reperfusion (Crimi et al., 2013), although not all studies have been positive (Verouhis et al., 2016). One large clinical study did demonstrate improved clinical outcomes with less HF hospitalization and cardiac death (Gaspar et al., 2018). In addition, follow-up studies of RIC-treated STEMI patients suggested an improvement in major adverse cardiac events at follow-up (Sloth et al., 2014; Stiermaier et al., 2019). However, despite these promising studies, the large, multicenter CONDI-2/ERIC-PPCI trial

of 5401 STEMI patients failed to find any improvement in rates of HF hospitalization and cardiac death at 12 months (Hausenloy, Kharbanda, et al., 2019). The reasons for this failure to translate limb RIC for patient benefit are not clear but may relate to the low-risk population recruited in this trial (Heusch and Gersh, 2020) (see Section IIIa3.).

Most clinical cardioprotective studies with limb RIC have applied 1 stimulus at the time of cardiac surgery or STEMI, but animal studies have suggested that cardioreparative effects of RIC may be induced by repeated daily episodes of limb RIC (Wei et al., 2011). Extended exposure to RIC may add further modulation of myocardial remodeling. Repeated RIC modifies the human inflammatory response and leukocyte adhesion (Shimizu et al., 2010) and improves coronary microcirculation in healthy volunteers and patients with HF (Jones et al., 2014). In contrast to single-occasion RIC, repeated RIC reduces blood pressure (Baffour-Awuah et al., 2021), allowing afterload reduction to modulate myocardial remodeling favorably. Nonetheless, the Daily REmote Ischemic Conditioning Following Acute Myocardial Infarction (DREAM) study demonstrated no effect of 4 weeks of daily RIC-treatment initiated 3 days after PPCI on ventricular function in 73 patients with reduced LV function after the acute coronary event (Vanezis et al., 2018). In pilot studies, repeated RIC as add-on to standard anti-congestive treatment in patients with stable chronic HF did not improve LV ejection fraction but decreased circulating NH₂-terminal pro-B-type natriuretic peptide and skeletal muscle function after 28 days of RIC treatment once daily (Pryds et al., 2017), whereas exercise capacity was not different (McDonald et al., 2014). However, prolonged periods of daily limb RIC have been reported to be beneficial in patients with intracranial stenosis at risk of stroke (Meng et al., 2012). Despite the failure to translate the cardioprotective effects of limb RIC into a clinical benefit in cardiac surgery or STEMI patients, it may still have potential in STEMI patients at elevated risk of compromised outcome (Cheskes et al., 2020; Hausenloy et al., 2020) and other settings of acute IRI, such as kidney transplantation (MacAllister et al., 2015).

3. *Pharmacological Cardioprotection.* A detailed description of comedication administered to treat patients' comorbidities and its impact on IRI as well as cardioprotective interventions will be discussed extensively in Section V. However, some pharmacological approaches derived from a better understanding of the signaling cascades involved in endogenous cardioprotection have also been evaluated in clinical trials (Table 2).

The most promising of these was CsA, a mPTP inhibitor that had been shown in small and large animal studies to reduce IS (Hausenloy et al., 2002; Argaud

et al., 2005; Skyschally et al., 2010), although not all studies had been positive (Karlsson et al., 2010; Lim et al., 2012). While initial phase 2 clinical studies with CsA reported reducing myocardial injury in cardiac surgery patients (Chiari et al., 2014; Hausenloy et al., 2014) and smaller IS in STEMI patients (Piot et al., 2008), 1 study did not show cardioprotection with CsA in STEMI patients (Ghaffari et al., 2013). Unfortunately, 2 large, multicenter clinical studies (CIRCUS and CYCLE) (Cung et al., 2015; Ottani et al., 2016) failed to demonstrate improved clinical outcomes with CsA administered prior to reperfusion in STEMI patients. Why these larger clinical trials failed to confirm the benefit of CsA on either reducing IS or clinical outcomes is unclear but may have been due to a type I error, insufficient dosing, the low-risk population, and the presence of P2Y₁₂ (chemoreceptor for adenosine diphosphate) inhibitors (see Section V).

Other mitochondrial targeting agents such as MTP-131 (which optimizes mitochondrial energetics and attenuates the production of ROS by selectively targeting cardiolipin in the inner mitochondrial membrane) failed to reduce IS in a phase 2 trial in a carefully selected group of anterior STEMI patients (Gibson et al., 2016). The mitochondrial protective agent, TRO40303, (which binds to the translocator protein in the outer mitochondrial membrane) reduced IS in small animals (Schaller et al., 2010) but not in large animals (Hansson et al., 2015) and did not reduce IS when administered to STEMI patients prior to PPCI (Atar et al., 2015).

While some experimental studies demonstrated cardioprotection with intravenous nitrite administered at the onset of reperfusion (Duranski et al., 2005), the National Heart Lung and Blood Institute Consortium for preclinical assessment of cARDioprotective therapies (CAESAR) Network failed to show IS reduction with nitrite using a multicenter approach in small and large animal I/R models (Lefer and Bolli, 2011; Jones, Tang, et al., 2015; Bolli, 2021). Also, 2 clinical studies failed to demonstrate a significant IS reduction with nitrite administered by either the intravenous (Siddiqi et al., 2014) or intracoronary (Jones, Pellaton, et al., 2015) route in PPCI-treated STEMI patients. The study by Janssens et al. also failed to report any cardioprotective effects with inhaled NO as an adjunct to PPCI in STEMI patients (Janssens et al., 2018), although some benefit was seen in nitrate-naive patients.

More recently, studies have investigated the cardioprotective effects of targeting interleukin-6 (IL-6), as this cytokine has been shown to contribute to inflammation in coronary artery disease and acute myocardial IRI (Sawa et al., 1998; Interleukin-6 Receptor Mendelian Randomization Analysis Consortium et al., 2012; Ritschel et al., 2013). An initial clinical study in non-ST elevation myocardial infarction patients

reported that pretreatment with a single intravenous 60-minute infusion of tocilizumab (an IL-6 receptor antibody) prior to PCI reduced inflammation and PCI-related myocardial injury when compared with placebo (Kleveland et al., 2016). The recently published ASSAIL-MI study in STEMI patients demonstrated that the same treatment regimen initiated during PCI improved myocardial salvage but did not significantly reduce MI size assessed by cardiac MRI performed on day 3 to 7 post-admission, when compared with placebo (Broch et al., 2021).

The importance of NLRP3 inflammasome-driven IL-1 β for cardiovascular events was studied in some clinical trials with anakinra (a recombinant IL-1 receptor antibody) in patients with previous MI (VCU-ART and VCUART2; MRC-ILA-Heart Study). These trials were performed in a relatively small number of patients, and the reported results are contentious. The CANTOS trial, which evaluated the long-term effect of canakinumab (a humanized monoclonal IL-1 β antibody) in 10061 MI patients, showed a significant 15% reduction in major adverse coronary events (MACE) compared with the placebo group; however, all-cause mortality did not differ between the canakinumab and placebo groups. Recently, the Colchicine Cardiovascular Outcome Trial using low-dose colchicine in 4745 MI patients as well as the subsequently conducted low-dose colchicine 2 trial in 5522 patients with chronic coronary artery disease confirmed a decrease in MACE (including cardiovascular death). Since colchicine can prevent NLRP3 inflammasome assembly, the clinical efficiency of colchicine supports the notion that NLRP3 inflammasome plays a key role in the pathogenesis of atherosclerosis and subsequent atherothrombotic events (for a detailed review see Takahashi, 2022).

B. Other Mechanical Approaches to Cardioprotection

A number of different mechanical approaches have recently been evaluated in STEMI patients treated by PPCI. Acute ventricular unloading prior to reperfusion has been shown in animal studies to reduce myocardial IS by decreasing myocardial workload (for review see Curran et al., 2019) (Table 1). A recent clinical study has tested the safety and feasibility of unloading the LV for 30 minutes before reperfusion using the percutaneous left ventricular support device, Impella CP, in anterior STEMI patients treated by PPCI. Interestingly, delaying reperfusion by 30 minutes did not increase IS when compared with applying the Impella CP device at the immediate onset of reperfusion (Kapur et al., 2019). The ongoing STEMI-DTU Trial is currently testing the efficacy of this approach on IS assessed by cardiac MRI in 668 anterior STEMI patients (NCT03947619). Therapeutic hypothermia has been reported to reduce IS in animal studies, but this has to be applied during myocardial ischemia, which might explain the lack of

cardioprotection seen in clinical studies applying therapeutic hypothermia at reperfusion in STEMI patients treated by PPCI, studies that also showed delays in PPCI and increase adverse events with this intervention (Erlinge et al., 2014; Nichol et al., 2015; Testori et al., 2019; Noc et al., 2021) (for review also see Testori et al., 2019). Prior preclinical studies have demonstrated cardioprotection with intermittent coronary sinus occlusion, a technique that increases myocardial salvage following AMI by improving myocardial perfusion (Guerci et al., 1987; Toggart et al., 1987; Beyar et al., 1989; Rydén et al., 1991). In patients with STEMI, pressure-controlled intermittent coronary sinus occlusion, using a balloon-tipped catheter placed in the coronary sinus that is cyclically inflated and deflated resulting in an intermittent increase in coronary sinus pressure, improved myocardial perfusion. In preliminary studies pressure-controlled intermittent coronary sinus occlusion reduced IS size in anterior STEMI both acutely and at 6 months (De Maria et al., 2018; Eged et al., 2020), and it reduced the index of microcirculatory resistance within 48 hours of revascularization (De Maria et al., 2018; Scarsini et al., 2022).

C. Potential Opportunities for Improving Clinical Translation of Cardioprotection

Overall, the results of clinical cardioprotection studies have been largely disappointing (Heusch, 2017; 2020; Heusch and Rassaf, 2016). In this section we describe some strategies for potentially improving the clinical translation of cardioprotection for patient benefit.

1. Improving Preclinical Assessment of Cardioprotective Strategies. One key reason for the failure to translate cardioprotection into the clinical arena has been the lack of rigorous and systematic preclinical testing of novel cardioprotective therapies, the consequence of which has been the premature clinical evaluation of treatments with inconsistent and less than robust cardioprotective effects (Bolli, 2021). Potential strategies for ensuring that only the most robust and reproducible novel cardioprotective therapies are tested in clinical studies include establishing guidelines and criteria for preclinical evaluation of novel cardioprotective therapies and establishing multicenter research networks for testing of novel cardioprotective therapies. The European Union-CARDIOPROTECTION Cooperation in Science and Technology Action CA16225, a pan-European research network of leading experts in experimental and clinical cardioprotection, aims to address some of these issues. It has already published practical guidelines to ensure rigor and reproducibility in preclinical cardioprotection studies (Bøtker, Hausenloy, et al., 2018) and has established the IMPROVING Preclinical Assessment of Cardioprotective Therapies (IMPACT) criteria for improving the in vivo preclinical evaluation of the efficacy of novel cardioprotective therapies (Lecour et al., 2021). Finally, the EU-CARDIOPROTECTION

TABLE 1
Major clinical cardioprotection studies of mechanical interventions in patients with AMI

Study	n	Patient criteria	Cardioprotection protocol	Main outcome	Notes
Ischemic postconditioning					
Staat et al., 2005	30	LAD/RCA STEMI ≤6 h ischemic time TIMI 0 pre-PPCI	4 × 1 min inflations and deflations of angioplasty balloon upstream of stent Direct stenting	36% reduction in MI size (72 h AUC CK) Better myocardial blush grade	First clinical study to translate ischemic PostC into clinical setting
Staat et al., 2005; Thibault et al., 2008	38	LAD/RCA only ≤6 h ischemic time TIMI 0 pre-PPCI	4 × 1 min inflations and deflations of angioplasty balloon upstream of stent Direct stenting	40% and 47% reductions in MI size (72 h AUC CK and troponin I) 39% reduction in MI size (SPECT at 6 months) 7% increase in LVEF (echo at 1 year)	First clinical study to demonstrate long- term benefit with ischemic PostC
Freixa et al., 2012; Heusch, 2012; Tarantini et al., 2012 POST-AMI	78	All STEMI <6 h ischemic time TIMI 0–1 pre-PPCI No collaterals	4 × 1 min inflations and deflations of angioplasty balloon within the stent Direct stenting and no thrombectomy performed	No difference in MI size (MRI 30 days)—trend to increase with ischemic PostC	First study to suggest possible detrimental effects with ischemic PostC
Freixa et al., 2012; Heusch, 2012; Tarantini et al., 2012	79	All STEMI TIMI 0–1 pre-PPCI No collaterals	4 × 1 min inflations and deflations of angioplasty balloon within the stent Direct stenting	No difference in MI size (MRI at 1 week or 6 months) Less myocardial salvage with ischemic PostC	First study to show detrimental effect of ischemic PostC in terms of less myocardial salvage
Engström et al., 2017 DANAMI 3	1,252	All STEMI TIMI 0–1 pre-PPCI	4 × 0.5 min inflations and deflations of angioplasty balloon at site of lesion	No difference in primary endpoint of all- cause death and HHF at median follow up time of 38 months	Largest outcome study to date with no beneficial effects of ischemic PostC
Remote ischemic conditioning					
Bötter et al., 2010 CONDI	142	All STEMI	4 × 5 min inflations/ deflations of cuff on upper arm in the ambulance before PPCI	Increase in myocardial salvage index at 30 days No difference in MI size (SPECT or peak troponin)	First study to show beneficial effect of RIC on myocardial salvage
Crimi et al., 2013	100	Anterior STEMI only	3 × 5 min inflations/ deflation of cuff on thigh at onset of reperfusion	20% reduction in 72 h AUC CK–MB	First study to show beneficial effects of RIC started at onset of reperfusion
White et al., 2015 ERIC-STEMI	83	All STEMI	4 × 5 min inflations/ deflations of cuff on upper arm at the hospital before PPCI	27% reduction in MI size by MRI 19% reduction in myocardial edema by MRI	First study to show beneficial effects of RIC on MI size and myocardial edema assessed by MRI
Eitel et al., 2015; Stiermaier et al., 2019 LIPSIA conditioning	333	All STEMI	4 × 5 min inflations/ deflations of cuff on upper arm at the hospital before PPCI plus ischemic PostC	Increased myocardial salvage with RIC + ischemic PostC versus control No difference in MI size or MVO	Improved myocardial salvage when ischemic PostC combined with RIC, but effect of RIC alone not tested
Verouhis et al., 2016	93	Anterior STEMI within 6 h chest pain	Variable number of 5 min cycles (7–9) of inflations/deflations of cuff on upper arm	No difference in MI size or myocardial salvage at MRI scan at day 4–7	First neutral study with RIC in STEMI
Vanezis et al., 2018 DREAM	73	STEMI with LVEF <45%	4 × 5 min inflations/ deflations of cuff on upper arm in started day 3 post-PPCI and continued daily for 28 days	No difference in MI and LV remodelling at 4 months post-PPCI	First study to test effects of daily RIC post-STEMI
Gaspar et al., 2018 RIC STEMI	516	All STEMI	3 × 5 min inflations/ deflations of cuff on thigh before PPCI	Primary endpoint of cardiac mortality and HHF at 12 months reduced by 35% Preserved LVEF at 6 months	First prospective study to show benefits on clinical outcomes
Hausenloy, Kharbanda, et al., 2019 CONDI-2/ERIC-PPCI	5400	All STEMI	4 × 5 min inflations/ deflations of cuff on upper arm before PPCI	No difference on primary endpoint of cardiac death and HHF at 12 months	Largest clinical study to investigate the effects of RIC on clinical outcomes

(continued)

TABLE 1—Continued

Study	n	Patient criteria	Cardioprotection protocol	Main outcome	Notes
Cheskes et al., 2020; Hausenloy et al., 2020	1726	All STEMI	4 × 5 min inflations/deflations of cuff on upper arm before PPCI	No difference in MACE at 90 days although benefit seen in patients presenting with cardiogenic shock or cardiac arrest	Not RCT but pre- and post-implementation designed study
Therapeutic hypothermia Erlinge et al., 2014	120	All STEMI within 6 h chest pain	Therapeutic hypothermia using IV infusion of cold saline to achieve <35°C for 1 h	No difference in myocardial salvage Possible benefit in anterior STEMI patients	9 min delay to PPCI with intervention
Nichol et al., 2015 VELOCITY	54	All STEMI	Therapeutic hypothermia using intraperitoneal infusion of cold saline for 3 h post-PPCI	No difference in MI size at 3–5 post-PPCI and significant increase in adverse events at 30 days	15 min delay to PPCI with intervention
Noc et al., 2021 COOL AMI EU Pivotal Trial	111	Anterior STEMI patients	Therapeutic hypothermia using IV infusion of cold saline to achieve 33°C for 1 h post-PPCI	No difference in MI size at 4–6 post-PPCI and significant increase in adverse events (cardiogenic shock) at 30 days	Prematurely stopped due to 44 min delay to PPCI with intervention
LV unloading with Impella CP Kapur et al., 2019 DTU STEMI pilot	50	Anterior STEMI patients	LV unloading by using the Impella CP	No difference in MI size with 30-min delay to reperfusion	Feasibility study for efficacy study; DTU STEMI
PICSO De Maria et al., 2018; Egred et al., 2020 OXAMI-PICSO	105	Anterior STEMI patients	PICSO	Smaller MI size on MRI at day 2 and 6 months. Improved coronary microvascular perfusion 48 h	
De Maria et al., 2018; Egred et al., 2020	92	Anterior STEMI patients	PICSO	Smaller MI size on MRI at day 5	
De Maria et al., 2018; Scarsini et al., 2022	108	All STEMI patients	PICSO	Improved coronary microvascular perfusion and vasodilatory activity and less MVO and smaller MI size at 48 h on MRI	

AUC, area under curve; CK, creatine kinase; HHF, hospitalization for heart failure; LAD, left anterior descending artery; LV, left ventricle; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MI, myocardial infarction; MVO, microvascular obstruction; PISCO, pressure-controlled intermittent coronary sinus occlusion; PostC, postconditioning; PPCI, primary percutaneous coronary intervention; RCA, right coronary artery; RIC, remote ischemic conditioning; SPECT, single-photon emission computed tomography; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

Cooperation in Science and Technology Action is currently establishing a research network for preclinical multicenter testing of novel cardioprotective therapies. The IMPACT small-animal research network is currently being set up to undertake multicenter evaluation of novel cardioprotective therapies in mice and rat models of acute myocardial IRI, and validation of the research network will be undertaken using ischemic PreC. The CIBERCV (the acronym for Spanish Network-Center for Cardiovascular Biomedical Research) has set up the Cardioprotection Large Animal Platform, a Spanish multicenter network of 5 research centers, to perform experimental pig acute myocardial IRI studies testing the efficacy and reproducibility of promising cardioprotective interventions based on a prespecified design and protocols, centralized randomization, blinding assessment, core laboratory analyses of cardiac MRI imaging, histopathology, and proteomics (Rossello et al., 2019). The network is currently

being validated using ischemic PreC. Also, it will be necessary in select preclinical studies to perform a more chronic follow-up and use the same endpoints as used in clinical trials (i.e., mortality over 6 to 12 months and the development of HF) (Heusch, 2018).

2. Multitargeted Approaches to Cardioprotection.

One potential strategy for improving the clinical translation is to use a multitarget approach using either single agents (that have more than 1 target) or 2 or more therapies with different targets. The multitargeted approach may be a more effective than a single-targeted approach, especially given the complexity and different proponents of acute myocardial IRI (e.g., cardiomyocytes, endothelial cells, immune cells, platelets, microvasculature) (Davidson, Ferdinandy, et al., 2019). The ongoing PITRI study is testing whether administration of the intravenous P2Y₁₂ platelet inhibitor, cangrelor, prior to PPCI can prevent microvascular obstruction and reduce

TABLE 2
Major recent clinical cardioprotection studies of pharmacological interventions in patients with AMI

Study	n	Patient criteria	Treatment protocol	Main outcome	Notes
Cyclosporin-A Piot et al., 2008	58	All STEMI	IV bolus of CsA administered 10 min prior to PPCI	Reduce MI size assessed by AUC CK. No difference in troponin I. Subset of 37 patients reduce MI size on MRI at day 5 post-PPCI	First clinical study to show cardioprotection with CsA
Cung et al., 2015; Ottani et al., 2016 CIRCUS	970	Anterior STEMI Pre-PPCI TIMI 0/1	IV bolus of CsA administered prior to PPCI	No difference in primary outcome worsening in-pt heart failure, HHF, or adverse LV remodeling at 1 yr	Largest outcome study with CsA
Cung et al., 2015; Ottani et al., 2016 CYCLE	410	All STEMI	IV bolus of CsA administered prior to PPCI	No difference in primary endpoint of $\geq 70\%$ ST-segment resolution 60 min after TIMI flow grade 3 or MI size (day 4 hs-cTnT) or LV remodeling at 6 mo.	
MTP-131 Gibson et al., 2016 EMBRACE-STEMI	118	Anterior STEMI Pre-PPCI TIMI 0/1	IV 60-min infusion of MTP-131 started prior to PPCI	No difference in primary endpoint of MI size (72 h AUC CK). No difference in MI size or LV remodeling on MRI at 4 and 30 days	
TRO40303 Atar et al., 2015 MITOCARE	163	All STEMI within 6 h chest pain Pre-PPCI TIMI 0/1	IV bolus of TRO40303 administered prior to PPCI	No difference in primary endpoint of MI size (72 h AUC CK or hs-cTnI)	There was a significant increase in major adverse events with the study drug compared with placebo
Nitrite Siddiqi et al., 2014 NIAMI	229	All STEMI TIMI 0/1	IV bolus of nitrite administered prior to PPCI	No difference in primary endpoint of MI size on MRI at day 6–8. No difference in LV remodeling or MI size by (72 h AUC CK or cTnI)	
Jones, Pellaton, et al., 2015	198	All STEMI	Intracoronary bolus of nitrite administered prior to PPCI	No difference in primary endpoint of MI size (72 h AUC CK or hs-cTnI)	
N-acetylcysteine + Nitroglycerin Hausenloy and Yellon, 2017; Pasupathy et al., 2017 NACIAM	75	All STEMI	IV infusion of NAC for 48 h initiated prior to PPCI. On background of IV GTN infusion	Reduction (by 33%) in primary endpoint of MI size by CMR at day 2–3 post-PPCI	
Inhaled nitric oxide Janssens et al., 2018 NOMI	250	All STEMI	Inhaled oxygen with NO started 10 min prior to PPCI and continued for 4 h	No difference in primary endpoint of MI size by MRI at day 2–3	
Tocilizumab (IL-6 receptor antibody) Kleveland et al., 2016	117	NSTEMI	IV 60-min infusion started prior to PPCI	Reduced hsCRP levels. Reduced median AUC for hs-cTnT by 30%	
Broch et al., 2021 ASSAIL-MI	199	All STEMI	IV 60-min infusion started during PPCI	Increased myocardial salvage by 5.6% on CMR (2–7 days) and less MVO but no difference in MI size	

AUC, area under curve; CMR: cardiac magnetic resonance; CK-MB, creatine kinase MB isoenzyme; GTN, glyceryl trinitrate; hs-cTnT/I, high-sensitive cardiac troponin T/I; HHF, hospitalization for heart failure; IV, intravenous; LAD, left anterior descending artery; MI, myocardial infarction; MVO, microvascular obstruction; NAC, N-acetylcysteine; NSTEMI, non-ST-segment elevation myocardial infarction; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

IS in STEMI patients (Bulluck et al., 2019) (Table 1). Cangrelor offers complete platelet inhibition with 1 to 2 minutes of administration, thereby potentially reducing the risk of MVO in STEMI patients, and has also been reported in small and large animal studies to reduce IS when given at reperfusion (Yang, Cui, et al., 2013; Yang, Liu, et al., 2013a, 2013b) (Table 2). The NACIAM study showed that the addition of an intravenous infusion of N-acetylcysteine on a background of nitroglycerin infusion reduced IS when compared with nitroglycerin infusion (Pasupathy et al., 2017) (Table 2).

The combined effects of limb RIC with ischemic PostC have been tested in a clinical study but were shown to have no additional cardioprotective effects in STEMI patients (Prunier et al., 2014). However, the LIPSIA study did report increased myocardial salvage and improved outcomes (less cardiac death, reinfarction, and new congestive HF at 3.6 years) in patients given both limb RIC and ischemic PostC when compared with control or ischemic PostC alone, although the effects of limb RIC alone were not tested (Eitel et al., 2015; Stiermaier et al., 2019). The ongoing CARIOCA (NCT03155022) study is also testing the combination of limb RIC and ischemic PostC in a large STEMI trial (Table 1). Based on the premise that limb RIC and exenatide had different cardioprotective targets (pig study) (Albuquerque-Béjar et al., 2015), the COMBAT MI study recently compared the IS-limiting effects of combining RIC with exenatide to that of limb RIC or exenatide alone in PPCI-treated STEMI patients. Unfortunately, the combination of RIC and exenatide did not translate into a reduction of IS and, more surprisingly, neither limb RIC nor exenatide alone reduced IS (García Del Blanco et al., 2021) (see Section V) (Table 1).

3. Targeting High-Risk Patients. One potential reason for the failure of limb RIC to improve clinical outcomes in STEMI patients in the CONDI2/ERIC-PPCI trial was the low-risk population recruited: they were optimally treated by PPCI and had relatively short ischemic times (median of 3 hours), and 96% of patients presented in Killip Class I and cardiac mortality (2.7%) was low at 12 months (Heusch and Gersh, 2020). RIC may be more effective in higher risk STEMI patients such as those presenting in HF or cardiogenic shock or those who were still treated by thrombolysis (Bøtker, 2020; Heusch and Gersh, 2020). In this regard, the FIRST study in which RIC was implemented in the clinical setting as part of a pre- and post-implementation study reported potential beneficial effects on MACE in those patients with cardiogenic shock or cardiac arrest (Cheskes et al., 2020). The planned RIC-AFRICA trial (NCT04813159) will evaluate RIC in higher risk STEMI patients treated by thrombolysis due to limited availability of PPCI (Hausenloy et al., 2020), and the RIP-HIGH trial will test the combination of RIC and local ischemic

PostC in STEMI patients with heart failure (Killip class ≥ 2) (i.e., those with severe hemodynamic impairment or cardiogenic shock) (NCT 04844931).

In summary, the translation of cardioprotection into the clinical setting for patient benefit has been largely disappointing. On the one hand, there is a wealth of pre-clinical studies unequivocally demonstrating cardioprotection in a variety of species and experimental models with different endpoints, such as arrhythmias, ventricular dysfunction, IS, and coronary MVO. On the other hand, despite several positive proof-of-concept clinical studies in STEMI patients demonstrating cardioprotection by mechanical and pharmacological approaches, there is now an increasing number of recent phase 2 studies showing no benefits on IS and several large phase 3 studies failing to show benefit on clinical outcomes despite positive phase 2 studies. This discrepancy results from the very different approaches inherent to preclinical research and clinical trials. Preclinical studies aim for novel knowledge and mechanistic understanding and therefore regularly use protocols that maximize the cardioprotective efficacy. In contrast, large clinical trials aim to identify a cure for disease in as many patients as possible and therefore regularly use an all-comer approach that does not consider the need of protection or potential confounders. The disappointment about the lack of translation then reflects the very different mutual expectations and a lack of communication between pre-clinical researchers and clinicians. The present review aims to improve such communication, with a particular focus on confounders.

On the preclinical side, potential reasons for failure in clinical translation include the lack of rigorous pre-clinical evaluation of novel cardioprotective therapies. Therefore, strategies for improving the preclinical assessment of novel cardioprotective therapies with the introduction of rigorous criteria that need to be fulfilled before proceeding to clinical studies and the use of multicenter networks of small and large animal research centers to blindly evaluate novel cardioprotective therapies are advocated (Lecour et al., 2021; Kreutzer et al., 2022). On the clinical side, targeting high-risk patients at risk of acute myocardial IRI (Heusch and Gersh, 2020) and consideration of confounders may improve the chances of successfully translating cardioprotection for patient benefit. With respect to our focus on confounders, it is important to note that most published clinical cardioprotection studies in AMI patients have not been suitably powered or specifically designed to test the confounding effects of comorbidities and comedications discussed in this article on the efficacy of cardioprotective therapeutic strategies, despite a significant proportion of recruited patients having these potential confounding factors. In an ideal world, we would propose that only those cardioprotective interventions that have fulfilled

stringent criteria and been established in a multicenter network as robust are taken forward from preclinical studies to be tested in a clinical trial, whereas less certain cardioprotective interventions would not even be tested clinically. Conversely, clinical trials for cardioprotection beyond that by reperfusion would be confined to those needing adjunct cardioprotection and not in an all-comer approach; at the least, a prespecified subgroup analysis for STEMI patients with Killip class ≥ 2 (i.e., those with severe hemodynamic impairment or cardiac shock) would be performed.

IV. Effects of Nonmodifiable Risk Factors and Comorbidities on Ischemia-Reperfusion Injury and Cardioprotective Strategies

A. Nonmodifiable Risk Factors

1. Aging.

a. Aging, IRI, and Cardioprotection. Age is, along with sex, the most prominent disease modifier. Not only does it increase the vulnerability of the heart to IRI, but it also hampers the therapeutic efficiency of several ischemic and pharmacologic conditioning strategies in many (but not all) experimental models and in some clinical studies, as recently reviewed (Ruiz-Meana, Boengler, et al., 2020; Ruiz-Meana, Bou-Teen, et al., 2020). The loss of cardioprotection during aging can be attributed to different factors, among them: (i) the higher burden of comorbidities (e.g., hypertension, metabolic disorders) that may impose additional damage to the heart (Andreadou et al., 2021), (ii) the more frequent use of concomitant medications that can cause therapeutic interferences (Ferdinandy et al., 2014), (iii) the coexistence of a chronic and deleterious proinflammatory myocardial environment (Ramos et al., 2017), (iv) the progressive accumulation of damaged and dysfunctional mitochondria within cardiomyocytes (Ruiz-Meana et al., 2019; Bou-Teen et al., 2022), and (v) the attenuation of some signaling pathways mechanistically involved in cell survival (Boengler, Schulz, et al., 2009). The majority of studies have described a loss of ischemic PreC-induced cardioprotection with age, yet some authors reported myocardial protection by ischemic PreC in old rat hearts (Webster et al., 2017). The cardioprotection provided by ischemic PostC has much greater therapeutic applicability than that afforded by ischemic PreC, but it is, in general, less robust and more dependent on the strength of the ischemic stimulus (Boengler et al., 2008). As in ischemic PreC, experimental evidence indicates an attenuation of its effectiveness with increasing age (Boengler et al., 2008; Przyklenk et al., 2008; Perez et al., 2016).

The age-dependent loss of ischemic PostC protection has also been described for rat hearts and isolated cardiomyocytes from aged rats (Chen, Gao, et al., 2016) and has been attributed to a defective autophagic response. Moreover, the age-dependent attenuation of

the cardioprotective properties of PostC appears to be sensitive to sex interaction, as inferred from a recent study in which a specific modality of PostC protocol induced by alternate atrial/ventricular pacing (pacing PostC; see Section IVc2), which was shown to be effective in Langendorff-perfused rat hearts from young animals, remained cardioprotective in the hearts of old females but had no therapeutic benefit in the hearts of old males (Babiker et al., 2019). Regarding the human heart, it seems clear that ischemic PostC can be protective (Staat et al., 2005), but the influence of age on the extent of cardioprotection is more confusing. In a small clinical study of aged patients assigned to receive 2 different ischemic PostC protocols during PPCI (either 4 cycles of 30-second inflation/deflation or 4 cycles of 60-second inflation/deflation), the authors reported a significant beneficial effect on enzyme release (creatinase kinase-MB and troponin I) in the postconditioned groups compared with controls, regardless of the ischemic algorithm (Zhang et al., 2018). Although promising, interpretation of clinical data are challenged by substantial interindividual variation in patients and the lack of studies in which the cardioprotective effect has been quantified with hard end-points measurements of IS.

RIC holds the potential of affording simultaneous protection to the heart and other organs susceptible to IRI (like the brain), making it particularly appealing for the systemic protection of elderly patients. Unfortunately, its effectiveness is less consistent than ischemic PreC and other conditioning strategies in rat hearts *ex vivo* (Lassen, Hjortbak, et al., 2021) and decreases even more with aging, as inferred from preclinical studies in rats *in vivo* (Behmenburg et al., 2017).

In a more clinically relevant context of patients undergoing CABG surgery with an average age of 76 years, RIC consisting of 4 5-minute inflations and deflations of a standard blood-pressure cuff on the upper arm, prior to anesthesia, did not result in any improvement in clinical outcomes (incidence of AMI, need of coronary revascularization, stroke, and death) (Hausenloy et al., 2015). It has been proposed that such an age-related decline in the ability of RIC to improve clinical outcomes might depend not only on the intrinsic changes developed by the aged heart but also on the loss of the cardioprotective properties of the released humoral factor(s) during aging (Heinen et al., 2018). Moreover, despite the positive results obtained in preclinical and small proof-of-concept clinical trials, the evaluation of its cardioprotective potential as adjunctive to PPCI in appropriately powered randomized controlled (RCT) clinical trials of patients with STEMI yielded neutral results, and RIC added no clinical benefit for outcomes when applied alone (Hausenloy, Kharbanda, et al., 2019) or in combination with exenatide (García Del Blanco et al., 2021), regardless of the subgroup of age.

b. Aging and Cardioprotective Signaling. Reduced expression or altered posttranslational modification of proteins involved in protective signaling cascades, including mitochondrial connexin 43, RISK, and SAFE pathways as well as changes in their subcellular localization, have been shown to participate in the loss of cardioprotection during aging, as extensively reviewed (Boengler et al., 2007; Boengler, Schulz, et al., 2009; Ruiz-Meana, Boengler, et al., 2020; Ruiz-Meana, Bou-Teen, et al., 2020). In addition to this, aged cardiomyocytes develop some idiosyncratic pathophysiological traits that reduce their tolerance to stress and injury and can outweigh the benefits of the therapeutic strategies. Among them, changes in calcium handling, excessive intracellular glycoxidative stress, mitochondrial calcium accumulation, and reduced number of healthy and metabolically competent mitochondria may play a relevant role (Ruiz-Meana et al., 2019; Bou-Teen et al., 2021). A broad spectrum of experimental studies suggests that restoration of the age-dependent loss of cardioprotection is possible through strategies like exercise protocols, dietary interventions (i.e., caloric restriction), and pharmacological agents (Calabrese, 2016a). In agreement with this concept, cardiac supplementation with a hydrogen sulfide donor (a gaseous neurotransmitter) has been recently shown to upregulate the hypoxia-inducible factor-1 α /nuclear factor erythroid 2-related factor 2 signaling pathway involved in the late phase of cardioprotection in hearts from aged rats subjected to RIC (left hind limb ischemia) and subsequent ex vivo I/R (Wang, Shi, et al., 2021). In the context of ischemic PostC, exogenous administration of hydrogen sulfide in isolated hearts from aged rats exposed to IRI upregulated the age-dependent reduction in autophagy via the adenosine 5'-monophosphate activated protein kinase adenosine 5'-monophosphate activated protein kinase/mechanistic target of rapamycin pathway and restored the cardioprotective response in the aged hearts (Chen, Gao, et al., 2016). The same line of evidence led to the hypothesis that aged hearts might require a stronger conditioning stimulus (higher number of ischemic cycles or cycles with longer duration) to counteract the defective cytoprotective response. However, the relevance of this approach remains uncertain, as is the relative contribution of the different cytoprotective pathways to the therapeutic success of conditioning during aging.

2. Sex, IRI, and Cardioprotection. Although ischemic heart disease is a major cause of mortality and morbidity in both males and females, sex differences exist in terms of susceptibility, mechanisms, and outcomes to IRI observed between men and women. Confounding factors (comorbidities, comedications) in ischemic heart disease may have sex-specific effects, and mechanisms underlying these differences are multiple and include gonadal hormones (for review see Perrino et al., 2021). Despite sex differences in IRI outcome, which occurs in

an age-dependent manner, no clinical studies have yet been able to highlight sex as a confounding factor in the cardioprotective strategy of conditioning (Staat et al., 2005). Although most of the preclinical data exploring the cardioprotective effect of ischemic conditioning have been investigated in healthy young male animals, few studies suggest a sex difference in the cardioprotective response of conditioning against IRI in structurally normal myocardium (for review see Querio et al., 2021). As discussed in Section IVc, notable sex-related differences, however, have been noted in hypertrophied myocardium.

In the preclinical setting, some animal studies suggest that ischemic PreC may be less cardioprotective in females than in males, an effect that is also highly dependent on the age of the animals. In mice, ischemic PreC improved the functional outcome of IRI in both 10- and 18-week-old male mice. In contrast, female mice failed to be protected at an age of 10 weeks (Song et al., 2003; Turcato et al., 2006). In Wistar rats, ischemic PreC successfully reduced IS in 12- and 18-week-old males and females but failed to confer an antiarrhythmic effect in 12-week-old females (Ledvenyiova et al., 2013). Whereas both male and female rats can be preconditioned with endotoxin, the protection in females was only observed with higher doses of endotoxin, thus suggesting that the conditioning threshold may differ between males and females (Pitcher et al., 2005). Similarly, delayed pharmacological PreC with isoflurane protected male but not female rabbits (Wang et al., 2006). It is suggested that the apparent lack of protection with ischemic PreC in young female animals is due to estrogen-mediated better tolerance against IRI compared with males (Song et al., 2003).

In contrast, no sex difference in the cardioprotective effect of ischemic PreC was observed in Lewis rats of mixed age ranging between 10 and 20 weeks (Lieder et al., 2019). Also, in anesthetized Göttinger minipigs, there was no difference in IS, area of coronary MVO, and protection by ischemic PreC between young adult female, castrated male, and male pigs (Kleinbongard, Lieder, et al., 2022a; Kleinbongard, Lieder, et al., 2022b).

Similar findings have been reported with ischemic PostC. Ischemic PostC improved cardiac function and IS in both female and male rat hearts, but the protection differed depending on sex and the severity of the IRI (Crisostomo et al., 2006; Penna et al., 2009). Again, the increased effectiveness of ischemic PostC in males versus females is likely a result of overall reduced IRI (lower IS, less oxidative stress and apoptosis) in females versus males (Ciocci Pardo et al., 2018).

The protective effect of RIC may or may not be sex dependent. Whereas RIC of either 1 or 2 limbs in Lewis rats conferred similar protection in both male and female hearts subjected to I/R (Lieder et al., 2019), plasma isolated from male and female volunteers and perfused into

isolated rat hearts subjected to I/R protected the heart in a sex- and age-dependent manner (Heinen et al., 2018). Male but not female plasma collected after RIC protected the isolated rat heart against IRI compared with the non-preconditioned plasma (Heinen et al., 2018).

b. Sex and Cardioprotective Signaling. As observed with aging, differences in the activation of classic cardioprotective signaling pathways are observed between males and females (for review see Perrino et al., 2021). Besides the role of gonadal hormones, multiple cell survival pathways are regulated differently in males and females in a sex hormone-dependent or -independent manner. Increased phosphorylation of protein kinases B or C in female hearts subjected to IRI (Bae and Zhang, 2005) together with an increase in NO and the phosphorylation of aldehyde dehydrogenase and alpha-ketoglutarate dehydrogenase leading to a decrease in ROS (Lagranha et al., 2010; Casin and Kohr, 2020), may be involved in the sex differences in the cardioprotective efficacy of conditioning strategies. Similarly, increased phosphorylation of STAT3 and TNF receptor 2 in females versus males may affect the response to ischemic conditioning (Wang et al., 2007; Wang et al., 2008). Sex-specific downregulation of sirtuins, mitochondrial antioxidative signaling molecules, and modulation of the proinflammatory status in the older hearts are other mechanisms that may influence the outcome of the cardioprotective conditioning therapy in males versus females (Barcena de Arellano et al., 2019).

B. Comorbidities

1. Hypertension.

a. Hypertension and IRI. According to World Health Organization data, the global prevalence of systemic arterial hypertension was estimated to be approximately 30% in the adult population (Mills et al., 2016; Timmis et al., 2022) and ranks first among the leading causes for disability-adjusted life years (GBD 2019 Risk Factors Collaborators, 2020). Systemic arterial hypertension coexists with other major comorbidities discussed elsewhere in this paper. In the presence of any of these comorbidities, elevation of blood pressure contributes powerfully as an additive risk for the development of atherosclerosis and ischemic heart disease (Forouzanfar et al., 2017).

Hypertension promotes structural and biochemical changes in the myocardium. These include the development of left ventricular hypertrophy (LVH), alterations in coronary microvascular perfusion, and myocardial fibrosis. Although arguably imprecise as a diagnostic label, the term “hypertensive heart disease” is applied to describe the coexistence and consequence of coronary vascular changes, myocardial structural alterations, and enhanced risks of morbidity and mortality that occur in uncontrolled hypertension (Diamond and Phillips, 2005; Nwabuo and Vasan, 2020).

Cardiomyocyte hypertrophy, mediated by hemodynamic loading and neurohormonal influences, serves to maintain cardiac output and minimize ventricular wall stress in the presence of increased afterload. While muscle adaptation occurs, microvascular proliferation is mismatched, compounded by interstitial and perivascular fibrosis driven by oxidative stress and hormonal factors (Kong et al., 2014). Ultimately, unless therapeutic intervention stabilizes or reverses the hemodynamic and neurohormonal disturbances, the hypertensive heart is at risk of diastolic and/or systolic failure, re-entrant electrical disturbances, and ischemic changes. Indeed, even moderate hypertension is a determinant of congestive HF, arrhythmias, sudden death, ischemic heart disease, and acute coronary events including AMI. Critically, the presence of LVH is an independent predictor of morbidity and mortality, and LVH regression is a key goal of anti-hypertensive therapy (Bourdillon and Vasan, 2020).

The response of the hypertrophied myocardium to acute IRI has been the subject of extensive laboratory investigation. Previous literature (Ferdinandy et al., 2007; Pagliaro and Penna, 2017) suggests that hypertrophied myocardium displays greater sensitivity and reduced tolerance to IRI. Various mechanisms have been proposed, including reduced capillary perfusion, increased oxygen consumption, altered intracellular calcium handling, alterations in multiple metabolic pathways, downregulation of cardioprotective signaling pathways, and increased oxidative stress (for reviews see Ferdinandy et al., 2007; Suleiman et al., 2011; Pagliaro and Penna, 2017; Andreadou et al., 2021). There is persuasive evidence from various animal models of hypertension that coronary artery occlusion is associated with the development of more severe arrhythmic disturbances during IRI and that recovery of contractile function is depressed in reperfusion (stunning).

The issue of sensitivity to lethal or irreversible tissue injury (i.e., infarction) has been more contentious. In many experimental studies, standardized protocols to produce infarction reveal an inconsistent picture of IS in hearts with LVH. For example, some rat studies (Ebrahim et al., 2007a, 2007b; Wagner et al., 2013) report no increased IS in LVH, whereas others (Dai et al., 2009; Mølgaard et al., 2016; Yano et al., 2011) reveal moderate to large IS increases. This ambivalence in the experimental literature is not obviously explained by different hypertension models, hypertension duration, heart mass, IRI conditions, animal age, or methods of IS assessment, nor is there a clear view from experimental studies of an altered pattern of cell death in LVH (necrosis, apoptosis, necroptosis, pyroptosis; see Section II).

In clinical studies, the question of IS in relation to LVH has been difficult to address, due largely to the relative imprecision of traditional methods of LVH

detection (ECG and echocardiography) and IS and risk zone quantification, as well as inconsistencies in the definition of normal LV mass thresholds. However, there are some noteworthy studies that have used cardiac MRI in STEMI patients. While MRI presents challenges in terms of standardization of technique and data interpretation, recent studies support the view that LVH is associated with increased IS in human subjects.

Nepper-Christensen et al. (2017) investigated the relationship between LVH (concentric or eccentric hypertrophy of various causes) and IS in a subgroup of the DANAMI-3 study in patients with STEMI. Despite similar onset-to-reperfusion time and target vessel involvement, patients with LVH showed higher peak troponin concentrations compared with patients without LVH. Acute and final IS were larger in patients with LVH, and the proportion of patients with MVO was higher. During 48 months of follow-up, the combined endpoint of all-cause mortality and hospitalization for HF was higher in the LVH group (9% vs 4%, $P = 0.003$). Similarly, Stiermaier et al. (2018) studied patients with and without LVH in a substudy of the AIDA STEMI trial. They applied MRI to assess IS, LV mass, and other parameters. IS was larger in patients with LVH compared with those without LVH, although clinical outcome (all-cause mortality, reinfarction, or congestive HF) at 12 months was not different between the groups.

Cohort studies are consistent with the broad messages from epidemiologic studies. They point to LVH as a useful risk stratification variable in STEMI, although its potential prognostic value as a determinant of long-term outcome after STEMI remains to be further evaluated in larger trials. Such studies are undoubtedly warranted, given that patients with LVH are at greater risk of AMI and other ischemic events. Moreover, hypertension was found to be an independent factor for underprescription of guideline-directed medical therapy post-AMI in the PROMETHEUS registry, which could further worsen long-term outcome for a substantial proportion of hypertensive patients (Ge et al., 2019).

Considering the increased risk of hypertensive patients developing ischemic heart disease and the greater susceptibility to IRI when LVH is present, cardioprotection of hypertrophied myocardium presents an important scientific and clinical challenge. During the past 3 decades, many experimental studies have reported a number of different approaches with varying degrees of success. More recent studies used IS as a robust endpoint of cardioprotection and reveal potential mechanistic insights.

b. Hypertension and Cardioprotection. Following the earliest description of ischemic PreC in LVH (Speechly-Dick et al., 1994), many further studies

confirmed that ischemic or pharmacological PreC protocols may reduce IS in hypertensive animals with LVH (Ferdinandy et al., 2007). However, a number of factors may attenuate the effectiveness of ischemic PreC in LVH. While these factors are not clearly defined, cardioprotection in LVH may be highly model dependent, influenced by the nature of the preconditioning stimulus, modified by hypertension duration, animal sex and age, and the progression to cardiac decompensation. Ebrahim et al. (2007b) showed that ex vivo hearts from male normotensive rats and spontaneously hypertensive rat (SHR) were protected against infarction by 2×5 minute ischemic PreC cycles in 3- to 4-month-old and 7- to 8-month-old animals. However, this was not the case in hearts from 12- to 13-month-old animals, either normotensive or SHR. Although the addition of the angiotensin II converting enzyme (ACE) inhibitor captopril, which enhances tissue kinin concentration, partially restored ischemic PreC efficacy in aged normotensive hearts, it did not do so in aged SHR hearts. In contrast to these findings, Dai et al. (2009) using an in vivo infarct model showed that 3×3 minute ischemic PreC cycles effectively limited IS in 16-month-old female normotensive rats and SHR. Fantinelli et al. (2013) established in an ex vivo infarct model that the threshold for ischemic PreC efficacy is shifted in SHR hearts. A single 5-minute ischemic PreC cycle protected SHR hearts against 35-minute index ischemia but was ineffective against 50-minute index ischemia, whereas a 3×2 minute ischemic PreC protocol was fully effective. Clearly, there are discrepancies in the key findings between closely aligned studies, and these may be related to many factors, including animal sex-related differences in key molecular components of cardioprotective signaling (see Section IVb), infarct model, and ischemic PreC protocol. However, it seems likely that, while key cardioprotective pathways activated by ischemic PreC can be recruited in moderate hypertrophy, the threshold for activation of these mechanisms may require an ischemic PreC stimulus of greater intensity than in normotensive hearts, but this is dependent on duration of hypertension, experimental LVH models, and index ischemia conditions.

Other forms of ischemic conditioning in LVH have received scant attention. Translation of RIC to elective clinical settings, most notably cardiac surgery, has been contentious (see Section III and Heusch et al., 2015; Zaugg and Lucchinetti, 2015). In a small study of patients with cardiac hypertrophy undergoing aortic valve replacement surgery, there was no evidence of benefit (morbidity outcomes, creatine kinase MB release, or troponin T release) in patients receiving RIC (upper limb ischemia), even when propofol was excluded as a confounding factor (Song et al., 2017) (see Section Vb2 for a discussion of anesthetic effects). Also, no cardioprotection was seen in patients undergoing

transcatheter aortic valve implantation for aortic stenosis (Kahlert et al., 2017).

Early evaluation of ischemic PostC in hypertrophied myocardium (Fantinelli and Mosca, 2007) suggested that ischemic PostC (3×30 second cycles) was equally effective in promoting post-ischemic contractile function in normotensive and SHR hearts *ex vivo*. However, Penna et al. (2010) showed that while ischemic PostC (5×10 second cycles) limited IS in normotensive rat hearts, the same protocol was ineffective in SHR hearts *ex vivo*. Additionally, 4-week treatment with captopril, while inducing LVH regression, did not restore the ability to postcondition SHR hearts. Similarly, in an *in vivo* model of AMI, neither of 2 ischemic PostC protocols, 3×30 second or 6×10 second cycles, conferred protection in young SHR with established LVH, although both protocols were effective in normotensive rats (Wagner et al., 2013). Moreover, phosphorylation (inhibition) of glycogen synthase kinase (GSK)- 3β was observed 5 minutes after ischemic PostC in normotensive hearts but not in SHR hearts.

As noted for ischemic PreC, it is likely that duration of hypertrophy, animal sex, age, gradual onset of decompensation, and other factors may contribute to discrepant findings for ischemic PostC between laboratories. Hernández-Reséndiz et al. (2013) studied ischemic PostC in rats with either compensated hypertrophy after 7 days angiotensin II treatment or dilated cardiomyopathy/decompensated hypertrophy after 14 days angiotensin II treatment. Perhaps surprisingly, in both groups Ischemic PostC (5×30 second cycles) was effective in limiting IS in LVH, comparable to protection seen in normotensive control rats. However, intriguing alterations in phosphorylation of RISK components occurred between 7 days and 14 days, suggesting that hypertrophy-related downregulation of 1 kinase may be compensated by the parallel upregulation of another kinase pathway.

Babiker et al. (2019) undertook an extensive series of experiments using pacing-induced PostC (3×30 second cycles of alternate atrial/ventricular pacing) in various rat models and explored the interactions of sex, age, and disease states. Interestingly, age and sex were major determinants of PostC efficacy. While effective in young animals of either sex, pacing postconditioning was ineffective in senescent male hearts yet still effective in senescent female hearts. Moreover, the effect of pacing PostC in LVH was preserved in mature female, but not male, SHR. This work underscores the importance of key biologic variables, as well as experimental conditions, which may impede ready interpretation of findings from different laboratories.

c. Hypertension and Cardioprotective Signaling.

A similarly controversial and unsettled picture has emerged for a variety of pharmacological preconditioning approaches in LVH. However, many of these studies provide helpful insights into modifications of

cardioprotective signaling mechanisms in LVH that may be relevant to our interpretation of contradictory experimental findings and, perhaps more importantly, our ability to make translational advances for clinical cardioprotection in LVH. For example, 10-minute pretreatment with bradykinin (an upstream autacoid trigger of ischemic PreC acting through the G-protein coupled bradykinin B2 receptor) induced concentration-dependent IS reduction in normotensive hearts, but the protective effect in moderate LVH was markedly attenuated (Ebrahim et al., 2007a). González Arbelaez et al. (2016) showed that CsA when given as a short pretreatment prior to index ischemia in SHR hearts was as effective as a single 5-minute cycle of ischemic PreC in limiting IS. Moreover, the effects of ischemic PreC and CsA were PKC-dependent and additive. Yano et al. (2011) investigated the effects of the δ -opioid receptor agonist, (D-Ala², D-Leu⁵)-enkephalin, or erythropoietin pretreatment in 3- to 4-month-old normotensive and hypertensive rats (SHR stroke-prone strain). While each of the agonists induced modest IS limitation in normotensive hearts, no protection was observed in hypertrophied hearts, although ischemic PreC (2×5 minute) was highly protective in both groups. Further, they showed that in a different model of pressure-overload hypertrophy (thoracic aorta constriction for 4 weeks), erythropoietin preconditioning was ineffective.

Chen, Wu, et al. (2016) reported that in 9- to 10-month-old SHR with moderate LVH, pharmacological PreC with 30-minute pretreatment with isoflurane was ineffective in limiting IS. Of interest, the efficacy of isoflurane preconditioning in normotensive animals was associated with augmentation of manganese-dependent superoxide dismutase activity, a key mitochondrial antioxidant. Despite higher baseline manganese-dependent superoxide dismutase activity in SHR mitochondria, isoflurane preconditioning did not increase it further.

While delayed ischemic PreC (“second window” preconditioning occurring between 24–72 hours after the preconditioning stimulus) have not been studied in LVH, delayed pharmacological PreC 24 hours after transient (1 hour) exposure to isoflurane (2.1% v/v) was not observed in LVH induced by thoracic aorta constriction (Ma et al., 2014). The loss of delayed protection after isoflurane was associated with a failure of induction of inducible NOS and cyclooxygenase 2, which have been previously implicated in the mechanism of delayed ischemic PreC (Baxter and Ferdinandy, 2001).

As discussed in Section Vb2, pharmacological PostC in LVH has received relatively little attention. Halogenated anesthetic PostC has been shown to be cardioprotective in normal myocardium in many experimental studies, sharing similar mechanisms of protection as ischemic PostC (via the RISK or SAFE pathways and

mPTP inhibition) (for review see Lemoine et al., 2016). However, in LVH induced by suprarenal aortic constriction, the IS-limiting effects of sevoflurane PostC and ischemic PostC were abolished. This was associated with abrogation of phosphorylation of the major RISK pathway components (Ma et al., 2013). The noble gas helium is an interesting and safe conditioning candidate, capable in normal subjects of inducing cardioprotection when substituted for nitrogen in room air and administered by inhalation, either as a PreC protocol (classic and delayed) prior to index ischemia or as a PostC protocol during early reperfusion (Smit et al., 2015). Oei et al. (2012) showed that helium PostC was ineffective at limiting IS in 3-month-old male SHR with rather modest LVH. The combination of delayed helium PreC (brief exposure 24 hours before ischemia), classic helium PreC (exposure immediately before ischemia), and helium PostC (exposure in early reperfusion) induced modest protection in the SHR heart. The loss of protection in SHR myocardium was not obviously associated with changes in GSK-3 β or protein PKC ϵ phosphorylation potential.

In summary, the experimental literature reveals an ambivalent picture of the effectiveness of conditioning approaches in LVH. While some studies suggest preservation of PreC and PostC potential in hypertension models, others suggest abrogation of protection, likely associated with perturbation of key cardioprotective signaling pathways. It is reasonable to conclude that a large number of experimental and biologic variables contribute to the discrepancies in experimental findings, notably animal sex, age, and stage of hypertension/hypertrophy. Nevertheless, given the equivocal nature of the experimental literature and the limited number of clinical studies in LVH, conditioning protocols cannot be assumed to be robustly effective in hypertensive patients with LVH (or possibly in patients with other forms of cardiac remodeling where similar structural and molecular maladaptations occur). The clinical picture may be further complicated by the chronic application of antihypertensive agents, barely modeled in experimental studies, which could induce regression of hypertrophy and/or potentiate endogenous cardioprotective mechanisms, independently of conditioning protocols (see Section V). Unfortunately, resolution of the experimental controversies is unlikely to be achieved through further experimental studies. Rather, the imperative is that the design of cardioprotection trials will control rigorously for LV mass, among many other clinical variables, as a key determinant of any measured outcomes. Given the prevalence of hypertension and LVH in the population eligible for cardioprotective intervention, such a cohort could represent a significant number of higher risk subjects in any future trial.

2. Hyperlipidemia.

a. Hyperlipidemia and IRI. Among the different comorbidities that are related to cardiovascular disease, dyslipidemias are present in 40% of patients with ischemic heart disease (Mazo et al., 2019). Hyperlipidemia shows the strongest association with AMI with an odds ratio of 8.39 (95% CI: 8.21–8.58) (Andreadou et al., 2021). The majority of preclinical studies and some small-scale clinical studies have shown that hyperlipidemia per se leads to a significant exacerbation of myocardial IRI. Hyperlipidemia, independently from the development of atherosclerosis, exerts direct myocardial effects such as impaired cardiac performance and diminished adaptation to ischemic stress (for review see Mazo et al., 2019). More recent studies confirm that besides elevated low-density lipoprotein cholesterol (LDL-C), triglycerides and proprotein convertase subtilisin/kexin type 9 (PCSK9) may independently modulate cardiovascular risk. In particular, PCSK9 indirectly affects cardiomyocytes by monitoring the plasma concentration of LDL-C and oxidized low-density lipoprotein (for a review, see Andreadou, Tsoumani, et al., 2020). PCSK9 is also expressed in the myocardium (Wolf et al., 2020) and impacts on IS development and cardiac function as well as on autophagy (Ding et al., 2018). Moreover, hyperlipidemia induces microvascular dysfunction mainly through oxidative stress and inflammation, mechanisms that may also explain the increased susceptibility of the myocardium to I/R (for a review, see Andreadou, Iliodromitis, et al., 2017).

b. Hyperlipidemia and Cardioprotection. The first evidence that comorbidities may hamper the cardioprotective effect of preconditioning maneuvers was published in hypercholesterolemic rodent models in the mid-1990s. Since then, the majority of studies have confirmed these original observations including some small-scale clinical trials (Ferdinandy et al., 2014; Andreadou, Iliodromitis, et al., 2017). Although the loss of the IS-limiting effect of ischemic PreC has been shown in different models of diet-induced hyperlipidemia in rats (for a review, see Ferdinandy et al., 2014), other studies have shown that ischemic PreC (2 \times 5 minute) significantly decreased IS in vivo (Iliodromitis et al., 2006) or in isolated hearts of hypercholesterolemic rabbits (D'Annunzio et al., 2012) (for a review, see Mazo et al., 2019). The divergence in the results could be attributed to different experimental models involving different animal species and different types and duration of diets. Although various animal models of different types of hyperlipidemia exist, only a few of them have been employed and published for studying myocardial IRI and cardioprotection (Andreadou, Schulz, et al., 2020).

A loss of the IS-limiting effect of ischemic PostC has been confirmed by several studies in different animal species such as hypercholesterolemic rats (Kupai et al., 2009; Wu et al., 2014) and rabbits (Iliodromitis et al., 2010; Andreadou et al., 2012).

Preclinical studies have investigated the effects of hyperlipidemia on RIC. Ma et al. demonstrated that RIC failed to reduce myocardial necrosis and apoptosis in hypercholesterolemic rat hearts undergoing I/R (Ma et al., 2017). RIC attenuated IS, delayed cardiomyocyte apoptosis, and improved cardiac systolic function in nonhypercholesterolemic mice, but these beneficial effects were not evident in hypercholesterolemic mice (Hong et al., 2019). In low-density lipoprotein receptor knockout mice with high-fat diet induced atherosclerosis and subjected to I/R with or without anesthesia-induced preconditioning or RIC, IS was reduced (Petermichl et al., 2021); however, lipid levels were not measured.

In summary, further studies are required to investigate at which stage of hyperlipidemia, atherosclerosis, and endothelial dysfunction of the coronary arteries, RIC, and pharmacological conditioning strategies may exert cardioprotective effects.

c. *Hyperlipidemia and Cardioprotective Signaling.*

Explanations for the mechanisms by which hyperlipidemia may interfere with conditioning mechanisms include dysregulation of cardioprotective cascades such as lack of activation or inactivation of the RISK pathway, failure to modulate the K_{ATP} channels activity, impaired NO availability, and a redistribution of the intracellular localization of connexin 43 in cardiomyocytes (reviewed in Andreadou, Iliodromitis, et al., 2017). The dysregulation of the RISK pathway has been recently confirmed, since RIC failed to reduce myocardial necrosis and apoptosis due to a failure of an increase of Akt and GSK-3 β phosphorylation in hypercholesterolemic rat myocardium (Ma et al., 2017). Similarly, cardioprotection induced by RIC was lost in cholesterol-fed mice exposed to I/R by alteration of the phosphatase and tensin homolog/Akt signaling pathway that inhibits GSK-3 β (Hong et al., 2019). The aforementioned studies suggest that GSK-3 β inhibition may be a novel therapeutic strategy for hypercholesterolemic subjects. The activation of the RISK pathway in hypercholesterolemic rat myocardium was restored when lycopene, a type of carotenoid, was given in combination with ischemic PostC, and this led to reduced IS and decreased cardiomyocyte apoptosis by increasing the phosphorylation levels of Akt, ERK1/2, and GSK-3 β (Duan et al., 2019). However, in another study, post-translational activation of ERK, rather than PI3K/Akt, participated in the cardioprotective effect of ischemic PreC and atorvastatin in hyperlipidemia (Sun et al., 2017).

Apart from dysregulation of the RISK pathway, inhibition of myocardial matrix metalloproteinases (MMP), and especially MMP-2, is involved in ischemic PreC-induced cardioprotection. MMP-2 inhibition by ischemic PreC was absent in hyperlipidemia (Giricz et al., 2006), and moderate inhibition of MMP-2 by ilomastat still provided cardioprotection in hyperlipidemia (Bencsik

et al., 2018). Although novel inhibitors of MMP-2 dose-dependently reduced IS in an in vivo rat AMI model, their cardioprotective effects at the most effective doses in normal animals were abolished by hypercholesterolemia (Gömöri et al., 2020). Hypercholesterolemia has been shown to alter cardiac gene expression profile including of miRs as demonstrated by a downregulation of cardiac miR 25 in hypercholesterolemic rats (Varga et al., 2013). The attenuated cardioprotective effect of ischemic PreC in hypercholesterolemia correlated to a diminished miR 125b-1-3p induction, indicating that diet-induced hypercholesterolemia blunts the cardiac overexpression of miR 125b-1-3p triggered by ischemic PreC (Szabó et al., 2020). Therefore, modulation of cardiac miR 125b-1-3p could be a feasible target for cardioprotection also in hypercholesterolemia (Varga et al., 2018).

The impact of hypercholesterolemia on mitochondrial membrane fluidity, mitochondrial energetics, and related pathophysiological changes in myocardial injury and function has been investigated in a type 1 diabetes rat model fed with a high fat-cholesterol diet. The authors concluded that the cholesterol enriched diet induced adverse remodeling, which negatively affected mitochondrial function, relating to distortion of the mitochondrial membrane protein lipid interactions, which led to inhibition of endogenously initiated cardioprotective mechanisms (Ferko et al., 2018).

Additional mechanisms refer to the observation that hypercholesterolemia attenuates cardiac autophagy in parallel with the activation of the mechanistic target of rapamycin pathway and an activation of apoptosis, demonstrating a strong relationship between increased cardiac apoptosis and hypercholesterolemia (Giricz et al., 2017). Therefore, the imbalance between prosurvival and death pathways might play a role in the abolishment of cardioprotection in hypercholesterolemia (Giricz et al., 2017).

Some cardioprotective interventions have been studied for their potential to provide cardioprotection or to reestablish cardioprotection in the presence of hyperlipidemia. Zinc supplementation during hyperlipidemia reestablished ischemic PreC (4 \times 5 minute) in rats (Kansal et al., 2015). Pioglitazone restored the cardioprotective effect of ischemic PreC (4 \times 5 minute) in hyperlipidemic rat heart, an effect that may be via PI3K and mechanistic target of rapamycin (Mittal et al., 2016). Preconditioning by dopamine (Gupta et al., 2015) or PreC and PostC by nicorandil (Li et al., 2015) exerted cardioprotection in the presence of hyperlipidemia in rats.

In summary, beyond the known molecular mechanisms that blunt the cardioprotective signaling of conditioning interventions in hyperlipidemia, recent evidence suggests that GSK-3 β inhibition, modulation of cardiac miR 125b-1-3p, moderate MMP inhibition,

and cardiac autophagy may represent novel cardioprotective therapeutic interventions for hypercholesterolemic subjects. Whether molecular and metabolic rearrangements in hyperlipidemia may modify the response of cardioprotective maneuvers in the clinic remains to be established.

3. Diabetes.

a. Diabetes and Cardioprotection. According to World Health Organization data, the global prevalence of diabetes mellitus in 2014 was estimated to be 9% (<https://www.who.int/nmh/publications/ncd-status-report-2014/en/>), with a variation from $\leq 4\%$ (e.g., in the United Kingdom) to $\geq 10\%$ (e.g., in Germany) in 2019 (Timmis et al., 2022). High fasting blood glucose ranks third among the leading risk factors for disability-adjusted life years (years lived with severe illness) based on the global burden of disease data for 2019 (GBD 2019 Risk Factors Collaborators, 2020), and patients' mortality increase with the duration of type 2 diabetes depending on the level of glycated hemoglobin achieved (37% increase over 11 years with glycated hemoglobin exceeding 7%) (Joseph et al., 2022).

Protection by ischemic PreC is lost in diabetes when the heart has become insulin resistant, and ischemic PreC cannot further increase glucose uptake (Ji et al., 2013), thereby reinforcing the importance of glucose metabolism for efficient conditioning interventions (see Section II). Several but not all studies reported that the cardioprotective effect of ischemic PreC is reduced in animal models of type 2 diabetes. Ischemic PreC (3×2 minute) failed to protect rat hearts with diabetic cardiomyopathy from IRI probably due to deteriorated mitochondrial function (Ansari and Kurian, 2020a). Pharmacological PreC with inhaled sevoflurane, however, remained cardioprotective during diabetes in mice, via adenosine 5'-monophosphate activated protein kinase-independent activation of a prosurvival mitogen-activated protein kinase member (Xie et al., 2020). In contrast, isoflurane pharmacological PreC failed to induce cardioprotection in obese type 2 diabetic (db/db) mice, and this effect was associated mainly with abnormal regulation of eNOS and mitochondrial respiratory complex I (Ge et al., 2018). Pharmacological PreC with hydrogen sulfide attenuated myocardial injury in diabetic rat hearts via an alternative to the PI3K pathway, although hydrogen sulfide PreC could not attenuate I/R-induced oxidative stress (Ansari and Kurian, 2020b). Hydrogen sulfide PreC also reduced IS in isolated rat hearts with diabetes and with diabetic cardiomyopathy (Ansari and Kurian, 2019). Recent studies have investigated the influence of the duration of type 2 diabetes on the cardioprotective effects of ischemic PreC. The metabolic and endocrine disruption in type 2 diabetes was associated with ischemic intolerance and inhibition of ischemic PreC's cardioprotective effects (Russell et al., 2019). The

duration of diabetes may influence the response to cardioprotective maneuvers because early-onset type 2 diabetes is associated with an endogenous cardioprotection characterized by underlying mechanisms distinct from those involved in exogenously induced cardioprotection by conditioning modalities (Povlsen et al., 2013; Kristiansen et al., 2019). However, when male Zucker diabetic fatty rats in different stages of diabetes were subjected to IRI in the Langendorff model and randomized to ischemic PreC stimulus (2×5 minute) or control, ischemic PreC reduced IS in all groups irrespective of the presence of diabetes and its duration (Hjortbak et al., 2018). This cardioprotective effect was associated with an adaptation to myocardial glucose oxidation capacity (Hjortbak et al., 2018).

Hyperglycemia also blunts IS reduction by ischemic PostC (Przyklenk et al., 2011; Chen et al., 2016c) and RIC (Kiss et al., 2014; Baranyai et al., 2015; Tyagi et al., 2019). While alpha-lipoic acid PreC and ischemic PostC did not protect isolated hearts from diabetic rats, adding both interventions reduced IS (Mokhtari et al., 2022). Similarly to alpha-lipoic acid, hydrogen sulfide PostC reduced IS in isolated hearts taken from diabetic rats (Ansari et al., 2022); minocycline given at reperfusion protected isolated hearts from diabetic rats (Sobot et al., 2022).

More recent studies indicate that fluctuations in circulating glucose levels influence the response to cardioprotective maneuvers more in nondiabetic than in diabetic models (Saito et al., 2016; Pælestik et al., 2017; Kristiansen et al., 2019). The clinical implications of these findings remain to be clarified. While clinical studies of ischemic PostC in STEMI patients have yielded mixed results in terms of limiting IS, most studies applying RIC demonstrated such reduction as measured by nuclear imaging or MRI techniques or myocardial biomarker release (Heusch, 2020). Data relying on post hoc analyses indicate that RIC protocols used in clinical settings also yield cardioprotection in patients with type 2 diabetes undergoing PPCI (Sloth et al., 2015). In patients with diabetes undergoing CABG surgery, RIC also induced cardioprotection, but the use of sulfonylureas abrogated protection (Kottenberg et al., 2014). However, it remains to be investigated whether any variation in IS reduction relates to hyperglycemia. Regardless of perturbations in circulating glucose levels, experimental studies indicate that type 2 diabetes blunt the cardioprotective response to ischemic PostC and RIC stimuli by impairing activation of the cardioprotective RISK and SAFE pathways.

In summary, type 2 diabetes appears to abolish the cardioprotective efficacy of both ischemic PreC and PostC, whereas some but not all pharmacological conditioning interventions seem to reduce IS in diabetic animals. Whether the confounding effects of diabetes

on cardioprotection observed in the experimental settings translate into the clinical setting remains to be settled (Kleinbongard et al., 2020). The number of patients that have been enrolled in currently available clinical studies are low, and the methods used to assess IS vary, so further studies are required to define the efficacy of conditioning strategies in humans with diabetes (Reinstadler et al., 2017).

b. Diabetes and Cardioprotective Signaling.

Among the underlying mechanisms that may attenuate the effect of cardioprotective maneuvers in diabetic subjects are failure to phosphorylate ERK, PI3K, and Akt (Tsang et al., 2005; Whittington et al., 2013), the maintenance of hexokinase II at the mitochondria (Gurel et al., 2013) and the cytoprotective regulation of the mPTP (Itoh et al., 2012), along with dysfunction of sarcolemma and mitochondrial K_{ATP} channels (Kersten et al., 2001; del Valle et al., 2003), upregulation of mechanistic target of rapamycin (Baranyai et al., 2015), and a decrease in autophagy (Qian et al., 2009; Kobayashi et al., 2012). Many studies have demonstrated that the attenuated response to ischemic PreC may be overcome by an intensified stimulus when a critical level of Akt phosphorylation is achieved to confer protection (Tsang et al., 2005; Hausenloy et al., 2013; Hjortbak et al., 2018; Kristiansen et al., 2019).

Additionally, cardioprotective interventions may also become inefficient when examined in the prediabetic state, knowing that in the early stage of diabetes the heart is often already in a protective state (Zuurbier et al., 2014). This may have implications for clinical studies, where patients are frequently in a nondiagnosed prediabetic state. Impairment in O-linked β -N-acetylglucosamine signaling (Jensen et al., 2013) and release of cardioprotective humoral factors, which depends on intact neural function, may contribute to attenuating RIC-induced cardioprotection (Jensen et al., 2012). Diabetes may increase ROS production (Ansley and Wang, 2013; Su et al., 2013; Baranyai et al., 2015) and inhibit autophagy to attenuate RIC-induced cardioprotection (Baranyai et al., 2015). Diabetes-induced reduction in NO bioavailability may also contribute to decreasing remote RIC-induced cardioprotection (Kiss et al., 2014). Finally, diabetes may reduce the phosphorylation of adenosine 5'-monophosphate activated protein kinase α (Han et al., 2014), with a possible role for elevated adipocyte-released microvessels containing miR 130b-3p for adenosine 5'-monophosphate activated protein kinase downregulation (Gan et al., 2020), and increase the phosphorylation of mechanistic target of rapamycin to attenuate cardioprotection of remote postconditioning (Tyagi et al., 2019). A recent study in Ossabaw minipigs which are prone to develop a full metabolic syndrome, including insulin resistance with progression to type 2 diabetes, hyperlipidemia, obesity, and hypertension with the subsequent development of

coronary atherosclerosis and occasional spontaneous myocardial infarction, demonstrated loss of protection by ischemic PreC in these pigs even before they had developed the diseased phenotype; the loss of protection was associated with lack of activation of STAT3 and a primordial genetic difference in mitochondrial function and STAT signaling from other pig strains. Thus, lack of cardioprotection can even become manifest before a metabolic syndrome has developed (Kleinbongard et al., 2022).

In summary, hyperglycemia and diabetes mellitus appear to attenuate the cardioprotective efficacy of mechanical conditioning strategies in experimental animal and human ex vivo heart tissue studies. Underlying mechanisms involve interference with the cardioprotective signaling pathways. The confounding effects of hyperglycemia and diabetes mellitus on cardioprotection can be overcome by increasing the conditioning stimulus. Evidence for these phenomena is not yet available from clinical studies.

4. Interim Coronary Events, IRI, and Cardioprotection.

There are 2 principal pathways by which coronary events could interfere with cardioprotection. A coronary event could induce cardioprotection per se and then either be additive to a cardioprotective intervention or limit the potential for a further cardioprotective intervention. Alternatively, a coronary event could attenuate the effect of a cardioprotective intervention by interfering with its mechanisms. Indeed, there is evidence for both these types of interference. In animal experiments, coronary microembolization, which mimics a minor acute coronary syndrome after plaque rupture or erosion, shortly before a sustained myocardial I/R neither induced (Skyschally et al., 2004) nor interfered with ischemic PreC protection in reducing IS (Skyschally et al., 2005); however, the coronary microembolization per se slightly increased IS.

In patients, pre-infarction angina is a prototypic event that is protective per se in that 1 or several episodes of myocardial ischemia in the presence of epicardial coronary atherosclerosis are precipitated by sympathetic activation such as stress or exercise and then exert an ischemic PreC effect on the myocardium for a limited period of time (Heusch, 2001; Rezkalla and Kloner, 2004). Pre-infarction angina in patients decreases IS (Andreotti et al., 1996; Iglesias-Garriz et al., 2001; Kloner et al., 1998; Lønborg, Kelbæk, Vejlstrup, Bøtker, Kim, Holmvang, Jørgensen, Helqvist, Saunamäki, Thuesen, et al., 2012; Reiter et al., 2013) and no-reflow (Karila-Cohen et al., 1999; Colonna et al., 2002; Niccoli et al., 2014), and it improves patients' prognosis (Lorgis et al., 2012; Herrett et al., 2014; Schmidt et al., 2015). However, the protection by pre-infarction angina is attenuated by nonmodifiable risk factors, such as age (Ishihara et al., 2000); modifiable risk factors, such as smoking; and comorbidities, such as

dyslipidemia (Niccoli et al., 2014). Also, the time interval between the prodromal angina and the onset of AMI is decisive and was between 1 (Kloner et al., 1998; Ishihara et al., 2000; Iglesias-Garriz et al., 2001; Reiter et al., 2013) and 7 (Karila-Cohen et al., 1999; Colonna et al., 2002; Lønborg Kelbæk, Vejstrup, Bøtker, Kim, Holmvang, Jørgensen, Helqvist, Saunamäki, Thuesen, et al., 2012; Herrett et al., 2014) or 14 days (Schmidt et al., 2015) when resulting in a clinical benefit. Prodromal peripheral ischemia in the presence of peripheral artery disease can also elicit a RIC-form of cardioprotection in patients with AMI (Herrett et al., 2014; Schmidt et al., 2015), whereas the presence of a nonculprit stenosis with a significantly reduced fractional flow reserve as such (no evidence for ischemia in this territory was provided) was not associated with better salvage in a larger cohort of STEMI patients (Ekström et al., 2021). Mechanistically, in experiments in pigs, coronary microembolization preceding a sustained myocardial I/R up-regulated myocardial TNF α which then reduced IS (Skyschally et al., 2007). Patients with prodromal angina have reduced platelet reactivity (Scalone et al., 2013) and better thrombolysis (Andreotti et al., 1996), suggesting a role for platelet function and coagulation in the protective effects of pre-infarction angina. The clinical observations on the benefits of pre-infarction angina and of prodromal peripheral ischemia underpin the concept of (remote) ischemic PreC as a tool to induce cardioprotection.

Interventional reperfusion obviously involves manipulation of the culprit atherosclerotic lesion and also entails the risk of further release and embolization of atherothrombotic debris into the coronary microcirculation, which there acts to extend the infarct (Heusch and Gersh, 2017). Direct stenting can attenuate the microvascular injury as measured by TIMI flow and ECG resolution (Loubeyre et al., 2002), but thromboaspiration did not reduce IS or microvascular obstruction, as measured by MRI (Desch et al., 2016). Ischemic PreC is not feasible in AMI since the time of its occurrence is not known. Manipulation of the culprit lesion by an ischemic PostC protocol of repeated balloon occlusion/reperfusion entails a further risk for embolization of atherothrombotic debris. In a pig model of reperfused AMI, ischemic PostC reduced IS, but in combination with induced coronary microembolization the IS was larger than without microembolization, reflecting the interference of mechanically induced microembolization with cardioprotection (Skyschally et al., 2013).

In summary, a preceding coronary event characterized by ischemia may induce a degree of cardioprotection, and there are several clinical series to substantiate this. It has yet not been possible to exactly identify the molecular mechanisms of benefit and to harness these into a therapeutic strategy. In contrast, a coronary event

characterized by necrosis and microvascular obstruction appears to be universally detrimental.

5. Atrial Fibrillation.

a. Atrial Fibrillation and IRI. Atrial fibrillation (AF) and coronary artery disease frequently coincide, particularly with advanced age. Up to 47% of patients exhibiting any form of AF also present with coronary artery disease, while among patients with coronary artery disease, up to 5% manifest with AF (Lieder, Breithardt, et al., 2018). Many established and emerging risk factors for AF are also fundamental for the development of coronary artery disease and IRI (Kirchhof et al., 2012; Andrade et al., 2014) and the 2 disease entities appear to share a common mechanistic basis that goes both ways (Vermond et al., 2015; Lieder, Breithardt, et al., 2018). Accordingly, the risk factor clusters encompassed by the CHADS₂ and CHA₂DS₂-VASc scores for risk of ischemic stroke in nonvalvular AF also predict fatal ischemic heart disease in these patients (Kim et al., 2011). Sympathetic drive is seen as 1 culprit link between AF and IRI (Lieder, Breithardt, et al., 2018), and these 2 diseases are likely to interact at both cellular and molecular levels. A recent study dissecting the differentially expressed genes concurrently associated with coronary artery disease and AF identified 3 highly enriched genes coding for proteins that contribute to the development of both diseases: membrane metalloendopeptidase (neprilysin), transferrin receptor-1, and lysosome-associated membrane glycoprotein-1 (Zheng and He, 2021).

The existence of coronary artery disease and a prior MI are accepted drivers of AF risk. A recently published Mendelian randomization study (Kwok and Schooling, 2021) that aimed to assess the bidirectional causal relationship between AF and major cardiovascular diseases, revealed that genetically predicted ischemic heart disease is positively associated with AF. Two recent Chinese studies further support a causal link between prior IRI and subsequent AF, particularly when associated with concomitant renal dysfunction, higher resting heart rate, and increased left atrial size (Luo et al., 2020; Luo et al., 2021), with each incremental millimeter increase in atrial size raising the risk of AF by 7%. However, the retrospective study design and the lack of clarity of whether AF was truly a first-onset phenomenon or simply the first diagnosis of previously unrecognized AF should be considered when interpreting the outcome of these studies. Conceptually, events occurring during IRI provide putative mechanistic determinants for the onset and perpetuation of AF. Reduced blood flow through the circumflex coronary artery as a result of stenotic or thrombotic occlusion will also cause hypoperfusion and impaired metabolism of the atria. Such punctual alterations may alter impulse conduction and drive electrical and structural remodeling, a constellation that will promote AF and increase its complexity (Opacic et al., 2016; Opacic et al., 2016; Dudink et al., 2021; Van Wagoner,

2021). Chronic atrial ischemia/infarction creates substrates for both spontaneous calcium driven atrial ectopy and sustained reentry due to conduction abnormalities (Nishida et al., 2011). Increased atrial cardiomyocyte excitability along with heterogeneity in atrial conduction could create reentry that could be further amplified by increases in atrial stretch due to the higher atrial pressure secondary to ischemia or ventricular dysfunction and by fibrotic remodeling of the infarcted myocardium (Lieder, Breithardt, et al., 2018; Liang and Wang, 2021). Even subclinical atherosclerosis, defined on the basis of increased intima-media thickness or coronary calcium scores, is significantly associated with incident AF (Willeit and Kiechl, 2014; Kristensen et al., 2020), and the extent of coronary artery disease has been linked to the degree of complexity of induced AF (Dudink et al., 2021).

Conversely, AF may also be seen as prognostic indicator with an increased risk for coronary artery disease and MI (Liang and Wang, 2021), although interpretation of data relating the contribution of AF to coronary artery disease and MI is somewhat hampered by the definition of coronary artery disease. This does not always differentiate clearly between atherosclerotic vessel disease and actual MI. One of the first prospective studies to examine the risk of incident MI in patients with AF and no coronary artery disease at baseline [Reasons for Geographic and Racial Differences in Stroke (REGARD) cohort; Soliman et al., 2014] highlighted AF as an independent risk factor for incident MI, raising the risk by approximately 2-fold even after adjustment for confounders. The Atherosclerosis Risk in Communities study subsequently reported that after multivariate analysis AF diagnosis was associated with a higher (80%) risk of non-ST elevation myocardial infarction but not STEMI (Soliman et al., 2015). More recent systematic reviews and meta-analyses (He and Chu, 2017; Ruddox et al., 2017) further underscore AF as a driver of subsequent MI in patients, although the direct causal relationship is more pronounced in patients who are free of coronary artery disease at baseline. Mendelian randomization did not associate genetically predicted AF with subsequent ischemic heart disease (Kwok and Schooling, 2021), indicating that exposure to environmental risks, lifestyle, and concomitant diseases may be more relevant for the 2-way interaction between AF and cardiac ischemia than random genetic variants at conception. Paroxysmal AF episodes often elicit angina-like symptoms, with mildly elevated troponin, even though no significant coronary artery disease is detected on angiography. Experimental evidence from a porcine model of AF induced by rapid atrial tachypacing implies acute impairment of microcirculatory blood flow in the ventricle as the potential culprit event (Goette et al., 2009). Mechanistically, this can be attributed to oxidative stress induced via the angiotensin II/nicotinamide adenine dinucleotide phosphate oxidase

axis, leading to a reduction in coronary flow reserve with subsequent releases of troponin I (Goette et al., 2009). AF fulfills Virchow's Triad of hypercoagulability, hemodynamic perturbation, and endothelial dysfunction and is associated with a chronic state of low-grade inflammation that can be seen as both cause and consequence of AF (Boos et al., 2006; Kallergis et al., 2008). Thus, episodes of uncontrolled AF punctually increase myocardial oxygen consumption while lowering diastolic coronary perfusion (Bertero et al., 2021). Coronary thromboembolism, although a relatively rare cause of myocardial infarction, is, when it occurs, predominantly driven by AF-associated hypercoagulation (Shibata et al., 2015; Borschel and Schnabel, 2019). Concurrent atherosclerotic stenosis of the coronary arteries, driven by AF-associated increases in sympathetic nerve activity, inflammatory signaling, oxidative stress, and endothelial dysfunction, will further exhaust coronary dilator reserve. The additional constellation of burdens that accompany the progression of AF—calcium overload, energy depletion and increased sympathetic drive—promotes a vicious cycle of global cardiac impairment (Korantzopoulos et al., 2018; Borschel and Schnabel, 2019) that will clearly sensitize the myocardium for IRI.

At the cellular and molecular level, priming for IRI in the setting of AF may be seen to encompass, among others, (i) the manifestation of a calmodulin-dependent protein kinase II/NLRP3 inflammasome nexus that induces calcium-handling dysfunction and disseminated inflammatory states (Yao et al., 2018; Liu et al., 2019; Heijman et al., 2020; Nattel et al., 2020; Wang, Chen, et al., 2021), (ii) local injury through increased calpain-mediated proteolysis (Letavernier et al., 2012; Li and Brundel, 2020), (iii) release of mitochondrial deoxyribonucleic acid from cardiomyocytes to the surrounding tissue and the circulation (Wiersma et al., 2020), and (iv) increased local and systemic ROS production (Kim et al., 2005; Reilly et al., 2011).

b. Atrial Fibrillation and Cardioprotection. Data on how AF impacts on cardiac conditioning and cardioprotection are sparse. One RCT examined patients with drug-refractory paroxysmal AF undergoing radiofrequency catheter ablation who received RIC by intermittent arm ischemia prior to ablation. Ablation-stimulated rises in troponin I, high-sensitive-C-reactive protein and IL-6 were notably attenuated by RIC, while early recurrence rates were modestly lowered (Han et al., 2016). These findings were verified in the recent RIPPAF-RTC, which additionally noted lower serum levels of MMP 9 and von Willebrand factor, markers for atrial remodeling and endothelial damage, respectively, in the cohort receiving RIC prior to ablation for paroxysmal AF (Han et al., 2018). Patients undergoing cardiac surgery frequently develop post-surgery AF, the major form of secondary AF. The conceptual model of post-surgery AF encompasses the

presence of a vulnerable substrate provided by an underlying atrial cardiomyopathy created by genetics, risk factors, and comorbidities such as heart failure, diabetes, or hypertension (Goette et al., 2017). Perioperative triggers such as surgery-induced hypoxia, trauma, inflammation, and oxidative stress provide an impetus above a critical threshold that then precipitates post-surgery AF (Dobrev et al., 2019). The incidence of post-surgery AF in patients undergoing CABG is reportedly reduced from 50% to 14% if arm-pressure cuff RIC is applied prior to surgery (Slagsvold et al., 2014). Atrial appendage biopsies collected prior to and after cross-clamping showed that RIC preserved mitochondrial respiratory capacity and prevented the induction of miR 1, while miR 338-3p was upregulated compared with non-RIC samples (Kim et al., 2020). However, a more recent meta-analysis of RCT did not support the notion that RIC protects against post-surgery AF development (Kumar et al., 2019). Whether the cardioprotective window provided by RIC is sufficient to limit future IRI in patients with AF requires further systematic study.

c. Atrial Fibrillation and Cardioprotective Signaling. Little data are available regarding the impact of AF on cardioprotective mediators and pathways. Patients with AF have been noted to show dynamic alterations in critical determinants of NO production and metabolism, specifically arginine, homoarginine asymmetric dimethylarginine, and symmetric dimethylarginine, the levels of which were strictly dependent on acute heart rhythm at blood sampling, the degree of AF progression, and the success rate of sinus rhythm restoration (Büttner et al., 2020). Thus, NO-dependent pathways of cardioprotection will therefore be difficult to predict in patients with AF. Likewise, adenosine represents an important adaptive mediator protecting against myocardial IRI, yet in the context of AF, adenosine, and its receptors promote AF development and its perpetuation (Guieu et al., 2020; Soattin et al., 2020). Adenosine levels in atria and the circulation are elevated in AF, predominantly associated with peripheral blood monocytes (Godoy-Marín et al., 2021), but how this could influence ischemic injury and cardioprotection remains unclear.

Although there are accumulating evidence to support a bidirectional causal relationship between AF and IRI, many aspects remain unclear and require further clarification and verification. The impact of AF on (i) the risk that a myocardial ischemic event will occur in the first place, (ii) the extent of IRI and infarct progression, and (iii) the endogenous cardioprotective pathways that counteract IRI acutely and in the long term all need to be directly addressed in future work.

6. Kidney Failure/Uremia. Kidney failure and uremia are important comorbidities for ischemic heart disease (as reviewed earlier; Ferdinandy et al., 2014).

Patients with a chronic kidney disease (CKD) have an increased in-hospital mortality after AMI compared with patients with normal renal function (Gansevoort et al., 2013). Experimentally, hearts from animals with CKD (5/6 nephrectomy) (Guo et al., 2018) or uremia (Dikow et al., 2004) had an increased susceptibility to IRI, even when hypertension was treated pharmacologically (Dikow et al., 2004). The mechanisms behind the increase in irreversible injury following I/R in CKD may be related to mitochondrial uncoupling (Taylor et al., 2015) and/or increased endoplasmic reticulum stress (Guo et al., 2018). Uremic rats also exhibited progressive impairment of LV function following MI (Dikow et al., 2010).

Since sex is an independent nonmodifiable risk factor (see previous discussion), more recently the importance of CKD for myocardial IRI and cardioprotective interventions was compared in males and females. While the severity of CKD was similar in males and females following 5/6 nephrectomy, only CKD males developed more severe LV hypertrophy and increased fibrosis. In both sexes, however, ischemic PreC decreased IS in sham and CKD animals. Interestingly, ischemic PreC increased the phospho-STAT3/STAT3 ratio in sham-operated but not CKD animals in both sexes, while no differences in phospho-AKT/AKT and phospho-ERK/ERK ratios existed (Sárközy et al., 2021). Thus, the underlying signaling events might differ between sham (SAFE-pathway-dependent) and CKD animals (SAFE- and RISK-pathway independent). Surprisingly, the effect of kidney failure on RIC has not been studied yet.

In conclusion, although CKD increases myocardial IRI, ischemic PreC still reduces IS in both female and male hearts; protection in males occurs despite the presence of LV hypertrophy and fibrosis. The underlying signaling events might involve endoplasmic reticulum stress as well as mitochondrial function. Other cardioprotective intervention (PostC or RIC) have not yet been studied in CKD and/or uremic animals. There are no data from humans on CKD and cardioprotective intervention available yet. Therefore, further preclinical studies in long-term experimental uremia models, as well as clinical studies, will be necessary to show if mechanical or pharmacological conditioning can still protect the heart in uremic patients.

V. Effects of Pharmacological Treatment of Comorbidities on Cardioprotection

Previous sections have shown how risk factors and comorbidities can reduce the effectiveness of cardioprotective strategies. However, many patients with risk factors as well as comorbidities will already be receiving multiple medications to treat these comorbidities, even before they experience a MI. Therefore, an additional important consideration is the effect that these comedications

might have on IRI per se and/or cardioprotective interventions. These effects may include attenuation of IRI that may leave less more room to further cardioprotection; however, some medications may negatively affect cardiomyocyte survival in hearts exposed to I/R or attenuate cardioprotective signaling, a phenomenon referred to as “hidden cardiotoxicity” (Ferdinandy et al., 2019). Finally, patients who undergo PPCI or CABG for MI will be administered a number of different analgesics and anesthetics, and these “background drugs” can also potentially affect the response of the heart to I/R and the efficacy of cardioprotective strategies (He et al., 2020; Kleinbongard et al., 2020). The following sections will summarize the current knowledge on different medications for cardioprotective interventions.

A. Antihypertensive Drugs (Also Used in Part to Treat Heart Failure With Reduced Ejection Fraction)

Effective treatment of hypertension to reduce arterial pressure below guideline thresholds reduces cardiovascular risk, notably from stroke, ischemic events, sudden death, and congestive HF (Soliman et al., 2017; Whelton et al., 2018). Beyond MACE reduction, a number of antihypertensive agents induce regression of LVH. Although blood pressure reduction is a primary determinant of LVH regression, the extent of LV mass reduction by different drug classes may not correlate well with the level of blood pressure reduction, suggesting that hemodynamic effects alone may be insufficient to explain LVH regression. For example, with L-type calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers, LV mass reduction is generally superior to that seen with direct vasodilator agents (Soliman and Prineas, 2017). The question of whether LV mass regression per se, beyond blood pressure lowering, is associated with reduced susceptibility to cardiovascular risk including IRI is unresolved (Soliman et al., 2017).

There is conflicting and inconsistent evidence from experimental and clinical studies suggesting that some antihypertensives either exert direct cardioprotective effects by recruiting cardioprotective signaling pathways or enhance protective conditioning responses, or even attenuate these responses. This may be especially relevant, not only in the context of hypertension being a frequent comorbidity but also because of the use of β -adrenoceptor antagonists and ACE inhibitors as adjuncts in the early management of STEMI and for secondary prevention.

1. β -Adrenoceptor Antagonists. β -adrenoceptor antagonists form a heterogeneous group of drugs, widely applied as antihypertensive agents since the 1960s and thus, with diuretics, the oldest group of antihypertensive agents in current use. A systematic review has suggested inferiority of first-line hypertension management with β -blockers (mainly atenolol or propranolol) on mortality compared with renin-angiotensin system inhibitors (Wysong et al., 2017), although hemodynamic benefits

of β -blockers are, at least in part, associated with suppression of the renin-angiotensin cascade. They are also used in the management of patients with established coronary artery disease (e.g., as anti-anginal agents) (Bertero et al., 2021). Although under review, US and European guidelines have advocated the use of particular antagonists in early management of acute coronary syndrome in hemodynamically stable patients (Giannakopoulos and Noble, 2021).

There is a wealth of preclinical data on IS reduction by β -blockers in animal studies of I/R, although, as noted later, none have been successfully and reproducibly translated to humans. Studies in pigs have shown MRI-based evidence for cardioprotection by metoprolol (Ibanez et al., 2007; Ibanez et al., 2011; García-Ruiz et al., 2016; Heusch and Kleinbongard, 2020; Lobo-Gonzalez et al., 2020), and histology-based evidence for cardioprotection by carvedilol (Bril et al., 1992; Feuerstein and Ruffolo, 1995), atenolol, and the short-acting β -blocker landiolol (Park et al., 2011). Carvedilol also reduced the area of no-reflow in pigs following I/R, assessed by myocardial contrast echocardiography (Zhao et al., 2008). There are mixed data suggesting that β_3 adrenergic receptor stimulation may be cardioprotective. The β_3 adrenergic receptor agonist BRL37344 reduces IS in mice and pigs (Aragon et al., 2011; García-Prieto et al., 2014), but mirabegron, a β_3 -agonist approved for human use, was not cardioprotective in pigs (Rossello et al., 2018).

Clinical studies conducted in the 1980s provided evidence that β -receptor blockade could reduce IS when given within 4 to 7 hours of symptom onset (Peter et al., 1978; Yusuf et al., 1983; International Collaborative Study Group, 1984; MIAMI Trial Research Group 1985); however, this was in the “pre-reperfusion era” before the use even of thrombolysis. A 2020 patient-pooled meta-analysis of randomized clinical trials testing early intravenous β -blockers in patients undergoing PPCI for STEMI, which included 4 trials and 1150 patients, found no difference in the main outcome of 1-year death or biomarker-based IS (Hoedemaker et al., 2020). Although initial studies reported reduced IS with intravenous metoprolol administered prior to reperfusion (Ibanez et al., 2013; Pizarro et al., 2014; Podlesnikar et al., 2020), the larger EARLY BAMI study of 683 STEMI patients failed to report a reduction in myocardial IS (Garcia-Ruiz et al., 2016; Roolvink et al., 2016; Fabris et al., 2020).

A role of endogenous catecholamines in eliciting ischemic PreC has long been recognized in several species, with contributions from α_1 -adrenoceptor being initially characterized in rabbit and rat heart (Tsuchida et al., 1994; Mitchell et al., 1995). Transient α_1 -adrenoceptor stimulation induces pharmacological PreC (Bankwala et al., 1994), and transient β_1 - or β_2 -adrenoceptor stimulation also induces pharmacological PreC in rat isolated

heart (Salie et al., 2011), with recruitment of similar mechanisms to ischemic PreC. However, the effects of β -blockade on cardioprotective and conditioning responses have been shown in experimental studies to be complex and inconsistent with some but not all studies suggesting a loss of ischemic PreC and ischemic PostC protection, volatile anesthetic PreC, or PostC or RIC in the presence of β -adrenoceptor antagonists (Ferdinandy et al., 2014). There is no obvious or consistent explanation based on the diverse pharmacodynamic profiles of different β -blockers (e.g., lipophilicity, β_1 receptor selectivity/cardioselectivity, α receptor antagonism, duration of action, or intrinsic sympathomimetic activity). However, limited evidence from experimental studies suggests that pharmacological PreC or PostC by volatile anesthetic involve recruitment of β -adrenergic signaling (Lange et al., 2009). In more recent clinical studies of conditioning-induced cardioprotection, concomitant β -blockade may be a substantial confounding factor. Cho et al. (2019) examined the effects of limb RIC in healthy human subjects. Plasma dialysate obtained from RIC-treated subjects reduced IS in isolated rat hearts perfused with human RIC dialysate prior to coronary artery occlusion. However, this transfer of protection, likely by some humoral factor in the RIC plasma was abolished if the subjects received RIC in the presence of carvedilol, a β -adrenoreceptor antagonist with ROS-scavenging properties (Feuerstein and Ruffolo, 1995). In a retrospective analysis of a small single-center RCT assessing RIC in patients undergoing CABG surgery, prior use of β -adrenoreceptor antagonists was not found to correlate with troponin I release, a marker of intraoperative IRI (Kleinbongard et al., 2016).

2. ACE Inhibitors and Angiotensin II Receptor Blocker. Inhibitors of the renin-angiotensin system are first-line antihypertensive treatments but are also widely used in the management of established ischemic heart disease and chronic HF. While transient exposure to angiotensin II is known to induce pharmacological PreC via activation of angiotensin II type 1 receptors, and PKC (Liu et al., 1995), several experimental studies have shown ACE inhibitors and angiotensin II receptor blockers (sartans) to be protective in IRI models and to enhance the protective effects of endogenous cardioprotective interventions (ischemic PreC and Ischemic PostC) (Ferdinandy et al., 2014). The mechanisms underlying this beneficial effect are likely to include the potentiation of the production or reduced catabolism of autocrine/paracrine mediators such as bradykinin, prostacyclin, and NO. In pigs with IRI, candesartan pretreatment reduced IS through activation of the angiotensin II type 2 receptor, bradykinin, and prostaglandins, and icatibant or indomethacin abrogated this protection (Jaloway et al., 1998). Sgarra et al. (Sgarra et al., 2014) described differential effects of pharmacological PostC with losartan and irbesartan in a rat isolated heart model of IRI. Losartan given as intermittent pulses during early reperfusion reduced IS

whereas continuous losartan perfusion, or intermittent irbesartan treatment, did not. This protective effect was abolished by icatibant (Hoe140), a bradykinin B2 receptor antagonist.

In SHR rats treated with olmesartan for 4 weeks, blood pressure and LV mass were significantly reduced and IS was markedly attenuated after coronary artery occlusion in vivo (Lu, Bi, Chen, and Wang, 2015). In a subsequent study the same group showed that RIC (3 \times 5 minute hind limb ischemia during coronary artery occlusion) was absent in SHR but was restored in animals treated with olmesartan for 4 weeks prior to myocardial ischemia (Lu, Bi, and Chen, 2015).

In a model of rapid pacing-induced PostC in rat isolated heart, the IS limiting effect of PostC was abolished in the presence of irbesartan, an angiotensin II type 1 receptor antagonist, suggesting that activation of the angiotensin II type 1 receptor and signaling via the RISK pathway may be involved in this form of conditioning (Babiker et al., 2016). However, both captopril and chymostatin, which inhibit angiotensin II production by ACE-dependent and ACE-independent pathways, respectively, were protective when administered at reperfusion but did not enhance or abolish the effects of superimposed PostC. Thus, the role of locally produced angiotensin II in mediating IRI and conditioning protection are unclear from this study, and the likelihood is that other peptide mediators are modulated by these drugs.

Acute administration of azilsartan during reperfusion was observed to protect isolated rat hearts against IRI, similarly to ischemic PostC. Whereas the effects of ischemic PostC were abrogated in hypercholesterolemic hearts, azilsartan restored the protective effect, likely through upregulation of eNOS activity (Li et al., 2017).

Clinical studies are limited, but given the widespread guideline-directed use of ACE inhibitors and angiotensin II receptor blocker in the management and prevention of multiple cardiovascular diseases, the drugs are frequently present in patients included in clinical cardioprotection trials. The experimental evidence broadly suggests that these drugs can exert independent cardioprotective effects or augment ischemic PreC and PostC responses and could therefore modify responses in trials of conditioning interventions in a variety of settings. Kleinbongard et al. (Kleinbongard et al., 2016), in further analyzing data from their trial of RIC in CABG patients, concluded that neither ACE inhibitors nor angiotensin II receptor blockers were determinants of the major endpoint of protection (plasma troponin I concentration). However, it seems plausible that further analysis of the use of these pleiotropic drugs as potential confounders in larger trials of conditioning interventions, especially in STEMI patients, is warranted.

More recently, neprilysin inhibitors in particular are gaining recognition as a candidate approach for multitarget cardioprotection, given the spectrum of neprilysin substrates that elicit additive or even synergistic cardioprotective signals, including natriuretic peptides, bradykinin, and apelin, among others (Bellis et al., 2020).

3. L-Type Calcium Channel Blockers. L-type calcium channel blockers are a chemically diverse class of agents used in the management of hypertension, certain arrhythmias, and ischemic heart disease. In the context of cardioprotection, extensive experimental evidence points to the IS-limiting potential of all classes of calcium channel blocker when administered prior to the onset of myocardial ischemia, probably by slowing intracellular calcium overload during ischemia. However, there is no benefit if the drugs are administered immediately prior to or during reperfusion. Thus, there is little rationale for their use as adjuncts to reperfusion in STEMI. However, the question of their potential to interfere with conditioning protocols or to confound interpretation of clinical conditioning interventions remains open. There is a paucity of experimental evidence, but nisoldipine did not interfere with ischemic PreC in pig heart (Wallbridge et al., 1996). However, it is plausible that chronic treatment of patients with calcium channel blocker might confer a reduction in susceptibility to IRI, making it difficult to reveal additive benefits of conditioning interventions. Again, further analysis of data from large trials might be helpful in elucidating ideal protocols and patient populations for targeted cardioprotection.

4. Nitrates (and Nitrate Tolerance). Organic nitrates have been widely used for many decades as one of the main drugs for coronary artery disease treatment. Glyceryl trinitrate (nitroglycerine) is a potent vasodilator that has been used in clinical practice for over a century (Nunez et al., 2005); however, the main constraint of nitrate chronic therapy is the development of rapid tolerance, mainly vascular tolerance, which leads to the loss of clinical efficacy (Csont and Ferdinandy, 2005; Bibli et al., 2019).

Meta-analysis of many experimental studies suggests that IS was limited compared with controls when nitrates were administered through different routes, during ischemia, and/or reperfusion and in different animal species (reviewed in Bice et al., 2016). For example, application of a nitroglycerine patch (designed to deliver 5 mg/d) reduced myocardial IS when applied to mice prior to reperfusion (Yellon et al., 2018). Similarly, low-dose nitroglycerine reduced IS when administered during ischemia both in normal and in animals exhibiting endothelial dysfunction, mainly through the S-nitrosylation and inhibition of cyclophilin D, a component of the mPTP (Bibli et al., 2019). Very recently, administration of a nitrate-functionalized cardiac patch with site-specific delivery of

NO directly into the infarcted myocardium demonstrated in a rat model of MI reduced injury at an early stage and suppressed adverse cardiac remodeling, with these results further confirmed in a more clinically relevant porcine model (Zhu et al., 2021).

Clinical trials have provided no consistent evidence of IS limitation associated with nitrate treatment as an adjunct to reperfusion (Bice et al., 2016). However, nitroglycerine showed cardioprotective effects when administered 24 hours before coronary angioplasty compared with patients who received saline (Heusch, 2001; Leesar et al., 2001). This was supported by a study indicating that intracoronary but not intravenous infusion of nitrites reduced IS in STEMI patients with completely occluded arteries (Jones, Pellaton, et al., 2015) and by a recent study indicating that long-term nitrate treatment is cardioprotective, although the mechanism is not fully elucidated (Hauerslev et al., 2018). Additionally, the acute administration of nitrates does not seem to interfere with RIC in patients undergoing CABG surgery under isoflurane anesthesia (Kleinbongard et al., 2013). Interestingly, inhaled NO was able to reduce IS only in a subgroup of nitroglycerine naive STEMI patients (Janssens et al., 2018). This suggests that these patients might be in a nitroglycerine tolerant state that might impair cardioprotection (i.e., an indirect evidence for the hidden cardiotoxic effect of nitroglycerine) (Ferdinandy et al., 2019).

Thus, although tolerance represents a major limitation of the organic nitrates used in the clinic, acute administration and/or site-specific delivery of NO into the myocardium seems to be cardioprotective and may support the translational potential of the use of nitrates as adjunct to reperfusion therapy for IS limitation.

B. Analgesics and Anesthetics

1. Cyclooxygenase Inhibitors. Aspirin may interfere with protection by some forms of ischemic conditioning in experimental studies (Birnbaum et al., 2021). Indomethacin pretreatment abrogates protection from IRI by ACE inhibition and angiotensin II type 1 receptor blockade (Ehring et al., 1994; Jalowy et al., 1998). Thus, cyclooxygenase inhibition can, in principle, interfere with cardioprotection. The cardiac safety of cyclooxygenase 2 inhibitors is still an area of investigation and controversy despite the withdrawal from the market due to increased occurrence of MI (Dubreuil et al., 2018; Abdellatif et al., 2021). Indeed, cyclooxygenase 2 inhibition seems to be cardioprotective in preclinical models; however, its potential hidden cardiotoxic effect has been recently shown in preclinical models of I/R and MI that may hinder their development and indicates safety problems of some cyclooxygenase inhibitors (Brenner et al., 2020).

2. Morphine and Anesthetics. Certain anesthetics are inhibitors of mitochondrial activity (Hanley and

Loiselle, 1998; Chen et al., 2018), and some anesthetics are also strong ROS scavengers (Murphy et al., 1992). Cardiac I/R and protection from it are critically dependent on the presence and type of anesthesia (Zaugg et al., 2014). Anesthesia is likely one of the critical factors hampering successful translation in large clinical trials, considering the often large discrepancies between anesthetic regimen in preclinical models (often pentobarbital, ketamine-xylazine) versus the clinical arena (fentanyl, morphine, volatile anesthetics, benzodiazepines, propofol).

The abrogation by propofol of protection by RIC in patients undergoing CABG surgery was first reported by Kottenberg et al. (Kottenberg et al., 2012). The use of propofol may have interfered with cardioprotection by RIC in the larger phase III trials in CABG patients. Also, RIC was beneficial in rats administered pentobarbital and sevoflurane but not in rats receiving propofol (Behmenburg et al., 2018). Subsequently, the effect of anesthesia using sevoflurane or propofol was studied by perfusing plasma dialysates from patients undergoing CABG into isolated rat hearts with I/R. Here, RIC was only protective when no anesthesia was used, whereas both sevoflurane and propofol abolished RIC protection (Cho et al., 2019). Propofol abrogates not only ischemic conditioning but also various pharmacological types of conditioning (Zuurbier et al., 2014; Lucchinetti et al., 2018; Xiao et al., 2021). It thus seems that analgesic and anesthetic agents used in the clinic (opioids, volatile anesthetics, propofol) can interfere with cardioprotective interventions, mandating the incorporation of these agents in preclinical models to improve translation. Such models were recently developed in rats, 1 showing protection by a caspase inhibitor, but not RIC, on a background of heparin, an opioid agonist, and a platelet-inhibitor (He et al., 2020), and another 1 showing protection by a NAD precursor, but not fingolimod, melatonin, or empagliflozin, on a background of fentanyl, benzodiazepine, and a platelet inhibitor (Xiao et al., 2021).

The opioid receptor system has been shown to represent an important candidate for clinical cardioprotection since it beneficially impacts all major determinants of IRI outcome (infarction/apoptosis, arrhythmogenesis, inflammation). A small number of clinical trials have provided evidence of cardiac benefit from morphine or remifentanyl in CABG or coronary angioplasty patients (Headrick et al., 2015). Morphine (Stiermaier et al., 2021) and volatile anesthetics can reduce IS following PPCI or CABG procedures (Zaugg et al., 2014) and thus limit the potential for further protective interventions. However, diabetes mellitus mitigates cardioprotective effects of remifentanyl PreC in I/R rat heart in association with antiapoptotic pathways of survival (Kim et al., 2010), and hypertrophy (Weil et al., 2006) may influence opioid receptor responses.

C. Antiplatelets and Anticoagulants

1. Antiplatelets.

For use of aspirin see Section Vb1. Clopidogrel, the first P2Y₁₂ inhibitor developed and examined, is now slowly being replaced by the faster-acting prasugrel or ticagrelor. Experimental studies have established that P2Y₁₂ receptor blockers reduce IS during cardiac IRI (Yang, Liu, et al., 2013a, 2013b). Cardioprotective signaling by cangrelor and ticagrelor overlap with the signaling pathways used by conditioning strategies such as ischemic PostC (Yang, Liu, et al., 2013a) and RIC (Cohen and Downey, 2017; He et al., 2020; Hjortbak et al., 2021). However, ischemic PreC remained effective in the presence of the P2Y₁₂ antagonist ticagrelor (Hjortbak et al., 2021). Pharmacological conditioning has been found to remain effective in the presence of P2Y₁₂ agents for the sodium/hydrogen-exchanger inhibitor cariporide (Yang, Cui, et al., 2013), caspase inhibitors (Audia et al., 2018; He et al., 2020), and the NAD⁺ precursor nicotinamide riboside (Xiao et al., 2021) but not for NLRP3 inhibitors (Penna et al., 2020).

In patients undergoing PPCI for STEMI, platelet reactivity in response to dual antiplatelet therapy is a key predictor of the extent of both myocardial and microvascular damage (Massalha et al., 2022). Whether P2Y₁₂ inhibitors indeed possess direct cardioprotective actions against AMI has not been demonstrated in large prospective clinical trials. However, there is some circumstantial evidence from small clinical or large retrospective studies. A recent study showed reduced IS with ticagrelor versus clopidogrel as indirect evidence that P2Y₁₂ agents can reduce IS independent of their platelet inhibitory action (Kim et al., 2017), a finding supported by recent retrospective studies (Hjortbak et al., 2021; Sabbah et al., 2020).

2. Anticoagulants.

For decades now, the anticoagulant heparin has been part of the standard of perioperative care during PPCI and cardiac surgical procedures. Experimental studies have established that heparin reduces IS during cardiac IRI (Black et al., 1995; Huang et al., 2017; He et al., 2020). Since 2005, platelet receptor antagonists were added to this standard of care for acute MI patients treated by PCI, and both heparin and P2Y₁₂ antagonists possess cardioprotective actions (Roubille et al., 2012; Kleinbongard et al., 2021). Given their protective potential, both heparin and P2Y₁₂ antagonists should therefore become part of preclinical models testing for cardioprotection, where these agents have been mostly missing (Cohen and Downey, 2017; He et al., 2020).

While oral anticoagulation is obligatory for thromboembolism prophylaxis in AF and for prevention of deep vein thrombosis and pulmonary embolism, current guidelines also recommend oral anticoagulation with the coumarin-derivative warfarin to prevent LV thrombosis in the 3 to 6 months after AMI (Levine et al.,

2016; Ibanez et al., 2018; Valgimigli et al., 2018). Increasingly, the direct oral anticoagulants (DOAC) are used off-label in this context (Iqbal et al., 2020). Currently available DOAC include the thrombin inhibitor dabigatran; inhibitors of activated coagulation factor X (FXa) are represented by rivaroxaban, apixaban, edoxaban, and betrixaban. A recently published observational study in patients with AMI who received either warfarin or 1 of rivaroxaban, apixaban, or edoxaban (Jones et al., 2021) showed earlier and greater LV thrombus resolution with the FXa inhibitors compared with warfarin, together with lower bleeding rates but comparable systemic thromboembolic events.

The influence of the activated coagulation system on cardiovascular biology and pathophysiology goes beyond thrombosis. The cardioprotection afforded by antithrombin in murine IRI is independent of its hemostatic effect (Wang et al., 2013). Similarly, the beneficial impact of RIC applied pre- and post-off-pump CABG also appears to be unrelated to perioperative improvement in platelet reactivity to adenosine diphosphate or coagulability status (Kim et al., 2020), pointing to existence of coagulation-independent actions. Thrombin and FXa directly promote endothelial dysfunction, oxidative stress, immune cell activation, cell growth and differentiation, as well as inflammation (Fender et al., 2017; Fender et al., 2020; Ten Cate et al., 2021) through cellular protease-activated receptors and thus need to be considered in the context of IRI and cardioprotection.

Regarding the candidate role of DOAC as cardioprotective agents, no benefit could be noted with dabigatran in a rabbit model of no-reflow after myocardial IRI (Hale and Kloner, 2015). In rodent models of cardiac IRI, application of the FXa inhibitor 1 hour prior to occlusion decreased IS by 21% (Guillou et al., 2020). A PostC benefit of rivaroxaban has also been observed in mice subjected to permanent ligation. Here, the cardioprotective window appeared to persist for 24 hours after ischemia; delaying treatment until day 3 after IRI abolished the observed benefits (Bode et al., 2018). If commenced immediately after surgery or up to 24 hours thereafter, rivaroxaban applied in chow prevents intravascular thrombosis, improved cardiac systolic function, and decreased IS and inflammatory markers to variable extents. Within the infarct zone, levels of TNF α , tissue growth factor β , and both protease-activated receptors 1 and 2 are reportedly suppressed, while noninfarcted areas exhibit lower levels of atrial natriuretic peptide and NH₂-terminal pro-B-type natriuretic peptide, activated ERK, and cardiomyocyte hypertrophy (Bode et al., 2018; Nakanishi et al., 2020). Rivaroxaban also improved cardiac function and survival and suppressed transcription of IL-6 and collagens in a mouse model of secondary IRI prevention. Here, rivaroxaban treatment was commenced after IRI evoked by temporary

occlusion and continued over 14 days; a second ischemic event was triggered on day 7 with the application of tissue factor (Goto et al., 2016). Mechanistically, the cardioprotective effects afforded by rivaroxaban could be largely attributed to a blunted signaling through FXa/protease-activated receptors 2 (Bode et al., 2018), and given that apixaban could also blunt post-IRI fibrosis in mice (Shi et al., 2018), it is likely that cardioprotection is a class effect of the FXa blockers rather than a phenomenon specific for rivaroxaban.

A recent study in mice with cardiac IRI elegantly demonstrates the apparent superiority of FXa inhibition versus thrombin inhibition (Gadi et al., 2021). Inhibition of thrombin or FXa was commenced 1 week prior to IRI and reinitiated 2 hours post-surgery and continued for 24 hours or 28 days to examine acute and chronic effects. The dose was adjusted to achieve equivalent anticoagulation. IS was markedly and comparably reduced by both interventions. Remarkable differences between the 2 pharmacological strategies were noted in terms of IRI-triggered inflammation. RNA sequencing analysis showed that approximately 75% of genes aberrantly up- or downregulated by IRI were restored by FXa blockade, while thrombin inhibition reversed only one-third of IRI-regulated genes. The most prominently affected pathways included those related to the NLRP3 inflammasome and fibro-inflammatory stress, with thrombin inhibition tending to increase, while FXa blockade tending to decrease, expression of IL-1 β , IL-6, TNF α , and inflammasome components. The authors proposed that the difference might be related to the unique ability of thrombin to induce the activated protein C pathway, which has previously been shown to protect against myocardial IRI (Wildhagen et al., 2014).

Rivaroxaban exerts a direct cytoprotective action in cardiomyocytes subjected to hypoxia/reoxygenation (Guillou et al., 2020). Possible contributing mechanisms include the preservation of mitochondrial function and metabolism through regulation of key mitophagy proteins including mitochondrial dynamin-related protein 1 and Parkin (López-Farré et al., 2014; Zamorano-Leon et al., 2020). Classic cardioprotective cascades such as the RISK and SAFE pathways do not appear to be modulated by FXa blockers; instead, positive regulation of the Wntless and Int-1 β -induced PI3K/AKT-activated protein C system may contribute to the cardioprotective benefits of these agents, as was recently reported for edoxaban (Shan et al., 2019). Additional cardioprotection may arise through upregulation of vascular endothelial NOS (Pham et al., 2019) and suppression of angiotensin II-stimulated inflammatory and fibrotic responses in cardiac fibroblasts. Rivaroxaban attenuated angiotensin II-stimulated signaling through nuclear factor κ B and mitogen-activated protein kinase/activator protein 1 pathways in mouse cardiac fibroblasts lowered expression of

inflammatory proteins and concentration-dependently blunted fibroblast migration and proliferation (Hashikata et al., 2015). Potentially, FXa blockade could help to limit IRI-driven fibrosis and remodeling. In line with this concept, apixaban attenuated fibrosis in mouse hearts subjected to permanent ligation (Shi et al., 2018). The underlying mechanism was shown to depend on inhibition of thrombin formation and suppressed signaling through protease-activated receptors 1/Gq/PKC in cardiac fibroblasts. Data related to the effects of the thrombin inhibitor dabigatran are more limited. At the cellular level, dabigatran counterbalances thrombin-stimulated oxidative stress, inflammatory cytokine expression, and sirtuins-driven autophagy in cardiomyocytes in vitro (Wang, Xu, et al., 2021). More recently, an elegant in silico docking study revealed that dabigatran may be a novel candidate inhibitor of c-jun-N terminal kinase (Zulfiqar et al., 2020).

In patients, data on DOAC and myocardial IRI and protection from it are sparse. The main patient population studied are those with AF. However, in anticoagulated patients with AF, the incidence of AMI is relatively low (Connolly et al., 2009). Thus, one could speculate that oral anticoagulation use goes in hand with a generally low risk of AMI. Early studies examining DOAC added to standard antiplatelet therapy include the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial. Addition of rivaroxaban (2.5 and 5 mg) reported an approximately 9% reduction in subsequent MI in patients with AMI, albeit at the cost of increased major bleeding, but not fatal cerebral bleeds (Mega et al., 2012). The subsequent Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial (Eikelboom et al., 2017), which added very low-dose rivaroxaban to aspirin in patients with chronic coronary and peripheral artery disease, reported a favorable outcome in terms of thrombotic event reduction but no reduction of MI. Standard-dose rivaroxaban alone showed no benefit regarding primary cardiovascular outcomes but increased bleeding rates compared with aspirin alone. The subsequent A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure (COMMANDER-HF) trial corroborated that addition of low-dose rivaroxaban on top of standard antiplatelet therapy lowers the rate of ischemic stroke but does not impact beneficially on MACE endpoints including MI (Zannad et al., 2018). Similarly, the Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial, which examined apixaban added to standard antiplatelet therapy in patients with recent AMI and

at least 2 additional ischemic risk factors, was terminated early because of increased major bleeding with no evident reduction in cardiovascular events including MI (Alexander et al., 2011).

Thus, appropriate use of triple therapy remains challenging. FXa blockers on top of standard antiplatelet therapy consistently increase bleeding risk, with no counterbenefit in terms of reduced MI (Khan et al., 2018). At least this is the case if substantial coronary artery disease and prior AMI are already evident. It remains to be determined whether DOAC can modulate either the propensity for a first myocardial event to occur, by influencing the underlying coronary artery disease as indicated by some experimental studies (Hara et al., 2015; van Gorp et al., 2021) or, alternatively, whether DOAC impact on the extent of injury and expansion in the aftermath of the infarct (see previous discussion). Thrombin and FXa are also linked to processes pertaining to post-IRI inflammation and remodeling (Raivio et al., 2009; Fender et al., 2019). The thrombin burst that occurs in the context of IRI despite heparinization (Raivio et al., 2006; Raivio et al., 2009) may therefore contribute adversely and in a long-lasting manner to IRI and its sequelae.

D. Antidiabetic Therapy

The burden of myocardial IRI may be higher in diabetic patients (see Section IVe); therefore, pharmacological therapy to protect the diabetic heart is of significant clinical importance. Experimental and clinical data suggest that antidiabetic therapy may either confer cardioprotection or interfere with cardioprotection elicited by conditioning maneuvers.

1. *Sulfonylureas.* Preclinical and clinical studies have shown that some sulfonylureas inhibit myocardial protection by conditioning strategies since these drugs have high affinity to myocardial SUR2A/Kir6.2 and smooth muscle SUR2B/Kir6.2 receptors and inhibit the activation of K_{ATP} channels (Gribble and Ashcroft, 1999). The cardiovascular effect of sulfonylureas in humans is inhibition of the cardioprotective effects of RIC (Loukogeorgakis et al., 2007; Kottenberg et al., 2014). At present, there is no evidence that these effects have clinical consequences. Cross-reactivity between pancreatic and cardiac K_{ATP} channels varies with the individual sulfonylureas, and in general the later generation sulphonylureas are more specific for the pancreas and therefore bind less to the cardiac K_{ATP} channels (Gribble and Ashcroft, 1999). The interaction of glimepiride or gliclazide with SUR2 is less than that of glibenclamide, and therefore they do not seem to blunt the cardioprotective effects of ischemic PreC, diazoxide, and nicorandil in isolated rat hearts with I/R (Mocanu et al., 2001; Maddock et al., 2004).

2. *Metformin.* Pre- and/or post-treatment with metformin protects the heart against IRI and reduces myocardial IS (reviewed in Ye et al., 2011). Metformin PostC reduced IS, attenuated apoptosis, and inhibited

myocardial fibrosis, which was largely dependent on the suppression of NLRP3 inflammasome activation in rat hearts and cardiomyocytes (Zhang et al., 2020). Although meta-analyses have supported the cardiovascular safety of metformin in patients with coronary artery disease and chronic HF independent of its glucose-lowering effects (Varjabedian et al., 2018), no acute protection by metformin during CABG was observed (El Messaoudi et al., 2015), questioning the translatability of metformin for protection against acute I/R settings in the clinical situation. Indeed, in contrast to rodent hearts, PostC with high-dose metformin when administered before reperfusion did not reduce myocardial IS or improve LV function in swine (Techiryan et al., 2018), highlighting the importance of rigorously testing therapies in large animal models to facilitate clinical translation of novel cardioprotective therapies.

3. Thiazolidinediones. The effect of thiazolidinediones on IRI is controversial (Riess et al., 2020). Pre-clinical studies in small animals have shown that these drugs administered either as PreC or PostC agents protect against IRI and limit myocardial IS. Pioglitazone in nondiabetic and diabetic rats reduced IS (Khodeer et al., 2016) and did so, too, in isolated rat hearts when administered prior to I/R (Wynne et al., 2005). Rosiglitazone, however, was associated with enhanced cardiac injury in a similar model (Riess et al., 2020). Rosiglitazone is associated with increased adverse cardiovascular events in diabetic patients (Lincoff et al., 2007).

4. Glucagon-Like Peptide-1 Receptor Agonists. Glucagon-like peptide 1 (GLP-1) receptor agonists exert diverse actions on distinct target tissues, which lead to reduction of blood glucose level and body weight, and they are approved drugs for consideration as monotherapy or in combination with other oral antihyperglycemics (Peng et al., 2016). GLP-1 receptor agonists administered either as PreC or PostC agents limit myocardial IS in small and large animal models (Bose et al., 2005; Sonne et al., 2008; Timmers et al., 2009). A recent meta-analysis indicated that GLP-1 receptor agonists reduced the incidence of MACE and MI in type 2 diabetes patients and attenuated cardiovascular mortality (Sattar et al., 2021 #3585). In rats with I/R, GLP-1 functions as a humoral factor of RIC, involving activation of vagal nerves and M3-muscarinic receptors (Basalay et al., 2016). In the clinical setting, an intravenous infusion of exenatide initiated prior to PPCI reduced myocardial IS in STEMI patients, especially in those patients presenting with short ischemic times from symptom onset (<132 minutes) (Lønborg, Kelbæk, Vejlsstrup, Bøtker, Kim, Holmvang, Jørgensen, Helqvist, Saunamäki, Terkelsen, et al., 2012; Lønborg, Vejlsstrup, et al., 2012; Woo et al., 2013). Another GLP-1 analog, liraglutide, when administered prior to PPCI and continued for 7 days, improved LV systolic function (Chen

et al., 2015). Exenatide activated cardioprotective pathways different from those of RIC and possessed additive effects with RIC on IS reduction in a pig model of I/R (Alburquerque-Béjar et al., 2015). However, in a 2 × 2 factorial follow-up study, neither RIC nor exenatide, nor its combination, reduced IS in STEMI patients when administered as an adjunct to PPCI (García Del Blanco et al., 2021), indicating that, although GLP-1 agonists were promising in preclinical models of MI, they failed in RCTs in humans.

5. Dipeptidyl Peptidase-IV Inhibitors. GLP-1 is enzymatically cleaved and inactivated by dipeptidyl peptidase IV (DPP-IV), leading to the development of DPP-IV inhibitors as potential therapeutics. In rodents and pigs, DPP-IV inhibitors (especially sitagliptin and vildagliptin) limited IS when administered either before or after ischemia. Vildagliptin restored the cardioprotective effects of ischemic PostC on diabetic hearts but did not reduce IS per se (Bayrami et al., 2018). A prospective clinical study assessed the effect of repaglinide and vildagliptin on ischemic PreC in patients with type 2 diabetes and coronary artery disease. Although repaglinide eliminated ischemic PreC, probably due to its effect on the K_{ATP} channel, vildagliptin did not cause any impairment of ischemic PreC, suggesting a good alternative treatment in these patients (Rahmi et al., 2013). Clinical trials have shown that hospitalization for HF was increased in saxagliptin-treated patients (Scirica et al., 2013), whereas major adverse cardiovascular events were not increased with alogliptin and sitagliptin as compared with placebo (White et al., 2013; Green et al., 2015). A recent Cochrane analysis did not show any beneficial effect of DPP-IV inhibitors on MACE, MI, or cardiovascular mortality (Kanie et al., 2021). In summary, further preclinical studies especially in large animals with diabetes and clinical trials will be warranted to confirm the myocardial protection afforded by DPP-IV inhibitors.

6. Sodium Glucose Cotransporter 2 Inhibitors. Sodium glucose cotransporter 2 (SGLT2) inhibitors are the newest class of antidiabetic drugs. They markedly reduce MACE in large clinical trials in HF patients (Andreadou, Bell, et al., 2020). SGLT2 inhibitors exert cardioprotective effects in animal models of AMI through reduction of IS (Andreadou, Efentakis, et al., 2017; Tanajak et al., 2018; Lim et al., 2019; Sayour et al., 2019; Uthman et al., 2019; Lahnwong et al., 2020; Nikolaou et al., 2021; Seefeldt et al., 2021) and a subsequent attenuation of HF development (Habibi et al., 2017; Yurista et al., 2019; Connelly et al., 2020). Multiple, parallel protective mechanisms of SGLT2 inhibitors have been proposed, such as the attenuation of cardiac and endothelial inflammation or an inhibition of oxidative stress improving cardiac structure and function (Lee et al., 2017; Ye et al., 2017; Andreadou,

Bell, et al., 2020). The effect of SGLT2 inhibitors on conditioning mechanisms has not yet been evaluated. Clinical trials examining a potential SGLT2 inhibitory effect on cardiac IRI during cardiac surgery or PPCI procedures are currently missing.

E. Statins and Antihyperlipidemic Medications

Statins decrease cardiovascular morbidity and mortality, since apart from their effect on cholesterol levels, they also have pleiotropic effects, which may provide additional benefits (Andreadou, Iliodromitis, et al., 2017; Mendieta et al., 2019). Hyperlipidemia is strongly correlated with increased oxidative stress and interferes with the conditioning cardioprotective mechanisms. Therefore, statins that modulate NO bioavailability and possess antioxidant properties may be beneficial in the hyperlipidemic myocardium (Andreadou et al., 2021). Recently, the pharmacological inhibition of PCSK9 has led to unquestionable benefits in terms of lowering cardiovascular risks, since low LDL-C levels are directly correlated with reduced risk of atherosclerotic cardiovascular disease (Andreadou, Tsoumani, et al., 2020).

Statins protect the heart against I/R but may interfere with the IS-limiting effect of conditioning strategies and, as such, display hidden cardiotoxic effects (Ferdinandy et al., 2014; Brenner et al., 2020). The combined effect of rosuvastatin and ischemic PreC or PostC synergistically protected the in vivo rat heart from IRI (Kelle et al., 2015). Sevoflurane postconditioning that was lost in the diabetic state was rescued by simvastatin through increasing NO levels (Grievink et al., 2019). Intravenous atorvastatin during MI limited cardiac damage, improved cardiac function, and alleviated remodeling to a larger extent than oral administration in a hypercholesterolemic pig model (Mendieta et al., 2020). To the best of our knowledge, the effect of statin treatment on RIC has not been tested yet in preclinical models. Very few studies so far have investigated the role of PCSK9 on myocardial IS in experimental animal models. The PCSK9 inhibitor, Pep2-8 trifluoroacetate, when administered 15 minutes before the onset of ischemia significantly reduced IS and improved LV function mainly due to attenuation of cardiac mitochondrial dysfunction and fission and decrease of the apoptotic process in the ischemic myocardium of rats (Palee et al., 2019). The effect of PCSK9 inhibitors on conditioning strategies has not been evaluated yet.

Statin pretreatment before elective PCI attenuates myocardial injury, as assessed by biomarker release (Herrmann et al., 2002; Patti et al., 2006). Acute statin loading in patients with an acute coronary syndrome before PPCI improves their outcome (Patti et al., 2007). First-time atorvastatin administration in 118 STEMI patients before PPCI prevented the occurrence of post-operative no-reflow and reduced the incidence of MACE (Li et al., 2018). The effect of long-term statin therapy

on IS, myocardial salvage index, and microvascular obstruction in consecutive patients with STEMI who underwent PPCI demonstrated that long-term statin therapy was associated with smaller IS and higher myocardial salvage index (Marenzi et al., 2015). Meta-analyses showed an increased effect of RIC in statin users (Sloth et al., 2015), whereas in a retrospective analysis of a randomized, double-blind trial of patients undergoing elective CABG with/without RIC prior to ischemic cardioplegic arrest, statins had no significant impact on RIC-induced cardioprotection (Kleinbongard et al., 2016). Although limited clinical data exist, there is evidence that PCSK9 inhibition is associated with a reduced incidence of MI in patients with increased cardiovascular risk (Andreadou, Tsoumani, et al., 2020). PCSK9 inhibitors have different effects on type and size of myocardial infarcts, since evolocumab had no effect on type 2 events (Wiviott et al., 2020) whereas alirocumab when added to intensive statin therapy attenuated the risk of type 2 MI events (White et al., 2019). A recent meta-analysis of 67 RCTs indicated that PCSK9 inhibitors plus statin treatment significantly reduced the risk of nonfatal MI (Chaiyasothi et al., 2019). Whether PCSK9 inhibitors interfere with conditioning strategies has not been evaluated yet.

F. Antiarrhythmic Drugs

A diverse range of drugs are used in the management of cardiac rhythm disturbances that occur either as a consequence of chronic cardiovascular disease (e.g., hypertensive heart disease, ischemic cardiomyopathy, or HF of any origin) or that present in acute IR settings such as AMI. It is important to consider possible effects of these agents in the context of cardioprotection, specifically IS limitation, since several may have inherent cardioprotective properties or can modify endogenous cardioprotective mechanisms recruited through conditioning interventions. In either case, the use of antiarrhythmic drugs may be a confounding factor in the design and interpretation of clinical cardioprotection trials.

Some agents used for their antiarrhythmic properties may be inherently cardioprotective and limit IS in IRI models. For example, intravenous adenosine or the L-type calcium channel blocker verapamil are used acutely in paroxysmal supraventricular tachycardia. Given the transient nature of paroxysmal supraventricular tachycardia, acute use of adenosine or verapamil is unlikely to present an issue in relation to IRI and cardioprotection. However, recurrent of paroxysmal supraventricular tachycardia and other arrhythmias may require chronic preventative treatment with heart rate-limiting calcium channel blocker (verapamil or diltiazem), which, as described earlier, show cardioprotective effects when given prior to the onset of myocardial ischemia.

Although its efficacy is controversial, the sodium channel blocker lidocaine has been used in the management of malignant ventricular arrhythmias in AMI. Some experimental studies suggest that lidocaine blunts or abrogates conditioning responses. For example, in the rat isolated heart, ischemic PreC (2×5 minute) in the presence of lidocaine was blunted but only at concentrations that could be regarded as beyond the normal therapeutic range (Barthel et al., 2004). It is possible that this effect is related to inhibition of K_{ATP} channels with higher concentrations of the drug (Olschewski et al., 1996). Similarly, in the rat isolated heart, anesthetic PostC (sevoflurane 1.5 MAC for 15 minutes at reperfusion) was abrogated by coadministration with lidocaine at high but not at low concentration (Yan et al., 2008).

Amiodarone is used for a variety of ventricular and supraventricular arrhythmias and has a complex mode of action involving multiple ion channel targets and antiadrenergic activity (Mujović et al., 2020). Amiodarone was shown to improve functional recovery during reperfusion of rat heart subjected to low-flow ischemia (Roche-taing et al., 2001). In a rat isolated working heart preparation, subjected to low-flow ischemia, amiodarone treatment during low-flow ischemia was protective, with IS limitation and reduced arrhythmia severity. However, the protective effects of ischemic PreC (3×5 minute global ischemia) against IS were not enhanced in the presence of amiodarone, and the antiarrhythmic action seen with ischemic PreC and amiodarone individually was lost (Koo et al., 2006). Dronedarone is a structural analog of amiodarone, used primarily for ventricular rate control in paroxysmal or persistent atrial fibrillation and sharing a similarly complex multiple-target mode of action. Dronedarone exerts direct cardioprotective effects. In anesthetized pigs subjected to low-flow ischemia, dronedarone infusion during early ischemia markedly limited IS, although a specific mechanism explaining this powerful effect has not been determined (Skyschally and Heusch, 2011). Whether dronedarone augments or abrogates cardioprotection induced by conditioning protocols is unknown.

Although not a first-line antiarrhythmic drug, digoxin may be used in the management of atrial fibrillation and atrial flutter, particularly when congestive HF is present. Several experimental reports suggest that sodium/potassium-ATPase inhibition exerts effects in IRI that impact on cardioprotection. Nawada et al. (Nawada et al., 1997) observed that digoxin blunted the IS-limiting effect of ischemic PreC in rabbit hearts. They proposed that ischemic PreC preserved sodium/potassium-ATPase activity in the early index ischemic period. Since that early report, further studies suggest that low-dose or transient doses of cardiac glycosides (ouabain, digoxin) can pharmacologically PreC or PostC the heart (Pierre et al., 2007; Belliard et al., 2016; Duan et al., 2018; Lauridsen et al., 2018).

Finally, other currently used antiarrhythmic drugs encountered in the management of AMI include flecainide, propafenone, and disopyramide. Whether they exert cardioprotective effects beyond their known antiarrhythmic effects in IRI has not been determined.

VI. Conclusions and Future Perspectives

The discovery of the remarkable cardioprotective effect of innate adaptive responses elicited by different conditioning strategies has fueled intensive research in the past 3 decades to find key cellular mechanisms, drug targets, and novel drug candidates for pharmacological cardioprotection as well as clinically applicable protocols for mechanical cardioprotection elicited by medical devices.

Most of the clinical trials with cardioprotective drugs or medical devices have been unsuccessful so far. One of the reasons might be that validation of drug targets and in vivo preclinical studies aiming to assess cardioprotective efficacy of drug candidates and performance of medical devices as well as their safety have been performed in juvenile, healthy animals subjected to IRI. Here we have summarized some data suggesting that validation of drug targets, assessment of in vivo efficacy of drugs, and performance of medical devices in comorbid animal models would be essential for successful clinical translation. Furthermore, we highlight observations that routine medications for cardiovascular and other diseases may exert undesirable effects on the ischemic heart and cardioprotective signaling mechanisms that should be also taken into account when developing cardioprotective therapies.

The body of evidence we have reviewed here underscores the critical importance of preclinical models and study designs that address cardioprotection specifically in relation to complicating disease states and risk factors. This more sophisticated approach is now an urgent necessity in experimental cardioprotection research to maximize the likelihood of identifying translatable effective approaches to therapeutic protection of the aged or diseased ischemic heart (Lecour et al., 2021).

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Participated in research design: Ferdinandy, Heusch, Hausenloy, Schulz.

Wrote or contributed to the writing of the manuscript: Ferdinandy, Andreadou, Baxter, Bøtker, Davidson, Dobrev, Gersh, Heusch, Lecour, Ruiz-Meana, Zuurbier, Hausenloy, Schulz.

References

Abbas N, Perbellini F, and Thum T (2020) Non-coding RNAs: emerging players in cardiomyocyte proliferation and cardiac regeneration. *Basic Res Cardiol* 115:52.

- Abdellatif KRA, Abdellal EKA, Elshemy HAH, Philoppes JN, Hassanein EHM, and Kahk NM (2021) Optimization of pyrazole-based compounds with 1,2,4-triazole-3-thiol moiety as selective COX-2 inhibitors cardioprotective drug candidates: design, synthesis, cyclooxygenase inhibition, anti-inflammatory, ulcerogenicity, cardiovascular evaluation, and molecular modeling studies. *Bioorg Chem* **114**:105122.
- Alavian KN, Beutner G, Lazrove E, Sacchetti S, Park HA, Licznerski P, Li H, Nabili P, Hockensmith K, Graham M et al. (2014) An uncoupling channel within the c-subunit ring of the F1FO ATP synthase is the mitochondrial permeability transition pore. *Proc Natl Acad Sci USA* **111**:10580–10585.
- Albuquerque-Béjar JJ, Barba I, Inserte J, Miró-Casas E, Ruiz-Meana M, Poncelas M, Vilardosa U, Valls-Lacalle L, Rodríguez-Sinovas A, and García-Dorado D (2015) Combination therapy with remote ischaemic conditioning and insulin or exenatide enhances infarct size limitation in pigs. *Cardiovasc Res* **107**:246–254.
- Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M et al.; APPRAISE-2 Investigators (2011) Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* **365**:699–708.
- Algoet M, Janssens S, Himmelreich U, Gsell W, Pusovnik M, Van den Eynde J, and Oosterlinck W (2022) Myocardial ischemia-reperfusion injury and the influence of inflammation. *Trends Cardiovasc Med*, in press.
- Anderson KA, Green MF, Huynh FK, Wagner GR, and Hirschey MD (2014) SnapShot: mammalian sirtuins. *Cell* **159**:956–956.e1.
- Andrade J, Khairy P, Dobrev D, and Nattel S (2014) The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* **114**:1453–1468.
- Andreadou I, Bell RM, Botker HE, and Zuurbier CJ (2020) SGLT2 inhibitors reduce infarct size in reperfused ischemic heart and improve cardiac function during ischemic episodes in preclinical models. *Biochim Biophys Acta Mol Basis Dis* **1866**:165770.
- Andreadou I, Daiber A, Baxter GF, Brizzi MF, Di Lisa F, Kaludercic N, Lazou A, Varga ZV, Zuurbier CJ, Schulz R et al. (2021) Influence of cardiometabolic comorbidities on myocardial function, infarction, and cardioprotection: role of cardiac redox signaling. *Free Radic Biol Med* **166**:33–52.
- Andreadou I, Efentakis P, Balafas E, Togliatto G, Davos CH, Varela A, Dimitriou CA, Nikolaou PE, Maratou E, Lambadiari V et al. (2017) Empagliflozin limits myocardial infarction *in vivo* and cell death *in vitro*: role of STAT3, mitochondria, and redox aspects. *Front Physiol* **8**:1077.
- Andreadou I, Farmakis D, Prokavas E, Sigala F, Zoga A, Spyridaki K, Papalois A, Papapetropoulos A, Anastasiou-Nana M, Kremastinos DT et al. (2012) Short-term statin administration in hypercholesterolaemic rabbits resistant to postconditioning: effects on infarct size, endothelial nitric oxide synthase, and nitro-oxidative stress. *Cardiovasc Res* **94**:501–509.
- Andreadou I, Iliodromitis EK, Lazou A, Görbe A, Giricz Z, Schulz R, and Ferdinandy P (2017) Effect of hypercholesterolemia on myocardial function, ischemia-reperfusion injury and cardioprotection by preconditioning, postconditioning and remote conditioning. *Br J Pharmacol* **174**:1555–1569.
- Andreadou I, Schulz R, Badimon L, Adameová A, Kleinbongard P, Lecour S, Nikolaou PE, Falcão-Pires I, Vilahur G, Woudberg N et al. (2020) Hyperlipidaemia and cardioprotection: animal models for translational studies. *Br J Pharmacol* **177**:5287–5311.
- Andreadou I, Tsoumani M, Vilahur G, Ikonomidis I, Badimon L, Varga ZV, Ferdinandy P, and Schulz R (2020) PCSK9 in myocardial infarction and cardioprotection: importance of lipid metabolism and inflammation. *Front Physiol* **11**:602497.
- Andreotti F, Pasceri V, Hackett DR, Davies GJ, Haider AW, and Maseri A (1996) Preinfarction angina as a predictor of more rapid coronary thrombolysis in patients with acute myocardial infarction. *N Engl J Med* **334**:7–12.
- Ansari M and Kurian GA (2019) Hydrogen sulfide preconditioning could ameliorate reperfusion associated injury in diabetic cardiomyopathy rat heart through preservation of mitochondria. *Biochimie* **158**:208–216.
- Ansari M and Kurian GA (2020a) Diabetic animal fed with high-fat diet prevents the protective effect of myocardial ischemic preconditioning effect in isolated rat heart perfusion model. *J Biochem Mol Toxicol* **34**:e22457.
- Ansari M and Kurian GA (2020b) Mechanism of hydrogen sulfide preconditioning-associated protection against ischemia-reperfusion injury differs in diabetic heart that develops myopathy. *Cardiovasc Toxicol* **20**:155–167.
- Ansari M, Prem PN, and Kurian GA (2022) Hydrogen sulfide postconditioning rendered cardioprotection against myocardial ischemia-reperfusion injury is compromised in rats with diabetic cardiomyopathy. *Microvasc Res* **141**:104322.
- Ansley DM and Wang B (2013) Oxidative stress and myocardial injury in the diabetic heart. *J Pathol* **229**:232–241.
- Aragón JP, Condit ME, Bhushan S, Predmore BL, Patel SS, Grinsfelder DB, Gundewar S, Jha S, Calvert JW, Barouch LA et al. (2011) Beta3-adrenoreceptor stimulation ameliorates myocardial ischemia-reperfusion injury via endothelial nitric oxide synthase and neuronal nitric oxide synthase activation. *J Am Coll Cardiol* **58**:2683–2691.
- Argaud L, Gateau-Roesch O, Muntean D, Chalabreysse L, Loufouat J, Robert D, and Ovize M (2005) Specific inhibition of the mitochondrial permeability transition prevents lethal reperfusion injury. *J Mol Cell Cardiol* **38**:367–374.
- Arslan F, Houtgraaf JH, Keogh B, Kazemi K, de Jong R, McCormack WJ, O'Neill LA, McGuirk P, Timmers L, Smeets MB et al. (2012) Treatment with OPN-305, a humanized anti-toll-like receptor-2 antibody, reduces myocardial ischemia/reperfusion injury in pigs. *Circ Cardiovasc Interv* **5**:279–287.
- Arslan F, Smeets MB, O'Neill LA, Keogh B, McGuirk P, Timmers L, Tersteeg C, Hoefler IE, Doevendans PA, Pasterkamp G et al. (2010) Myocardial ischemia/reperfusion injury is mediated by leukocytic toll-like receptor-2 and reduced by systemic administration of a novel anti-toll-like receptor-2 antibody. *Circulation* **121**:80–90.
- Atar D, Arheden H, Berdeaux A, Bonnet JL, Carlsson M, Clemmensen P, Cuvier V, Danchin N, Dubois-Randé JL, Engblom H et al. (2015) Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. *Eur Heart J* **36**:112–119.
- Audia JP, Yang XM, Crockett ES, Housley N, Haq EU, O'Donnell K, Cohen MV, Downey JM, and Alvarez DF (2018) Caspase-1 inhibition by VX-765 administered at reperfusion in P2Y₁₂ receptor antagonist-treated rats provides long-term reduction in myocardial infarct size and preservation of ventricular function. *Basic Res Cardiol* **113**:32.
- Babiker F, Al-Jarallah A, and Al-Awadi M (2019) Effects of cardiac hypertrophy, diabetes, aging, and pregnancy on the cardioprotective effects of postconditioning in male and female rats. *Cardiol Res Pract* **2019**:3403959.
- Babiker F, Al-Jarallah A, and Joseph S (2016) The interplay between the renin angiotensin system and pacing postconditioning induced cardiac protection. *PLoS One* **11**:e0165777.
- Bae S and Zhang L (2005) Gender differences in cardioprotection against ischemia/reperfusion injury in adult rat hearts: focus on Akt and protein kinase C signaling. *J Pharmacol Exp Ther* **315**:1125–1135.
- Baffour-Awuah B, Dieberg G, Pearson MJ, and Smart NA (2021) The effect of remote ischaemic conditioning on blood pressure response: a systematic review and meta-analysis. *Int J Cardiol Hypertens* **8**:100081.
- Bajpai G, Bredemeyer A, Li W, Zaitsev K, Koenig AL, Lokshina I, Mohan J, Ivey B, Hsiao HM, Weinheimer C et al. (2019) Tissue resident CCR2- and CCR2+ cardiac macrophages differentially orchestrate monocyte recruitment and fate specification following myocardial injury. *Circ Res* **124**:263–278.
- Bakhta O, Pascaud A, Dieu X, Beaumont J, Kouassi Nzougheh J, Kamel R, Croyal M, Tamarelle S, Simard G, Chao de la Barca JM et al. (2020) Tryptophan-kynurenine pathway in the remote ischemic conditioning mechanism. *Basic Res Cardiol* **115**:13.
- Bankwala Z, Hale SL, and Kloner RA (1994) Alpha-adrenoceptor stimulation with exogenous norepinephrine or release of endogenous catecholamines mimics ischemic preconditioning. *Circulation* **90**:1023–1028.
- Baranyai T, Giricz Z, Varga ZV, Koncsos G, Lukovic D, Makkos A, Sárközy M, Pávó N, Jakab A, Czibalmos C et al. (2017) In vivo MRI and ex vivo histological assessment of the cardioprotection induced by ischemic preconditioning, postconditioning and remote conditioning in a closed-chest porcine model of reperfused acute myocardial infarction: importance of microvasculature. *J Transl Med* **15**:67.
- Baranyai T, Nagy CT, Koncsos G, Onódi Z, Károlyi-Szabó M, Makkos A, Varga ZV, Ferdinandy P, and Giricz Z (2015) Acute hyperglycemia abolishes cardioprotection by remote ischemic preconditioning. *Cardiovasc Diabetol* **14**:151.
- Barcena de Arellano ML, Pozdniakova S, Kühn AA, Baczko I, Ladilov Y, and Regitz-Zagrosek V (2019) Sex differences in the aging human heart: decreased sirtuins, pro-inflammatory shift and reduced anti-oxidative defense. *Aging (Albany NY)* **11**:1918–1933.
- Barsukevich V, Basalay M, Sanchez J, Mroczek A, Whittle J, Ackland GL, Gourine AV, and Gourine A (2015) Distinct cardioprotective mechanisms of immediate, early and delayed ischaemic postconditioning. *Basic Res Cardiol* **110**:452.
- Barthel H, Ebel D, Müllenheim J, Obal D, Preckel B, and Schlack W (2004) Effect of lidocaine on ischaemic preconditioning in isolated rat heart. *Br J Anaesth* **93**:698–704.
- Basalay MV, Mastitskaya S, Mroczek A, Ackland GL, Del Arroyo AG, Sanchez J, Sjoquist PO, Pernow J, Gourine AV, and Gourine A (2016) Glucagon-like peptide-1 (GLP-1) mediates cardioprotection by remote ischaemic conditioning. *Cardiovasc Res* **112**:669–676.
- Bauer B, Simkhovich BZ, Kloner RA, and Przyklenk K (1993) Does preconditioning protect the coronary vasculature from subsequent ischemia/reperfusion injury? *Circulation* **88**:659–672.
- Baxter GF (2002) The neutrophil as a mediator of myocardial ischemia-reperfusion injury: time to move on. *Basic Res Cardiol* **97**:268–275.
- Baxter GF and Ferdinandy P (2001) Delayed preconditioning of myocardium: current perspectives. *Basic Res Cardiol* **96**:329–344.
- Bayoumi AS, Park KM, Wang Y, Teoh JP, Aonuma T, Tang Y, Su H, Weintraub NL, and Kim IM (2018) A carvedilol-responsive microRNA, miR-125b-5p protects the heart from acute myocardial infarction by repressing pro-apoptotic bak1 and klf13 in cardiomyocytes. *J Mol Cell Cardiol* **114**:72–82.
- Bayrami G, Karimi P, Agha-Hosseini F, Feyzizadeh S, and Badalzadeh R (2018) Effect of ischemic postconditioning on myocardial function and infarct size following reperfusion injury in diabetic rats pretreated with vildagliptin. *J Cardiovasc Pharmacol Ther* **23**:174–183.
- Behmenburg F, Heinen A, Bruch LV, Hollmann MW, and Huhn R (2017) Cardioprotection by remote ischemic preconditioning is blocked in the aged rat heart *in vivo*. *J Cardiothorac Vasc Anesth* **31**:1223–1226.
- Behmenburg F, van Caster P, Bunte S, Brandenburger T, Heinen A, Hollmann MW, and Huhn R (2018) Impact of anesthetic regimen on remote ischemic preconditioning in the rat heart *in vivo*. *Anesth Analg* **126**:1377–1380.
- Bei Y, Xu T, Lv D, Yu P, Xu J, Che L, Das A, Tigges J, Toxavidis V, Ghiran I et al. (2017) Exercise-induced circulating extracellular vesicles protect against cardiac ischemia-reperfusion injury. *Basic Res Cardiol* **112**:38.
- Belliard A, Gulati GK, Duan Q, Alves R, Brewer S, Madan N, Sottejeau Y, Wang X, Kalisz J, and Pierre SV (2016) Ischemia/reperfusion-induced alterations of enzymatic and signaling functions of the rat cardiac Na⁺/K⁺-ATPase: protection by ouabain preconditioning. *Physiol Rep* **4**:4.
- Bellis A, Mauro C, Barbato E, Di Gioia G, Sorriento D, Trimarco B, and Morisco C (2020) The rationale of neprilysin inhibition in prevention of myocardial ischemia-reperfusion injury during ST-elevation myocardial infarction. *Cells* **9**:2134.
- Bencsik P, Kupai K, Görbe A, Kenyeres É, Varga ZV, Pálóczi J, Gáspár R, Kovács L, Weber L, Takács F et al. (2018) Development of matrix metalloproteinase-2 inhibitors for cardioprotection. *Front Pharmacol* **9**:296.
- Bertero E, Heusch G, Münzel T, and Maack C (2021) A pathophysiological compass to personalize antianginal drug treatment. *Nat Rev Cardiol* **18**:838–852.

- Beyar R, Guerici AD, Halperin HR, Tsitlik JE, and Weisfeldt ML (1989) Intermittent coronary sinus occlusion after coronary arterial ligation results in venous retroperfusion. *Circ Res* **65**:695–707.
- Bibli SI, Papapetropoulos A, Iliodromitis EK, Daiber A, Randriamboavonjy V, Steven S, Brouckaert P, Chatzianastasiou A, Kypreos KE, Hausenloy DJ et al. (2019) Nitroglycerine limits infarct size through S-nitrosation of cyclophilin D: a novel mechanism for an old drug. *Cardiovasc Res* **115**:625–636.
- Bice JS, Jones BR, Chamberlain GR, and Baxter GF (2016) Nitric oxide treatments as adjuncts to reperfusion in acute myocardial infarction: a systematic review of experimental and clinical studies. *Basic Res Cardiol* **111**:23.
- Birnbaum Y, Ye R, and Ye Y (2021) Aspirin blocks the infarct-size limiting effect of ischemic postconditioning in the rat. *Cardiovasc Drugs Ther* DOI: 10.1007/s10557-021-07241-8 [published ahead of print].
- Black SC, Gralinski MR, Friedrichs GS, Kilgore KS, Driscoll EM, and Lucchesia BR (1995) Cardioprotective effects of heparin or N-acetylleparin in an in vivo model of myocardial ischaemic and reperfusion injury. *Cardiovasc Res* **29**:629–636.
- Bo W, Ma Y, Xi Y, Liang Q, Cai M, and Tian Z (2021) The roles of FGF21 and ALCAT1 in aerobic exercise-induced cardioprotection of postmyocardial infarction mice. *Oxid Med Cell Longev* **2021**:8996482.
- Bochaton T, Claeys MJ, Garcia-Dorado D, Mewton N, Bergerot C, Jossan C, Amaz C, Boussaha I, Thibault H, and Ovize M (2019) Importance of infarct size versus other variables for clinical outcomes after PPCI in STEMI patients. *Basic Res Cardiol* **115**:4.
- Bode MF, Auriemma AC, Grover SP, Hisada Y, Rennie A, Bode WD, Vora R, Subramanian S, Cooley B, Andrade-Gordon P et al. (2018) The factor Xa inhibitor rivaroxaban reduces cardiac dysfunction in a mouse model of myocardial infarction. *Thromb Res* **167**:128–134.
- Bodi V, Ruiz-Nodar JM, Feliu E, Minana G, Nunez J, Husser O, Martinez-Elvira J, Ruiz A, Bonanad C, Mommenueu JV et al. (2014) Effect of ischemic postconditioning on microvascular obstruction in reperfused myocardial infarction. Results of a randomized study in patients and of an experimental model in swine. *Int J Cardiol* **175**:138–146.
- Boengler K, Buechert A, Heinen Y, Roeskes C, Hilfiker-Kleiner D, Heusch G, and Schulz R (2008) Cardioprotection by ischemic postconditioning is lost in aged and STAT3-deficient mice. *Circ Res* **102**:131–135.
- Boengler K, Dodoni G, Rodriguez-Sinovas A, Cabestrero A, Ruiz-Meana M, Gres P, Konietzka I, Lopez-Iglesias C, Garcia-Dorado D, Di Lisa F et al. (2005) Connexin 43 in cardiomyocyte mitochondria and its increase by ischemic preconditioning. *Cardiovasc Res* **67**:234–244.
- Boengler K, Hilfiker-Kleiner D, Heusch G, and Schulz R (2010) Inhibition of permeability transition pore opening by mitochondrial STAT3 and its role in myocardial ischemia/reperfusion. *Basic Res Cardiol* **105**:771–785.
- Boengler K, Konietzka I, Buechert A, Heinen Y, Garcia-Dorado D, Heusch G, and Schulz R (2007) Loss of ischemic preconditioning's cardioprotection in aged mouse hearts is associated with reduced gap junctional and mitochondrial levels of connexin 43. *Am J Physiol Heart Circ Physiol* **292**:H1764–H1769.
- Boengler K, Lochnit G, and Schulz R (2018) Mitochondria “THE” target of myocardial conditioning. *Am J Physiol Heart Circ Physiol* **315**:H1215–H1231.
- Boengler K, Schulz R, and Heusch G (2009) Loss of cardioprotection with ageing. *Cardiovasc Res* **83**:247–261.
- Boengler K, Stahlhofen S, van de Sand A, Gres P, Ruiz-Meana M, Garcia-Dorado D, Heusch G, and Schulz R (2009) Presence of connexin 43 in subsarcolemmal, but not in inter-fibrillar cardiomyocyte mitochondria. *Basic Res Cardiol* **104**:141–147.
- Boengler K, Ungefug E, Heusch G, Leybaert L, and Schulz R (2013) Connexin 43 impacts on mitochondrial potassium uptake. *Front Pharmacol* **4**:73.
- Boengler K, Ungefug E, Heusch G, and Schulz R (2013) The STAT3 inhibitor statin impairs cardiomyocyte mitochondrial function through increased reactive oxygen species formation. *Curr Pharm Des* **19**:6890–6895.
- Bolli R (2021) CAESAR's legacy: a new era of rigor in preclinical studies of cardioprotection. *Basic Res Cardiol* **116**:33.
- Bonora M, Morganti C, Morciano G, Pedriali G, Lebedzinska-Arciszewska M, Aquila G, Giorgi C, Rizzo P, Campo G, Ferrari R et al. (2017) Mitochondrial permeability transition involves dissociation of F₁F₀ ATP synthase dimers and C-ring conformation. *EMBO Rep* **18**:1077–1089.
- Boos CJ, Anderson RA, and Lip GY (2006) Is atrial fibrillation an inflammatory disorder? *Eur Heart J* **27**:136–149.
- Börschel CS and Schnabel RB (2019) The imminent epidemic of atrial fibrillation and its concomitant diseases—myocardial infarction and heart failure—a cause for concern. *Int J Cardiol* **287**:162–173.
- Bose AK, Mocanu MM, Carr RD, Brand CL, and Yellon DM (2005) Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. *Diabetes* **54**:146–151.
- Botker HE (2020) The future of cardioprotection—pointing toward patients at elevated risk as the target populations. *J Cardiovasc Pharmacol Ther* **25**:487–493.
- Botker HE, Hausenloy D, Andreadou I, Antonucci S, Boengler K, Davidson SM, Deshwal S, Devaux Y, Di Lisa F, Di Sante M et al. (2018) Practical guidelines for rigor and reproducibility in preclinical and clinical studies on cardioprotection. *Basic Res Cardiol* **113**:39.
- Botker HE, Kharbanda R, Schmidt MR, Böttcher M, Kaltoft AK, Terkelsen CJ, Munk K, Andersen NH, Hansen TM, Trautner S et al. (2010) Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet* **375**:727–734.
- Botker HE, Lassen TR, and Jespersen NR (2018) Clinical translation of myocardial conditioning. *Am J Physiol Heart Circ Physiol* **314**:H1225–H1252.
- Bou-Teen D, Fernandez-Sanz C, Miro-Casas E, Nichtova Z, Bonzon-Kulichenko E, Casós K, Inserte J, Rodriguez-Sinovas A, Benito B, Sheu SS et al. (2022) Defective dimerization of FoF₁-ATP synthase secondary to glycation favors mitochondrial energy deficiency in cardiomyocytes during aging. *Aging Cell* **21**:e13564.
- Bou-Teen D, Kaludercic N, Weissman D, Turan B, Maack C, Di Lisa F, and Ruiz-Meana M (2021) Mitochondrial ROS and mitochondria-targeted antioxidants in the aged heart. *Free Radic Biol Med* **167**:109–124.
- Bourdillon MT and Vasan RS (2020) A contemporary approach to hypertensive cardiomyopathy: reversing left ventricular hypertrophy. *Curr Hypertens Rep* **22**:85.
- Brenner GB, Makkos A, Nagy CT, Onódi Z, Sayour NV, Gergely TG, Kiss B, Görbe A, Sággy É, Zádori ZS et al. (2020) Hidden cardiotoxicity of rofecoxib can be revealed in experimental models of ischemia/reperfusion. *Cells* **9**:551.
- Bril A, Shlyak M, DiMartino MJ, Feuerstein GZ, Linee P, Poyser RH, Ruffolo RR Jr, and Smith 3rd EF (1992) Cardioprotective effects of carvedilol, a novel beta adrenoceptor antagonist with vasodilating properties, in anaesthetised minipigs: comparison with propranolol. *Cardiovasc Res* **26**:518–525.
- Broch K, Anstensrud AK, Woxholt S, Sharma K, Tøllefsen IM, Bendz B, Aakhus S, Ueland T, Amundsen BH, Damås JK et al. (2021) Randomized trial of interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction. *J Am Coll Cardiol* **77**:1845–1855.
- Buerke M, Murohara T, and Lefer AM (1995) Cardioprotective effects of a C1 esterase inhibitor in myocardial ischemia and reperfusion. *Circulation* **91**:393–402.
- Buja LM (2022) Pathobiology of myocardial ischemia and reperfusion injury: models, modes, molecular mechanisms, modulation and clinical applications. *Cardiol Rev* DOI: 10.1097/CRD.0000000000000440 [published ahead of print].
- Bulluck H, Chan MHH, Bryant JA, Chai P, Chawla A, Chua TS, Chung YC, Fei G, Ho HH, Ho AFW et al. (2019) Platelet inhibition to target reperfusion injury trial: rationale and study design. *Clin Cardiol* **42**:5–12.
- Bulluck H, Rosmini S, Abdel-Gadir A, White SK, Bhuvan AN, Treibel T, Fontana M, Ramlall M, Hamarneh A, Sirkar A et al. (2016) Residual myocardial iron following intramyocardial hemorrhage during the convalescent phase of reperfused ST-segment-elevation myocardial infarction and adverse left ventricular remodeling. *Circ Cardiovasc Imaging* **9**:e004940.
- Burwell LS, Nadochiyal SM, and Brookes PS (2009) Cardioprotection by metabolic shut-down and gradual wake-up. *J Mol Cell Cardiol* **46**:804–810.
- Büttner P, Bahls M, Böger RH, Hindricks G, Thiele H, Schwedhelm E, and Kornej J (2020) Arginine derivatives in atrial fibrillation progression phenotypes. *J Mol Med (Berl)* **98**:999–1008.
- Cai L, Qi B, Wu X, Peng S, Zhou G, Wei Y, Xu J, Chen S, and Liu S (2019) Circular RNA Ttc3 regulates cardiac function after myocardial infarction by sponging miR-15b. *J Mol Cell Cardiol* **130**:10–22.
- Calabrese EJ (2016a) Pre- and post-conditioning hormesis in elderly mice, rats, and humans: its loss and restoration. *Biogerontology* **17**:681–702.
- Calabrese EJ (2016b) Preconditioning is hormesis part I: documentation, dose-response features and mechanistic foundations. *Pharmacol Res* **110**:242–264.
- Candilio L and Hausenloy D (2017) Is there a role for ischaemic conditioning in cardiac surgery? *F1000 Res* **6**:563.
- Candilio L, Malik A, Ariti C, Barnard M, Di Salvo C, Lawrence D, Hayward M, Yap J, Roberts N, Sheikh A et al. (2015) Effect of remote ischaemic preconditioning on clinical outcomes in patients undergoing cardiac bypass surgery: a randomised controlled clinical trial. *Heart* **101**:185–192.
- Casin KM and Kohr MJ (2020) An emerging perspective on sex differences: intersecting S-nitrosylation and aldehyde signaling in the heart. *Redox Biol* **31**:101441.
- Cellier L, Tamareille S, Kalakech H, Guillou S, Lenaers G, Prunier F, and Mirebeau-Prunier D (2016) Remote ischemic conditioning influences mitochondrial dynamics. *Shock* **45**:192–197.
- Chaiyasothi T, Nathisuwan S, Dilokthornsakul P, Vathesatogkit P, Thakkinian A, Reid C, Wongcharoen W, and Chaiyakunapruk N (2019) Effects of non-statin lipid-modifying agents on cardiovascular morbidity and mortality among statin-treated patients: a systematic review and network meta-analysis. *Front Pharmacol* **10**:547.
- Chao de la Barca JM, Bakhta O, Kalakech H, Simard G, Tamareille S, Catros V, Callebert J, Gadrac C, Tessier L, Reynier P et al. (2016) Metabolic signature of remote ischemic preconditioning involving a cocktail of amino acids and biogenic amines. *J Am Heart Assoc* **5**:e003891.
- Chen CH, Wu CW, Shih CD, Lien WH, Huang SL, and Huang CC (2016) Attenuation of isoflurane preconditioning-induced acute cardioprotection in hypertensive hypertrophied hearts. *J Cardiothorac Vasc Anesth* **30**:1317–1323.
- Chen J, Gao J, Sun W, Li L, Wang Y, Bai S, Li X, Wang R, Wu L, Li H et al. (2016) Involvement of exogenous H₂S in recovery of cardioprotection from ischemic post-conditioning via increase of autophagy in the aged hearts. *Int J Cardiol* **220**:681–692.
- Chen L, Chen M, Du J, Wan L, Zhang L, and Gu E (2016c) Hyperglycemia attenuates remifentanyl postconditioning-induced cardioprotection against hypoxia/reoxygenation injury in H9c2 cardiomyoblasts. *J Surg Res* **203**:483–490.
- Chen Q, Younus M, Thompson J, Hu Y, Hollander JM, and Lesnfsky EJ (2018) Intermediary metabolism and fatty acid oxidation: novel targets of electron transport chain-driven injury during ischemia and reperfusion. *Am J Physiol Heart Circ Physiol* **314**:H787–H795.
- Chen WR, Hu SY, Chen YD, Zhang Y, Qian G, Wang J, Yang JJ, Wang ZF, Tian F, and Ning QX (2015) Effects of liraglutide on left ventricular function in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am Heart J* **170**:845–854.
- Cheskes S, Koh M, Turner L, Heslegrave R, Verbeek R, Dorian P, Scales DC, Singh B, Amlani S, Natarajan M et al. (2020) Field implementation of remote ischemic conditioning in st-segment-elevation myocardial infarction: The FIRST Study. *Can J Cardiol* **36**:1278–1288.
- Chiari P, Angoulvant D, Mewton N, Desebbe O, Obadia JF, Robin J, Farhat F, Jegaden O, Bastien O, Lehot JJ et al. (2014) Cyclosporine protects the heart during aortic valve surgery. *Anesthesiology* **121**:232–238.
- Cho YJ, Nam K, Kim TK, Choi SW, Kim SJ, Hausenloy DJ, and Jeon Y (2019) Sevoflurane, propofol and carvedilol block myocardial protection by limb remote ischemic preconditioning. *Int J Mol Sci* **20**:269.
- Chong J, Bulluck H, Fw Ho A, Boisvert WA, and Hausenloy DJ (2019) Chronic remote ischemic conditioning for cardiovascular protection. *Cond Med* **2**:164–169.

- Chouchani ET, Methner C, Nadochiy SM, Logan A, Pell VR, Ding S, James AM, Cochemé HM, Reinhold J, Lilley KS et al. (2013) Cardioprotection by S-nitrosation of a cysteine switch on mitochondrial complex I. *Nat Med* **19**:753–759.
- Chouchani ET, Pell VR, Gaude E, Aksestijević D, Sundier SY, Robb EL, Logan A, Nadochiy SM, Ord ENJ, Smith AC et al. (2014) Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. *Nature* **515**:431–435.
- Ciocci Pardo A, Scuri S, González Arbeláez LF, Caldiz C, Fantinelli J, and Mosca SM (2018) Survival kinase-dependent pathways contribute to gender difference in the response to myocardial ischemia-reperfusion and ischemic post-conditioning. *Cardiovasc Pathol* **33**:19–26.
- Clarke SJ, Khaliulini I, Das M, Parker JE, Heesom KJ, and Halestrap AP (2008) Inhibition of mitochondrial permeability transition pore opening by ischemic preconditioning is probably mediated by reduction of oxidative stress rather than mitochondrial protein phosphorylation. *Circ Res* **102**:1082–1090.
- Cohen MV and Downey JM (2017) The impact of irreproducibility and competing protection from P2Y₁₂ antagonists on the discovery of cardioprotective interventions. *Basic Res Cardiol* **112**:64.
- Cohen MV, Yang XM, and Downey JM (2008) Acidosis, oxygen, and interference with mitochondrial permeability transition pore formation in the early minutes of reperfusion are critical to postconditioning's success. *Basic Res Cardiol* **103**:464–471.
- GBD 2019 Risk Factors Collaborators (2020) Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **396**:1223–1249.
- Colonna P, Cadeddu C, Montisci R, Ruscazio M, Selem AH, Chen L, Onnis E, Meloni L, and Iliceto S (2002) Reduced microvascular and myocardial damage in patients with acute myocardial infarction and preinfarction angina. *Am Heart J* **144**:796–803.
- Connelly KA, Zhang Y, Desjardins JF, Nghiem L, Visram A, Batchu SN, Yerra VG, Kabir G, Thai K, Advani A et al. (2020) Load-independent effects of empagliflozin contribute to improved cardiac function in experimental heart failure with reduced ejection fraction. *Cardiovasc Diabetol* **19**:13.
- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J et al.; RE-LY Steering Committee and Investigators (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* **361**:1139–1151.
- Consegal M, Núñez N, Barba I, Benito B, Ruiz-Meana M, Inserte J, Ferreira-González I, and Rodríguez-Sinovas A (2021) Citric acid cycle metabolites predict infarct size in pigs submitted to transient coronary artery occlusion and treated with succinate dehydrogenase inhibitors or remote ischemic preconditioning. *Int J Mol Sci* **22**:4151.
- Correa F, García N, Gallardo-Pérez J, Carreno-Fuentes L, Rodríguez-Enríquez S, Marín-Hernández A, and Zazueta C (2008) Post-conditioning preserves glycolytic ATP during early reperfusion: a survival mechanism for the reperfused heart. *Cell Physiol Biochem* **22**:635–644.
- Crimi G, Pica S, Raineri C, Bramucci E, De Ferrari GM, Klersy C, Ferlini M, Marinoni B, Repetto A, Romeo M et al. (2013) Remote ischemic post-conditioning of the lower limb during primary percutaneous coronary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial. *JACC Cardiovasc Interv* **6**:1055–1063.
- Crisostomo PR, Wang M, Wairiuko GM, Terrell AM, and Meldrum DR (2006) Postconditioning in females depends on injury severity. *J Surg Res* **134**:342–347.
- Crochemore C, Mekki M, Corbière C, Karoui A, Noël R, Vendeville C, Vaugeois JM, and Monteil C (2015) Subsarcolemmal and interfibrillar mitochondria display distinct superoxide production profiles. *Free Radic Res* **49**:331–337.
- Csont T and Ferdinandy P (2005) Cardioprotective effects of glyceryl trinitrate: beyond vascular nitrate tolerance. *Pharmacol Ther* **105**:57–68.
- Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, Bonnefoy-Cudraz E, Guérin P, Elbaz M, Delarche N et al. (2015) Cyclosporine before PCI in patients with acute myocardial infarction. *N Engl J Med* **373**:1021–1031.
- Curran J, Burkhoff D, and Kloner RA (2019) Beyond reperfusion: acute ventricular unloading and cardioprotection during myocardial infarction. *J Cardiovasc Transl Res* **12**:95–106.
- D'Annunzio V, Donato M, Buchholz B, Pérez V, Miksztoewicz V, Berg G, and Gelpi RJ (2012) High cholesterol diet effects on ischemia-reperfusion injury of the heart. *Can J Physiol Pharmacol* **90**:1185–1196.
- Dai W, Simkhovich BZ, and Kloner RA (2009) Ischemic preconditioning maintains cardioprotection in aging normotensive and spontaneously hypertensive rats. *Exp Gerontol* **44**:344–349.
- Daiber A, Steven S, Euler G, and Schulz R (2021) Vascular and cardiac oxidative stress and inflammation as targets for cardioprotection. *Curr Pharm Des* **27**:2112–2130.
- Dalgas C, Povlsen JA, Løfgren B, Erichsen SB, and Bøtker HE (2012) Effects of fatty acids on cardioprotection by pre-ischaemic inhibition of the malate-aspartate shuttle. *Clin Exp Pharmacol Physiol* **39**:878–885.
- Dambrova M, Zuurbier CJ, Borutaite V, Liepinsh E, and Makrecka-Kuka M (2021) Energy substrate metabolism and mitochondrial oxidative stress in cardiac ischemia/reperfusion injury. *Free Radic Biol Med* **165**:24–37.
- Davidson SM, Adameová A, Barile L, Cabrera-Fuentes HA, Lazou A, Pagliaro P, Stensløkken KO, Garcia-Dorado D; EU-CARDIOPROTECTION COST Action (CA16225) (2020) Mitochondrial and mitochondrial-independent pathways of myocardial cell death during ischaemia and reperfusion injury. *J Cell Mol Med* **24**:3795–3806.
- Davidson SM, Andreadou I, Barile L, Birnbaum Y, Cabrera-Fuentes HA, Cohen MV, Downey JM, Girao H, Pagliaro P, Penna C et al. (2019) Circulating blood cells and extracellular vesicles in acute cardioprotection. *Cardiovasc Res* **115**:1156–1166.
- Davidson SM, Ferdinandy P, Andreadou I, Bøtker HE, Heusch G, Ibáñez B, Ovize M, Schulz R, Yellon DM, Hausenloy DJ et al.; CARDIOPROTECTION COST Action (CA16225) (2019) Multitarget strategies to reduce myocardial ischemia/reperfusion injury: JACC review topic of the week. *J Am Coll Cardiol* **73**:89–99.
- Davidson SM, Hausenloy D, Duchon MR, and Yellon DM (2006) Signalling via the reperfusion injury signalling kinase (RISK) pathway links closure of the mitochondrial permeability transition pore to cardioprotection. *Int J Biochem Cell Biol* **38**:414–419.
- Davidson SM, Riquelme JA, Takov K, Vicencio JM, Boi-Doku C, Khoo V, Doreth C, Radenkovic D, Lavandero S, and Yellon DM (2018) Cardioprotection mediated by exosomes is impaired in the setting of type II diabetes but can be rescued by the use of non-diabetic exosomes in vitro. *J Cell Mol Med* **22**:141–151.
- Davidson SM, Riquelme JA, Zheng Y, Vicencio JM, Lavandero S, and Yellon DM (2018) Endothelial cells release cardioprotective exosomes that may contribute to ischaemic preconditioning. *Sci Rep* **8**:15885.
- De Maria GL, Alkhalil M, Borlotti A, Wolfrum M, Gaughran L, Dall'Armellina E, Langrish JP, Lucking AJ, Choudhury RP, Kharbada RK et al. (2018) Index of microcirculatory resistance-guided therapy with pressure-controlled intermittent coronary sinus occlusion improves coronary microvascular function and reduces infarct size in patients with ST-elevation myocardial infarction: the Oxford Acute Myocardial Infarction Pressure-controlled Intermittent Coronary Sinus Occlusion study (OxAMI-PICOS study). *EuroIntervention* **14**:e352–e359.
- de Waha S, Patel MR, Granger CB, Ohman EM, Maehara A, Eitel I, Ben-Yehuda O, Jenkins P, Thiele H, and Stone GW (2017) Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. *Eur Heart J* **38**:3502–3510.
- DeFily DV and Chilian WM (1993) Preconditioning protects coronary arteriolar endothelium from ischemia-reperfusion injury. *Am J Physiol* **265**:H700–H706.
- del Valle HF, Lascano EC, Negroni JA, and Crottogini AJ (2003) Absence of ischemic preconditioning protection in diabetic sheep hearts: role of sarcolemmal KATP channel dysfunction. *Mol Cell Biochem* **249**:21–30.
- Desch S, Stiermaier T, de Waha S, Lurz P, Gutberlet M, Sandri M, Mangner N, Boudriot E, Woinke M, Erbs S et al. (2016) Thrombus aspiration in patients with ST-segment elevation myocardial infarction presenting late after symptom onset. *JACC Cardiovasc Interv* **9**:113–122.
- Di Lisa F, Menabò R, Canton M, Barile M, and Bernardi P (2001) Opening of the mitochondrial permeability transition pore causes depletion of mitochondrial and cytosolic NAD⁺ and is a causative event in the death of myocytes in postischemic reperfusion of the heart. *J Biol Chem* **276**:2571–2575.
- Diamond JA and Phillips RA (2005) Hypertensive heart disease. *Hypertens Res* **28**:191–202.
- Dikow R, Kihm LP, Zeier M, Kapitza J, Törnig J, Amann K, Tiefenbacher C, and Ritz E (2004) Increased infarct size in uremic rats: reduced ischemia tolerance? *J Am Soc Nephrol* **15**:1530–1536.
- Dikow R, Schmidt U, Kihm LP, Schaier M, Schwenger V, Gross ML, Katus HA, Zeier M, and Hardt SE (2010) Uremia aggravates left ventricular remodeling after myocardial infarction. *Am J Nephrol* **32**:13–22.
- Ding Z, Wang X, Liu S, Shahanaawaz J, Theus S, Fan Y, Deng X, Zhou S, and Mehta JL (2018) PCSK9 expression in the ischaemic heart and its relationship to infarct size, cardiac function, and development of autophagy. *Cardiovasc Res* **114**:1738–1751.
- Dobrev D, Aguilar M, Heijman J, Guichard JB, and Nattel S (2019) Postoperative atrial fibrillation: mechanisms, manifestations and management. *Nat Rev Cardiol* **16**:417–436.
- Donato M, Buchholz B, Rodríguez M, Pérez V, Inserte J, Garcia-Dorado D, and Gelpi RJ (2013) Role of the parasympathetic nervous system in cardioprotection by remote hindlimb ischaemic preconditioning. *Exp Physiol* **98**:425–434.
- Driesen RB, Zaleski J, Vanden Driessche N, Vermeulen K, Bogaert J, Spido KR, Van de Werf F, and Claus P (2012) Histological correlate of a cardiac magnetic resonance imaged microvascular obstruction in a porcine model of ischemia-reperfusion. *Cardiovasc Pathol* **21**:129–131.
- Duan L, Liang C, Li X, Huang Z, Liu S, Wu N, and Jia D (2019) Lycopene restores the effect of ischemic postconditioning on myocardial ischemia-reperfusion injury in hypercholesterolemic rats. *Int J Mol Med* **43**:2451–2461.
- Duan Q, Xu Y, Marck PV, Kalisz J, Morgan EE, and Pierre SV (2018) Preconditioning and postconditioning by cardiac glycosides in the mouse heart. *J Cardiovasc Pharmacol* **71**:95–103.
- Dubreuil M, Louie-Gao Q, Peloquin CE, Choi HK, Zhang Y, and Neogi T (2018) Risk of myocardial infarction with use of selected non-steroidal anti-inflammatory drugs in patients with spondyloarthritis and osteoarthritis. *Ann Rheum Dis* **77**:1137–1142.
- Dudink EAMP, Bidar E, Jacobs J, van Hunnik A, Zeemering S, Weijs B, Luermans JGLM, Maesen BAE, Cheriex EC, Maessen JG et al. (2021) The relation between the atrial blood supply and the complexity of acute atrial fibrillation. *Int J Cardiol Heart Vasc* **34**:100794.
- Duranski MR, Greer JJ, Dejam A, Jaganmohan S, Hogg N, Langston W, Patel RP, Yet SF, Wang X, Kevil CG et al. (2005) Cytoprotective effects of nitrite during in vivo ischemia-reperfusion of the heart and liver. *J Clin Invest* **115**:1232–1240.
- Dwyer NB, Mikami Y, Hilland D, Aljazeera A, Friedrich MG, Traboulsi M, and Anderson TJ (2013) No cardioprotective benefit of ischemic postconditioning in patients with ST-segment elevation myocardial infarction. *J Interv Cardiol* **26**:482–490.
- Ebrahim Z, Yellon DM, and Baxter GF (2007a) Attenuated cardioprotective response to bradykinin, but not classical ischaemic preconditioning, in DOCA-salt hypertensive left ventricular hypertrophy. *Pharmacol Res* **55**:42–48.
- Ebrahim Z, Yellon DM, and Baxter GF (2007b) Ischemic preconditioning is lost in aging hypertensive rat heart: independent effects of aging and longstanding hypertension. *Exp Gerontol* **42**:807–814.
- Egred M, Bagnall A, Spyridopoulos I, Purcell IF, Das R, Palmer N, Grech ED, Jain A, Stone GW, Nijveldt R et al. (2020) Effect of pressure-controlled intermittent

- coronary sinus occlusion (PiCSO) on infarct size in anterior STEMI: PiCSO in ACS study. *Int J Cardiol Heart Vasc* **28**:1005-26.
- Ehring T, Baumgart D, Krajcar M, Hümmelgen M, Kompa S, and Heusch G (1994) Attenuation of myocardial stunning by the ACE inhibitor ramiprilat through a signal cascade of bradykinin and prostaglandins but not nitric oxide. *Circulation* **90**:1368-1385.
- Ehring T, Krajcar M, Baumgart D, Kompa S, Hümmelgen M, and Heusch G (1995) Cholinergic and alpha-adrenergic coronary vasomotion [corrected] with increasing ischemia-reperfusion injury. *Am J Physiol* **268**:H886-H894.
- Eicher JD, Wakabayashi Y, Vitseva O, Esa N, Yang Y, Zhu J, Freedman JE, McManus DD, and Johnson AD (2016) Characterization of the platelet transcriptome by RNA sequencing in patients with acute myocardial infarction. *Platelets* **27**:230-239.
- Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS et al.; COMPASS Investigators (2017) Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* **377**:1319-1330.
- Eitel I, Stiermaier T, Rommel KP, Fuernau G, Sandri M, Mangner N, Linke A, Erbs S, Lurz P, Boudriot E et al. (2015) Cardioprotection by combined intrahospital remote ischaemic preconditioning and postconditioning in ST-elevation myocardial infarction: the randomized LIPSIA CONDITIONING trial. *Eur Heart J* **36**:3049-3057.
- Ekström K, Nielsen JWV, Nepper-Christensen L, Ahtarovski KA, Kyhl K, Goransson C, Bertelsen L, Ghotbi AA, Kelbaek H, Hofsten DE, Kober L, Schoos MM, Vejstrup N, Lønborg J and Engstrøm T (2021) Ischemia from nonculprit stenoses is not associated with reduced culprit infarct size in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Imaging* **14**:e012209.
- El Messaoudi S, Nederlof R, Zuurbier CJ, van Swieten HA, Piekkers P, Noye L, Dieker HJ, Coenen MJ, Donders AR, Vos A et al. (2015) Effect of metformin pretreatment on myocardial injury during coronary artery bypass surgery in patients without diabetes (MetCAB): a double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol* **3**:615-623.
- Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvegaard L, Clemmensen P, Holmvang L, Jørgensen E, Pedersen F, Saunamaki K et al.; Third Danish Study of Optimal Acute Treatment of Patients With ST Elevation Myocardial Infarction-Ischemic Postconditioning (DANAMI-3-iPOST) Investigators (2017) Effect of Ischemic postconditioning during primary percutaneous coronary intervention for patients with ST-segment elevation myocardial infarction: a randomized clinical trial. *JAMA Cardiol* **2**:490-497.
- Epps J, Dieberg G, and Smart NA (2016) Repeat remote ischaemic pre-conditioning for improved cardiovascular function in humans: a systematic review. *Int J Cardiol Heart Vasc* **11**:55-58.
- Erlinge D, Göberg M, Lang I, Holzer M, Noc M, Clemmensen P, Jensen U, Metzler B, James S, Bötter HE et al. (2014) Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. The CHILL-MI trial: a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. *J Am Coll Cardiol* **63**:1857-1865.
- Fabris E, Hermanides R, Roolvink V, Ibanez B, Ottervanger JP, Pizarro G, van Royen N, Mateos-Rodriguez A, Dambink JH, Albarran A et al. (2020) Beta-blocker effect on ST-segment: a prespecified analysis of the EARLY-BAMI randomised trial. *Open Heart* **7**:e001386.
- Fang EF, Lautrup S, Hou Y, Demarest TG, Croteau DL, Mattson MP, and Bohr VA (2017) NAD⁺ in aging: molecular mechanisms and translational implications. *Trends Mol Med* **23**:899-916.
- Fantinielli JC and Mosca SM (2007) Comparative effects of ischemic pre and postconditioning on ischemia-reperfusion injury in spontaneously hypertensive rats (SHR). *Mol Cell Biochem* **296**:45-51.
- Fantinielli JC, Pérez Núñez IA, González Arbeláez LF, Schinella GR, and Mosca SM (2013) Participation of mitochondrial permeability transition pore in the effects of ischemic preconditioning in hypertrophied hearts: role of NO and mitoKATP. *Int J Cardiol* **166**:173-180.
- Fender AC, Kleeschulte S, Stolte S, Leineweber K, Kamler M, Bode J, Li N, and Dobrev D (2020) Thrombin receptor PAR4 drives canonical NLRP3 inflammasome signaling in the heart. *Basic Res Cardiol* **115**:10.
- Fender AC, Rauch BH, Geisler T, and Schrör K (2017) Protease-activated receptor PAR-4: an inducible switch between thrombosis and vascular inflammation? *Thromb Haemost* **117**:2013-2025.
- Fender AC, Wakili R, and Dobrev D (2019) Straight to the heart: pleiotropic antiarrhythmic actions of oral anticoagulants. *Pharmacol Res* **145**:104257.
- Ferdinandy P, Baczkó I, Bencsik P, Giricz Z, Görbe A, Pacher P, Varga ZV, Varró A, and Schulz R (2019) Definition of hidden drug cardiotoxicity: paradigm change in cardiac safety testing and its clinical implications. *Eur Heart J* **40**:1771-1777.
- Ferdinandy P, Hausenloj DJ, Heusch G, Baxter GF, and Schulz R (2014) Interaction of risk factors, comorbidities, and comedications with ischemia/reperfusion injury and cardioprotection by preconditioning, postconditioning, and remote conditioning. *Pharmacol Rev* **66**:1142-1174.
- Ferdinandy P, Schulz R, and Baxter GF (2007) Interaction of cardiovascular risk factors with myocardial ischemia/reperfusion injury, preconditioning, and postconditioning. *Pharmacol Rev* **59**:418-458.
- Ferdinandy P, Szilvassy Z, and Baxter GF (1998) Adaptation to myocardial stress in disease states: is preconditioning a healthy heart phenomenon? *Trends Pharmacol Sci* **19**:223-229.
- Ferko M, Farkasova V, Jasova M, Kancirova I, Ravingerova T, Duris Adameova A, Andelova N, and Waczulikova I (2018) Hypercholesterolemia antagonized heart adaptation and functional remodeling of the mitochondria observed in acute diabetes mellitus subjected to ischemia/reperfusion injury. *J Physiol Pharmacol* **69**: DOI: 10.26402/jpp.2018.5.03 [published ahead of print].
- Fernández-Jiménez R, García-Prieto J, Sánchez-González J, Agüero J, López-Martín GJ, Galán-Arriola C, Molina-Iracheta A, Doohan R, Fuster V, and Ibáñez B (2015) Pathophysiology underlying the bimodal edema phenomenon after myocardial ischemia/reperfusion. *J Am Coll Cardiol* **66**:816-828.
- Feuerstein GZ and Ruffolo RR Jr (1995) Carvedilol, a novel multiple action antihypertensive agent with antioxidant activity and the potential for myocardial and vascular protection. *Eur Heart J* **16**(Suppl F):38-42.
- Folts JD (1999) Deleterious hemodynamic effects of thrombotic/embolic materials on the distal myocardial vasculature. *Cardiovasc Res* **42**:6-8.
- Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Hassen Abate K, Akinyemiju TF et al. (2017) Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA* **317**:165-182.
- Freixa X, Bellera N, Ortiz-Pérez JT, Jiménez M, Paré C, Bosch X, De Caralt TM, Betriu A, and Masotti M (2012) Ischaemic postconditioning revisited: lack of effects on infarct size following primary percutaneous coronary intervention. *Eur Heart J* **33**:103-112.
- Frey UH, Klaassen M, Ochsenfarth C, Murke F, Thielmann M, Kottenberg E, Kleinbongard P, Klenke S, Engler A, Heusch G et al. (2019) Remote ischaemic preconditioning increases serum extracellular vesicle concentrations with altered micro-RNA signature in CABG patients. *Acta Anaesthesiol Scand* **63**:483-492.
- Gadi I, Fatima S, Elwakiel A, Nazir S, Mohanad Al-Dabet M, Rana R, Bock F, Manoharan J, Gupta D, Biemann R et al. (2021) Different DOACs control inflammation in cardiac ischemia-reperfusion differently. *Circ Res* **128**:513-529.
- Gadicherla AK, Wang N, Bulic M, Agullo-Pascual E, Lissoni A, De Smet M, Delmar M, Bultynck G, Krysko DV, Camara A et al. (2017) Mitochondrial Cx43 hemichannels contribute to mitochondrial calcium entry and cell death in the heart. *Basic Res Cardiol* **112**:27.
- Galaup A, Gomez E, Souktani R, Durand M, Cazes A, Monnot C, Teillon J, Le Jan S, Bouleti C, Briois G et al. (2012) Protection against myocardial infarction and no-reflow through preservation of vascular integrity by angiotensin-like 4. *Circulation* **125**:140-149.
- Gallinat A, Vilahur G, Padró T, and Badimon L (2022) Network-assisted systems biology analysis of the mitochondrial proteome in a pre-clinical model of ischemia, revascularization and post-conditioning. *Int J Mol Sci* **23**:2087.
- Gan L, Xie D, Liu J, Bond Lau W, Christopher TA, Lopez B, Zhang L, Gao E, Koch W, Ma XL et al. (2020) Small extracellular microvesicles mediated pathological communications between dysfunctional adipocytes and cardiomyocytes as a novel mechanism exacerbating ischemia/reperfusion injury in diabetic mice. *Circulation* **141**:968-983.
- Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, and Wen CP (2013) Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* **382**:339-352.
- Gao J, Min F, Wang S, Lv H, Liang H, Cai B, Jia X, Gao Q, and Yu Y (2022) Effect of Rho-kinase and autophagy on remote ischemic conditioning-induced cardioprotection in rat myocardial ischemia/reperfusion injury model. *Cardiovasc Ther* **2022**:6806427.
- García-Dorado D, Andres-Villarreal M, Ruiz-Meana M, Inserte J, and Barba I (2012) Myocardial edema: a translational view. *J Mol Cell Cardiol* **52**:931-939.
- García-Prieto J, García-Ruiz JM, Sanz-Rosa D, Pun A, García-Alvarez A, Davidson SM, Fernández-Friera L, Nuno-Ayala M, Fernández-Jiménez R, Bernal JA et al. (2014) β_3 adrenergic receptor selective stimulation during ischemia/reperfusion improves cardiac function in translational models through inhibition of mPTP opening in cardiomyocytes. *Basic Res Cardiol* **109**:422.
- García-Prieto J, Villena-Gutiérrez R, Gómez M, Bernardo E, Pun-García A, García-Lunar I, Crainiciuc G, Fernández-Jiménez R, Sreeramkumar V, Bourio-Martínez R et al. (2017) Neutrophil stunning by metoprolol reduces infarct size. *Nat Commun* **8**:14780.
- García-Ruiz JM, Fernández-Jiménez R, García-Alvarez A, Pizarro G, Galán-Arriola C, Fernández-Friera L, Mateos A, Nuno-Ayala M, Agüero J, Sánchez-González J et al. (2016) Impact of the timing of metoprolol administration during STEMI on infarct size and ventricular function. *J Am Coll Cardiol* **67**:2093-2104.
- García Del Blanco B, Otaegui I, Rodríguez-Palomares JF, Bayés-Genis A, Fernández-Nofreñas E, Vilalta Del Olmo V, Carrillo X, Ibáñez B, Wornor F, Casanova J et al. (2021) Effect of COMBination therapy with remote ischemic conditioning and xenatide on the myocardial infarct size: a two-by-two factorial randomized trial (COMBAT-MI). *Basic Res Cardiol* **116**:4.
- Gaspar A, Lourenço AP, Pereira MA, Azevedo P, Roncon-Albuquerque R Jr, Marques J, and Leite-Moreira AF (2018) Randomized controlled trial of remote ischaemic conditioning in ST-elevation myocardial infarction as adjuvant to primary angioplasty (RIC-STEMI). *Basic Res Cardiol* **113**:14.
- Gatica D, Chiong M, Lavandero S, and Klionsky DJ (2022) The role of autophagy in cardiovascular pathology. *Cardiovasc Res* **118**:934-950.
- Gattullo D, Linden RJ, Losano G, Pagliaro P, and Westerhof N (1999) Ischaemic preconditioning changes the pattern of coronary reactive hyperaemia in the goat: role of adenosine and nitric oxide. *Cardiovasc Res* **42**:57-64.
- Ge Z, Baber U, Claessen BE, Farhan S, Chandrasekhar J, Li SX, Sartori S, Kini AS, Rao SV, Weiss S et al. (2019) The prevalence, predictors and outcomes of guideline-directed medical therapy in patients with acute myocardial infarction undergoing PCI: an analysis from the PROMETHEUS registry. *Catheter Cardiovasc Interv* **93**:E112-E119.
- Ge ZD, Li Y, Qiao S, Bai X, Warltier DC, Kersten JR, Bosnjak ZJ, and Liang M (2018) Failure of isoflurane cardiac preconditioning in obese type 2 diabetic mice involves aberrant regulation of microRNA-21, endothelial nitric-oxide synthase, and mitochondrial complex I. *Anesthesiology* **128**:117-129.
- Gelpi RJ, Morales C, Cohen MV, and Downey JM (2002) Xanthine oxidase contributes to preconditioning's preservation of left ventricular developed pressure in isolated rat heart: developed pressure may not be an appropriate end-point for studies of preconditioning. *Basic Res Cardiol* **97**:40-46.
- Ghaffari S, Kazemi B, Toluey M, and Sepelhrvand N (2013) The effect of prethrombolytic cyclosporine-A injection on clinical outcome of acute anterior ST-elevation myocardial infarction. *Cardiovasc Ther* **31**:e34-e39.

- Ghahremani R, Damirchi A, Salehi I, Komaki A, and Esposito F (2018) Mitochondrial dynamics as an underlying mechanism involved in aerobic exercise training-induced cardioprotection against ischemia-reperfusion injury. *Life Sci* **213**:102–108.
- Giannakopoulos G and Noble S (2021) Should we be using upstream beta-blocker therapy for acute myocardial infarction? *Curr Cardiol Rep* **23**:66.
- Gibson CM, Giugliano RP, Kloner RA, Bode C, Tendera M, Jánosi A, Merkely B, Godlewski J, Halaby R, Korjian S et al. (2016) EMBRACE STEMI study: a phase 2a trial to evaluate the safety, tolerability, and efficacy of intravenous MTP-131 on reperfusion injury in patients undergoing primary percutaneous coronary intervention. *Eur Heart J* **37**:1296–1303.
- Giorgio V, von Stockum S, Antoniel M, Fabbro A, Fogolari F, Forte M, Glick GD, Petronilli V, Zoratti M, Szabó I et al. (2013) Dimers of mitochondrial ATP synthase form the permeability transition pore. *Proc Natl Acad Sci USA* **110**:5887–5892.
- Giricz Z, Koncos G, Rajtik T, Varga ZV, Baranyai T, Csoska C, Szobi A, Adameová A, Gottlieb RA, and Ferdinandy P (2017) Hypercholesterolemia downregulates autophagy in the rat heart. *Lipids Health Dis* **16**:60.
- Giricz Z, Lalu MM, Csoska C, Bencsik P, Schulz R, and Ferdinandy P (2006) Hyperlipidemia attenuates the infarct size-limiting effect of ischemic preconditioning: role of matrix metalloproteinase-2 inhibition. *J Pharmacol Exp Ther* **316**:154–161.
- Giricz Z, Varga ZV, Baranyai T, Sipos P, Pálóczi K, Kittel Á, Buzás EI, and Ferdinandy P (2014) Cardioprotection by remote ischemic preconditioning of the rat heart is mediated by extracellular vesicles. *J Mol Cell Cardiol* **68**:75–78.
- Godoy-Marin H, Duroux R, Jacobson KA, Soler C, Colino-Lage H, Jiménez-Sábado V, Montiel J, Hove-Madsen L, and Ciruela F (2021) Adenosine A_{2A} receptors are upregulated in peripheral blood mononuclear cells from atrial fibrillation patients. *Int J Mol Sci* **22**:3467.
- Goette A, Bukowska A, Dobrev D, Pfeiffenberger J, Morawietz H, Strugala D, Wiswedel I, Röhl FW, Wolke C, Bergmann S et al. (2009) Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles. *Eur Heart J* **30**:1411–1420.
- Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D et al. (2017) EHRA/HRS/APHS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Heart Rhythm* **14**:e3–e40.
- Gömöri K, Szabados T, Kenyeres É, Pipis J, Földesi I, Siska A, Dormán G, Ferdinandy P, Görbe A, and Bencsik P (2020) Cardioprotective effect of novel matrix metalloproteinase inhibitors. *Int J Mol Sci* **21**:6990.
- González Arbeláez LF, Ciocci Pardo A, Fantinelli JC, and Mosca SM (2016) Cyclosporine-A mimicked the ischemic pre- and postconditioning-mediated cardioprotection in hypertensive rats: role of PKC ϵ . *Exp Mol Pathol* **100**:266–275.
- Görgens SW, Eckardt K, Jensen J, Drevon CA, and Eckel J (2015) Exercise and regulation of adipokine and myokine production. *Prog Mol Biol Transl Sci* **135**:313–336.
- Gorog DA, Farag M, Spinthakis N, Yellon DM, Bøtker HE, Kharbada RK, and Hausenloy DJ (2021) Effect of remote ischaemic conditioning on platelet reactivity and endogenous fibrinolysis in ST-elevation myocardial infarction: a substudy of the CONDI-2/ERIC-PPCI randomized controlled trial. *Cardiovasc Res* **117**:623–634.
- Goto M, Miura S, Suematsu Y, Idemoto Y, Takata K, Imaizumi S, Uehara Y, and Saku K (2016) Rivaroxaban, a factor Xa inhibitor, induces the secondary prevention of cardiovascular events after myocardial ischemia reperfusion injury in mice. *Int J Cardiol* **220**:602–607.
- Granfeldt A, Jiang R, Wang NP, Mykytenko J, Eldaif S, Deneve J, Zhao ZQ, Guyton RA, Tønnesen E, and Vinten-Johansen J (2012) Neutrophil inhibition contributes to cardioprotection by postconditioning. *Acta Anaesthesiol Scand* **56**:48–56.
- Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S et al.; TECOS Study Group (2015) Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* **373**:232–242.
- Gribble FM and Ashcroft FM (1999) Differential sensitivity of beta-cell and extrapancreatic K(ATP) channels to gliclazide. *Diabetologia* **42**:845–848.
- Grievink H, Kuzmina N, Chevion M, and Drenger B (2019) Sevoflurane postconditioning is not mediated by ferritin accumulation and cannot be rescued by simvastatin in isolated streptozotocin-induced diabetic rat hearts. *PLoS One* **14**:e0211238.
- Groennebaek T, Sieljacks P, Nielsen R, Pryds K, Jespersen NR, Wang J, Carlsen CR, Schmidt MR, de Paoli FV, Miller BF et al. (2019) Effect of blood flow restricted resistance exercise and remote ischemic conditioning on functional capacity and myocellular adaptations in patients with heart failure. *Circ Heart Fail* **12**:e006427.
- Guerci AD, Ciuffo AA, DiPaula AF, and Weisfeldt ML (1987) Intermittent coronary sinus occlusion in dogs: reduction of infarct size 10 days after reperfusion. *J Am Coll Cardiol* **9**:1075–1081.
- Guiou R, Deharo JC, Maille B, Crotti L, Torresani E, Brignole M, and Parati G (2020) Adenosine and the cardiovascular system: the good and the bad. *J Clin Med* **9**:1336.
- Guillou S, Beaumont J, Tamareille S, Giraud S, Mirebeau-Prunier D, Prunier F, and Macchi L (2020) Direct rivaroxaban-induced factor XA inhibition proves to be cardioprotective in rats. *Shock* **53**:730–736.
- Guo J, Zhu J, Ma L, Shi H, Hu J, Zhang S, Hou L, Xu F, An Y, Yu H et al. (2018) Chronic kidney disease exacerbates myocardial ischemia reperfusion injury: role of endoplasmic reticulum stress-mediated apoptosis. *Shock* **49**:712–720.
- Gupta V, Goyal R, and Sharma PL (2015) Preconditioning offers cardioprotection in hyperlipidemic rat hearts: possible role of dopamine (D2) signaling. *BMC Cardiovasc Disord* **15**:77.
- Gurel E, Smeele KM, Eerbeek O, Koeman A, Demirci C, Hollmann MW and Zuurbier CJ (2009) Ischemic preconditioning affects hexokinase activity and HKII in different subcellular compartments throughout cardiac ischemia-reperfusion. *J Appl Physiol* (1985) **106**:1909–1916.
- Gurel E, Ustunova S, Kapucu A, Yilmazer N, Eerbeek O, Nederlof R, Hollmann MW, Demirci-Tansel C, and Zuurbier CJ (2013) Hexokinase cellular trafficking in ischemia-reperfusion and ischemic preconditioning is altered in type I diabetic heart. *Mol Biol Rep* **40**:4153–4160.
- Guth BD, Martin JF, Heusch G, and Ross J Jr (1987) Regional myocardial blood flow, function and metabolism using phosphorus-31 nuclear magnetic resonance spectroscopy during ischemia and reperfusion in dogs. *J Am Coll Cardiol* **10**:673–681.
- Habibi J, Aroor AR, Sowers JR, Jia G, Hayden MR, Garro M, Barron B, Mayoux E, Rector RS, Whaley-Connell A et al. (2017) Sodium glucose transporter 2 (SGLT2) inhibition with empagliflozin improves cardiac diastolic function in a female rodent model of diabetes. *Cardiovasc Diabetol* **16**:9.
- Hadebe N, Cour M, and Lecour S (2018) The SAFE pathway for cardioprotection: is this a promising target? *Basic Res Cardiol* **113**:9.
- Hagar JM, Hale SL, and Kloner RA (1991) Effect of preconditioning ischemia on reperfusion arrhythmias after coronary artery occlusion and reperfusion in the rat. *Circ Res* **68**:61–68.
- Hale SL, Herring MJ, and Kloner RA (2013) Delayed treatment with hypothermia protects against the no-reflow phenomenon despite failure to reduce infarct size. *J Am Heart Assoc* **2**:e004234.
- Hale SL and Kloner RA (2015) Dabigatran treatment: effects on infarct size and the no-reflow phenomenon in a model of acute myocardial ischemia/reperfusion. *J Thromb Thrombolysis* **39**:50–54.
- Halestrap AP and Richardson AP (2015) The mitochondrial permeability transition: a current perspective on its identity and role in ischaemia/reperfusion injury. *J Mol Cell Cardiol* **78**:129–141.
- Han R, Liu X, Yin X, Zheng M, Sun K, Liu X, Tian Y, and Yang X (2016) Effect of remote ischemic preconditioning on myocardial injury and inflammatory response induced by ablation for atrial fibrillation: a randomized controlled trial. *Int J Cardiol* **222**:396–400.
- Han R, Liu X, Zheng M, Zhao R, Liu X, Yin X, Liu X, Tian Y, Shi L, Sun K et al. (2018) Effect of remote ischemic preconditioning on left atrial remodeling and prothrombotic response after radiofrequency catheter ablation for atrial fibrillation. *Pacing Clin Electrophysiol* **41**:246–254.
- Han Z, Cao J, Song D, Tian L, Chen K, Wang Y, Gao L, Yin Z, Fan Y, and Wang C (2014) Autophagy is involved in the cardioprotection effect of remote limb ischemic postconditioning on myocardial ischemia/reperfusion injury in normal mice, but not diabetic mice. *PLoS One* **9**:e86838.
- Hanley PJ and Loiselle DS (1998) Mechanisms of force inhibition by halothane and isoflurane in intact rat cardiac muscle. *J Physiol* **506**:231–244.
- Hansson MJ, Llywyd O, Morin D, de Paulis D, Arnoux T, Gouarné C, Koul S, Engblom H, Bordet T, Tissier R et al. (2015) Differences in the profile of protection afforded by TRO40303 and mild hypothermia in models of cardiac ischemia/reperfusion injury. *Eur J Pharmacol* **760**:7–19.
- Hara T, Fukuda D, Tanaka K, Higashikuni Y, Hirata Y, Nishimoto S, Yagi S, Yamada H, Soeki T, Wakatsuki T et al. (2015) Rivaroxaban, a novel oral anticoagulant, attenuates atherosclerotic plaque progression and destabilization in ApoE-deficient mice. *Atherosclerosis* **242**:639–646.
- Hashikata T, Yamaoka-Tojo M, Namba S, Kitasato L, Kameda R, Murakami M, Niwano H, Shimohama T, Tojo T, and Aki J (2015) Rivaroxaban inhibits angiotensin II-induced activation in cultured mouse cardiac fibroblasts through the modulation of NF- κ B pathway. *Int Heart J* **56**:544–550.
- Hauerslev M, Mørk SR, Pryds K, Contractor H, Hansen J, Jespersen NR, Johnsen J, Heusch G, Kleinbongard P, Kharbada R et al. (2018) Influence of long-term treatment with glyceryl trinitrate on remote ischemic conditioning. *Am J Physiol Heart Circ Physiol* **315**:H150–H158.
- Hausenloy DJ, Kunst G, Boston-Griffiths E, Kolvekar S, Chaubey S, John L, Desai J, and Yellon D (2014) The effect of cyclosporin-A on peri-operative myocardial injury in adult patients undergoing coronary artery bypass graft surgery: a randomised controlled clinical trial. *Heart* **100**:544–549.
- Hausenloy DJ, Barrabes JA, Bøtker HE, Davidson SM, Di Lisa F, Downey J, Engstrøm T, Ferdinandy P, Carbrera-Fuentes HA, Heusch G et al. (2016) Ischaemic conditioning and targeting reperfusion injury: a 30 year voyage of discovery. *Basic Res Cardiol* **111**:70.
- Hausenloy DJ, Bøtker HE, Ferdinandy P, Heusch G, Ng GA, Redington A, and Garcia-Dorado D (2019) Cardiac innervation in acute myocardial ischaemia/reperfusion injury and cardioprotection. *Cardiovasc Res* **115**:1167–1177.
- Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J et al.; ERICCA Trial Investigators (2015) Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med* **373**:1408–1417.
- Hausenloy DJ, Chilian W, Crea F, Davidson SM, Ferdinandy P, Garcia-Dorado D, van Royen N, Schulz R, and Heusch G (2019) The coronary circulation in acute myocardial ischaemia/reperfusion injury: a target for cardioprotection. *Cardiovasc Res* **115**:1143–1155.
- Hausenloy DJ, Garcia-Dorado D, Bøtker HE, Davidson SM, Downey J, Engel FB, Jennings R, Lecour S, Leor J, Madonna R et al. (2017) Novel targets and future strategies for acute cardioprotection: position paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart. *Cardiovasc Res* **113**:564–585.
- Hausenloy DJ, Kharbada RK, Møller UK, Ramlall M, Aarøe J, Butler R, Bulluck H, Clayton T, Dana A, Dodd M et al.; CONDI-2/ERIC-PPCI Investigators (2019) Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial. *Lancet* **394**:1415–1424.
- Hausenloy DJ, Maddock HL, Baxter GF, and Yellon DM (2002) Inhibiting mitochondrial permeability transition pore opening: a new paradigm for myocardial preconditioning? *Cardiovasc Res* **55**:534–543.
- Hausenloy DJ, Mwamure PK, Venugopal V, Harris J, Barnard M, Grundy E, Ashley E, Vichare S, Di Salvo C, Kolvekar S et al. (2007) Effect of remote

- ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet* **370**:575–579.
- Hausenloy DJ, Ntseke M, and Yellon DM (2020) A future for remote ischaemic conditioning in high-risk patients. *Basic Res Cardiol* **115**:35.
- Hausenloy DJ, Whittington HJ, Wynne AM, Begum SS, Theodorou L, Riksen N, Mocanu MM, and Yellon DM (2013) Dipeptidyl peptidase-4 inhibitors and GLP-1 reduce myocardial infarct size in a glucose-dependent manner. *Cardiovasc Diabetol* **12**:154.
- Hausenloy DJ and Yellon DM (2004) New directions for protecting the heart against ischaemia-reperfusion injury: targeting the reperfusion injury salvage kinase (RISK)-pathway. *Cardiovasc Res* **61**:448–460.
- Hausenloy DJ and Yellon DM (2017) Combination therapy to target reperfusion injury after ST-segment-elevation myocardial infarction: a more effective approach to cardioprotection. *Circulation* **136**:904–906.
- Hausenloy DJ, Yellon DM, Mani-Babu S, and Duchon MR (2004) Preconditioning protects by inhibiting the mitochondrial permeability transition. *Am J Physiol Heart Circ Physiol* **287**:H841–H849.
- He W and Chu Y (2017) Atrial fibrillation as a prognostic indicator of myocardial infarction and cardiovascular death: a systematic review and meta-analysis. *Sci Rep* **7**:3360.
- He Z, Davidson SM, and Yellon DM (2020) The importance of clinically relevant background therapy in cardioprotective studies. *Basic Res Cardiol* **115**:69.
- Headrick JP, See Hoe LE, Du Toit EF, and Peart JN (2015) Opioid receptors and cardioprotection—“opioidergic conditioning” of the heart. *Br J Pharmacol* **172**:2026–2050.
- Hegyesi H, Pallinger É, Mecsei S, Hornyák B, Kovácsázi C, Brenner GB, Giricz Z, Pálóci K, Kittel A, Tóvári J et al. (2022) Circulating cardiomyocyte-derived extracellular vesicles reflect cardiac injury during systemic inflammatory response syndrome in mice. *Cell Mol Life Sci* **79**:84.
- Heijman J, Muna AP, Veleva T, Molina CE, Sutanto H, Tekook M, Wang Q, Abu-Taha IH, Gorka M, Künzel S et al. (2020) Atrial myocyte NLRP3/CaMKII nexus forms a substrate for postoperative atrial fibrillation. *Circ Res* **127**:1036–1055.
- Heinen A, Behmenburg F, Aytulun A, Dierkes M, Zerbin L, Kaisers W, Schaefer M, Meyer-Treschan T, Feit S, Bauer I et al. (2018) The release of cardioprotective humoral factors after remote ischemic preconditioning in humans is age- and sex-dependent. *J Transl Med* **16**:112.
- Heinzel FR, Luo Y, Li X, Boengler K, Buechert A, Garcia-Dorado D, Di Lisa F, Schulz R, and Heusch G (2005) Impairment of diazoxide-induced formation of reactive oxygen species and loss of cardioprotection in connexin 43 deficient mice. *Circ Res* **97**:583–586.
- Hernandez-Resendiz S, Prunier F, Girao H, Dorn G, Hausenloy DJ; EU-CARDIOPROTECTION COST Action (CA16225) (2020) Targeting mitochondrial fusion and fission proteins for cardioprotection. *J Cell Mol Med* **24**:6571–6585.
- Hernández-Reséndiz S, Roldán FJ, Correa F, Martínez-Abundis E, Osorio-Valencia G, Ruiz-de-Jesus O, Alexanderson-Rosas E, Viguera RM, Franco M, and Zazueta C (2013) Postconditioning protects against reperfusion injury in hypertensive dilated cardiomyopathy by activating MEK/ERK1/2 signaling. *J Card Fail* **19**:135–146.
- Herrett E, Bhaskaran K, Timmis A, Denaxas S, Hemingway H, and Smeeth L (2014) Association between clinical presentations before myocardial infarction and coronary mortality: a prospective population-based study using linked electronic records. *Eur Heart J* **35**:2363–2371.
- Herrmann J, Lerman A, Baumgart D, Volbracht L, Schulz R, von Birgelen C, Haude M, Heusch G, and Erbel R (2002) Preprocedural statin medication reduces the extent of periprocedural non-Q-wave myocardial infarction. *Circulation* **106**:2180–2183.
- Heusch G (2001) Nitroglycerin and delayed preconditioning in humans: yet another new mechanism for an old drug? *Circulation* **103**:2876–2878.
- Heusch G (2012) Reduction of infarct size by ischaemic post-conditioning in humans: fact or fiction? *Eur Heart J* **33**:13–15.
- Heusch G (2015) Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. *Circ Res* **116**:674–699.
- Heusch G (2016) The coronary circulation as a target of cardioprotection. *Circ Res* **118**:1643–1658.
- Heusch G (2017) Critical issues for the translation of cardioprotection. *Circ Res* **120**:1477–1486.
- Heusch G (2018) Cardioprotection research must leave its comfort zone. *Eur Heart J* **39**:3393–3395.
- Heusch G (2019a) Coronary microvascular obstruction: the new frontier in cardioprotection. *Basic Res Cardiol* **114**:45.
- Heusch G (2019b) Myocardial ischemia: lack of coronary blood flow, myocardial oxygen supply-demand imbalance, or what? *Am J Physiol Heart Circ Physiol* **316**:H1439–H1446.
- Heusch G (2019c) The spleen in myocardial infarction. *Circ Res* **124**:26–28.
- Heusch G (2020) Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nat Rev Cardiol* **17**:773–789.
- Heusch G, Bötter HE, Przyklenk K, Redington A, and Yellon D (2015) Remote ischemic conditioning. *J Am Coll Cardiol* **65**:177–195.
- Heusch G and Gersh BJ (2017) The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. *Eur Heart J* **38**:774–784.
- Heusch G and Gersh BJ (2020) Is cardioprotection salvageable? *Circulation* **141**:415–417.
- Heusch G and Kleinbongard P (2020) Is metoprolol more cardioprotective than other beta-blockers? *Eur Heart J* **41**:4441–4443.
- Heusch G, Libby P, Gersh B, Yellon D, Böhm M, Lopuschek G, and Opie L (2014) Cardiovascular remodelling in coronary artery disease and heart failure. *Lancet* **383**:1933–1943.
- Heusch G, Musiolik J, Gedik N, and Skyschally A (2011) Mitochondrial STAT3 activation and cardioprotection by ischemic postconditioning in pigs with regional myocardial ischemia/reperfusion. *Circ Res* **109**:1302–1308.
- Heusch G, Musiolik J, Kottenberg E, Peters J, Jakob H, and Thielmann M (2012) STAT5 activation and cardioprotection by remote ischemic preconditioning in humans: short communication. *Circ Res* **110**:111–115.
- Heusch G and Rassaf T (2016) Time to give up on cardioprotection? A critical appraisal of clinical studies on ischemic pre-, post-, and remote conditioning. *Circ Res* **119**:676–695.
- Higginson LA, White F, Heggveit HA, Sanders TM, Bloor CM, and Covell JW (1982) Determinants of myocardial hemorrhage after coronary reperfusion in the anesthetized dog. *Circulation* **65**:62–69.
- Hirschhäuser C, Lissoni A, Gorge PM, Lampe PD, Heger J, Schlüter KD, Leybaert L, Schulz R, and Boengler K (2021) Connexin 43 phosphorylation by casein kinase 1 is essential for the cardioprotection by ischemic preconditioning. *Basic Res Cardiol* **116**:21.
- Hjortbak MV, Hjort J, Povlsen JA, Jensen RV, Støttrup NB, Laursen MR, Jespersen NR, Løfgren B, and Bøtker HE (2018) Influence of diabetes mellitus duration on the efficacy of ischemic preconditioning in a Zucker diabetic fatty rat model. *PLoS One* **13**:e0192981.
- Hjortbak MV, Olesen KKW, Seefeldt JM, Lassen TR, Jensen RV, Perkins A, Dodd M, Clayton T, Yellon D, Hausenloy DJ et al.; CONDI-2/ERIC-PPCI Investigators (2021) Translation of experimental cardioprotective capability of P2Y₁₂ inhibitors into clinical outcome in patients with ST-elevation myocardial infarction. *Basic Res Cardiol* **116**:36.
- Hoedemakers NP, Roolvink V, de Winter RJ, van Royen N, Fuster V, Garcia-Ruiz JM, Er F, Gassanov N, Hanada K, Okumura K et al. (2020) Early intravenous beta-blockers in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a patient-pooled meta-analysis of randomized clinical trials. *Eur Heart J Acute Cardiovasc Care* **9**:469–477.
- Holmuhamedov EL, Oberlin A, Short K, Terzic A, and Jahangir A (2012) Cardiac subsarcolemmal and interfibrillar mitochondria display distinct responsiveness to protection by diazoxide. *PLoS One* **7**:e44667.
- Honda T, He Q, Wang F, and Redington AN (2019) Acute and chronic remote ischemic conditioning attenuate septic cardiomyopathy, improve cardiac output, protect systemic organs, and improve mortality in a lipopolysaccharide-induced sepsis model. *Basic Res Cardiol* **114**:15.
- Hong DM, Lee EH, Kim HJ, Min JJ, Chin JH, Choi DK, Bahk JH, Sim JY, Choi IC, and Jeon Y (2014) Does remote ischaemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery? Remote ischaemic preconditioning with postconditioning outcome trial. *Eur Heart J* **35**:176–183.
- Hong J, Ge HW, Liu JQ, Sun RH, and Kong FJ (2019) Pharmacological inhibition of PTEN restores remote ischemic postconditioning cardioprotection in hypercholesterolemic mice: potential role of PTEN/AKT/GSK3 β signals. *Shock* **52**:522–531.
- Huang C, Liu Y, Beenken A, Jiang L, Gao X, Huang Z, Hsu A, Gross GJ, Wang YG, Mohammadi M et al. (2017) A novel fibroblast growth factor-1 ligand with reduced heparin binding protects the heart against ischemia-reperfusion injury in the presence of heparin co-administration. *Cardiovasc Res* **113**:1585–1602.
- Ibanez B, Cimmino G, Prat-González S, Vilahur G, Hutter R, Garcia MJ, Fuster V, Sanz J, Badimon L, and Badimon JJ (2011) The cardioprotection granted by metoprolol is restricted to its administration prior to coronary reperfusion. *Int J Cardiol* **147**:428–432.
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Godevenos JA, Halvorsen S et al.; ESC Scientific Document Group (2018) 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* **39**:119–177.
- Ibanez B, Macaya C, Sánchez-Brunete V, Pizarro G, Fernández-Friera L, Mateos A, Fernández-Ortiz A, Garcia-Ruiz JM, Garcia-Álvarez A, Iñiguez A et al. (2013) Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the effect of metoprolol in cardioprotection during an acute myocardial infarction (METOCARD-CNIC) trial. *Circulation* **128**:1495–1503.
- Ibanez B, Prat-González S, Speidl WS, Vilahur G, Pinero A, Cimmino G, García MJ, Fuster V, Sanz J, and Badimon JJ (2007) Early metoprolol administration before coronary reperfusion results in increased myocardial salvage: analysis of ischemic myocardium at risk using cardiac magnetic resonance. *Circulation* **115**:2909–2916.
- Iglesias-Garriz I, Corral F, Rodríguez MA, Garrote C, Montes M, and Sevillano E (2001) Pre-infarction angina elicits greater myocardial viability on reperfusion after myocardial infarction: a dobutamine stress echocardiographic study. *J Am Coll Cardiol* **37**:1846–1850.
- Ikonomidis I, Vlastos D, Andreadou I, Gazouli M, Efentakis P, Varoudi M, Makavos G, Kapelouzou A, Lekakis J, Parissis J et al. (2021) Vascular conditioning prevents adverse left ventricular remodelling after acute myocardial infarction: a randomised remote conditioning study. *Basic Res Cardiol* **116**:9.
- Iliodromitis EK, Andreadou I, Prokova E, Zoga A, Farmakis D, Fotopoulou T, Ioannidis K, Paraskevaidis IA, and Kremastinos DT (2010) Simvastatin in contrast to postconditioning reduces infarct size in hyperlipidemic rabbits: possible role of oxidative/nitrosative stress attenuation. *Basic Res Cardiol* **105**:193–203.
- Iliodromitis EK, Zoga A, Vrettou A, Andreadou I, Paraskevaidis IA, Kakkamanis L, and Kremastinos DT (2006) The effectiveness of postconditioning and preconditioning on infarct size in hypercholesterolemic and normal anesthetized rabbits. *Atherosclerosis* **188**:356–362.
- Insarte J, Hernando V, Ruiz-Meana M, Poncelas-Nozal M, Fernández C, Agulló L, Sartorio C, Vilarrosa U, and Garcia-Dorado D (2014) Delayed phospholamban phosphorylation in post-conditioned heart favours Ca²⁺ normalization and contributes to protection. *Cardiovasc Res* **103**:542–553.

- Inserte J, Hernando V, Vilardosa Ú, Abad E, Poncelas-Nozal M, and Garcia-Dorado D (2013) Activation of cGMP/protein kinase G pathway in postconditioned myocardium depends on reduced oxidative stress and preserved endothelial nitric oxide synthase coupling. *J Am Heart Assoc* **2**:e005975.
- Inserte J, Ruiz-Meana M, Rodriguez-Sinovas A, Barba I, and Garcia-Dorado D (2011) Contribution of delayed intracellular pH recovery to ischemic postconditioning protection. *Antioxid Redox Signal* **14**:923–939.
- Interleukin-6 Receptor Mendelian Randomisation Analysis Consortium, Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JE, Shah T, Sofat R, Guo Y, Chung C, Peasey A, et al. (2012) The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet* **379**:1214–1224.
- International Collaborative Study Group (1984) Reduction of infarct size with the early use of timolol in acute myocardial infarction. *N Engl J Med* **310**:9–15.
- Iqbal H, Straw S, Craven TP, Stirling K, Wheatcroft SB, and Witte KK (2020) Direct oral anticoagulants compared to vitamin K antagonist for the management of left ventricular thrombus. *ESC Heart Fail* **7**:2032–2041.
- Ishihara M, Sato H, Tateishi H, Kawagoe T, Shimatani Y, Ueda K, Noma K, Yumoto A, and Nishioka K (2000) Beneficial effect of prodromal angina pectoris is lost in elderly patients with acute myocardial infarction. *Am Heart J* **139**:881–888.
- Itoh H, Ueda M, Suzuki M, and Kohmura-Kobayashi Y (2022) Developmental origins of metaflammation; a bridge to the future between the DOHaD theory and evolutionary biology. *Front Endocrinol (Lausanne)* **13**:839436.
- Itoh T, Kouzu H, Miki T, Tanno M, Kuno A, Sato T, Sunaga D, Murase H, and Miura T (2012) Cytoprotective regulation of the mitochondrial permeability transition pore is impaired in type 2 diabetic Goto-Kakizaki rat hearts. *J Mol Cell Cardiol* **53**:870–879.
- Jalowy A, Schulz R, Dörge H, Behrends M, and Heusch G (1998) Infarct size reduction by AT1-receptor blockade through a signal cascade of AT2-receptor activation, bradykinin and prostaglandins in pigs. *J Am Coll Cardiol* **32**:1787–1796.
- Janssens SP, Bogaert J, Zalewski J, Toth A, Adriaenssens T, Belmans A, Bennett J, Claus P, Desmet W, Dubois C et al.; NOMI investigators (2018) Nitric oxide for inhalation in ST-elevation myocardial infarction (NOMI): a multicenter, double-blind, randomized controlled trial. *Eur Heart J* **39**:2717–2725.
- Jenkins DP, Pugsley WB, Alkhalaf AM, Kemp M, Hooper J, and Yellon DM (1997) Ischaemic preconditioning reduces troponin T release in patients undergoing coronary artery bypass surgery. *Heart* **77**:314–318.
- Jensen RV, Støttrup NB, Kristiansen SB, and Bøtker HE (2012) Release of a humoral circulating cardioprotective factor by remote ischemic preconditioning is dependent on preserved neural pathways in diabetic patients. *Basic Res Cardiol* **107**:285.
- Jensen RV, Zachara NE, Nielsen PH, Kimose HH, Kristiansen SB, and Bøtker HE (2013) Impact of O-GlcNAc on cardioprotection by remote ischaemic preconditioning in non-diabetic and diabetic patients. *Cardiovasc Res* **97**:369–378.
- Ji L, Zhang X, Liu W, Huang Q, Yang W, Fu F, Ma H, Su H, Wang H, Wang J et al. (2013) AMPK-regulated and Akt-dependent enhancement of glucose uptake is essential in ischemic preconditioning-alleviated reperfusion injury. *PLoS One* **8**:e69910.
- Jones DA, Pellaton C, Velmurugan S, Rathod KS, Andiapan M, Antoniou S, van Eijl S, Webb AJ, Westwood MA, Parmar MK et al. (2015) Randomized phase 2 trial of intracoronary nitrite during acute myocardial infarction. *Circ Res* **116**:437–447.
- Jones DA, Wright P, Alizadeh MA, Fhadil S, Rathod KS, Guttman O, Knight C, Timmis A, Baumbach A, Wrang A et al. (2021) The use of novel oral anticoagulants compared to vitamin K antagonists (warfarin) in patients with left ventricular thrombus after acute myocardial infarction. *Eur Heart J Cardiovasc Pharmacother* **7**:398–404.
- Jones H, Hopkins N, Bailey TG, Green DJ, Cable NT, and Thijssen DH (2014) Seven-day remote ischemic preconditioning improves local and systemic endothelial function and microcirculation in healthy humans. *Am J Hypertens* **27**:918–925.
- Jones SP, Tang XL, Guo Y, Steenbergen C, Lefler DJ, Kukreja RC, Kong M, Li Q, Bhushan S, Zhu X et al. (2015) The NHLBI-sponsored Consortium for preclinical assessment of cardioprotective therapies (CAESAR): a new paradigm for rigorous, accurate, and reproducible evaluation of putative infarct-sparing interventions in mice, rabbits, and pigs. *Circ Res* **116**:572–586.
- Jong WM, Leemans JC, Weber NC, Juffermans NP, Schultz MJ, Hollmann MW, and Zuurbier CJ (2014) Nlrp3 plays no role in acute cardiac infarction due to low cardiac expression. *Int J Cardiol* **177**:41–43.
- Joseph JJ, Deedwania P, Acharya T, Aguilar D, Bhatt DL, Chyun DA, Di Palo KE, Golden SH, and Sperling LS; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; and Council on Hypertension (2022) Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a scientific statement from the American Heart Association. *Circulation* **145**:e722–e759.
- Jusic A, Devaux Y; Action EU-CC; EU-CardioRNA COST Action (CA17129) (2020) Mitochondrial noncoding RNA-regulatory network in cardiovascular disease. *Basic Res Cardiol* **115**:23.
- Kaefler N, Richard V, François A, Lallemand F, Henry JP, and Thuillez C (1996) Preconditioning prevents chronic reperfusion-induced coronary endothelial dysfunction in rats. *Am J Physiol* **271**:H842–H849.
- Kaefler N, Richard V, and Thuillez C (1997) Delayed coronary endothelial protection 24 hours after preconditioning: role of free radicals. *Circulation* **96**:2311–2316.
- Kahlert P, Hildebrandt HA, Patsalis PC, Al-Rashid F, János RA, Nensa F, Schlosser TW, Schlamann M, Wendt D, Thielmann M et al. (2017) No protection of heart, kidneys and brain by remote ischemic preconditioning before transfemoral transcatheter aortic valve implantation: Interim-analysis of a randomized single-blinded, placebo-controlled, single-center trial. *Int J Cardiol* **231**:248–254.
- Kaljusto ML, Bautin A, Jakobsen I, Wilimski R, Brunborg C, Wennemo M, Karpova L, Nergaard Aas K, Arendarczyk A, Landsverk SA et al. (2022) Effects of ischaemic postconditioning in aortic valve replacement: a multicenter randomized controlled trial. *Eur J Cardiothorac Surg* **61**:1144–1152.
- Kallergis EM, Manios EG, Kanoupakis EM, Mavrakis HE, Kolyvaki SG, Lyrarakis GM, Chlouverakis GI, and Vardas PE (2008) The role of the post-cardioversion time course of HS-CRP levels in clarifying the relationship between inflammation and persistence of atrial fibrillation. *Heart* **94**:200–204.
- Kanie T, Mizuno A, Takaoka Y, Suzuki T, Yoneoka D, Nishikawa Y, Tam WWS, Morze J, Rynkiewicz A, Xin Y et al. (2021) Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors for people with cardiovascular disease: a network meta-analysis. *Cochrane Database Syst Rev* **10**:CD013650.
- Kansal SK, Jyoti U, Sharma S, Kaura A, Deshmukh R, and Goyal S (2015) Effect of zinc supplements in the attenuated cardioprotective effect of ischemic preconditioning in hyperlipidemic rat heart. *Naunyn-Schmiedeberg's Arch Pharmacol* **388**:635–641.
- Kapur NK, Alkhouli MA, DeMartini TJ, Faraz H, George ZH, Goodwin MJ, Hernandez-Montfort JA, Iyer VS, Josephy N, Kalra S et al. (2019) Unloading the left ventricle before reperfusion in patients with anterior ST-segment-elevation myocardial infarction. *Circulation* **139**:337–346.
- Karila-Cohen D, Czotrom D, Brochet E, Faraggi M, Seknadji P, Himbert D, Juliard J-M, Assayag P, and Steg PG (1999) Decreased non-reflow in patients with anterior myocardial infarction and pre-infarction angina. *Eur Heart J* **20**:1724–1730.
- Karlsson LO, Zhou AX, Larsson E, Åström-Olsson K, Månsson C, Åkyrök LM, and Grip L (2010) Cyclosporine does not reduce myocardial infarct size in a porcine ischemia-reperfusion model. *J Cardiovasc Pharmacol Ther* **15**:182–189.
- Kaski JC, Crea F, Gersh BJ, and Camici PG (2018) Reappraisal of ischemic heart disease. *Circulation* **138**:1463–1480.
- Kaudewitz D, Skrobilin P, Bender LH, Barwari T, Willeit P, Pechlaner R, Sunderland NP, Willeit K, Morton AC, Armstrong PC et al. (2016) Association of MicroRNAs and YRNAs with platelet function. *Circ Res* **118**:420–432.
- Kawaguchi M, Takahashi M, Hata T, Kashima Y, Usui F, Morimoto H, Izawa A, Takahashi Y, Masumoto J, Koyama J et al. (2011) Inflammation activation of cardiac fibroblasts is essential for myocardial ischemia/reperfusion injury. *Circulation* **123**:594–604.
- Kelle I, Akkoç H, Uyar E, Erdiç M, Evliyaoglu O, Sarıbaş S, Tunik S, and Özoğul C (2015) The combined effect of rosuvastatin and ischemic pre- or post-conditioning on myocardial ischemia-reperfusion injury in rat heart. *Eur Rev Med Pharmacol Sci* **219**:468–2476.
- Kersten JR, Montgomery MW, Ghassemi T, Gross ER, Toller WG, Pagel PS, and Warltier DC (2001) Diabetes and hyperglycemia impair activation of mitochondrial K(ATP) channels. *Am J Physiol Heart Circ Physiol* **280**:H1744–H1750.
- Keul P, van Borren MM, Ghanem A, Müller FU, Baartscheer A, Verkerk AO, Stümpel F, Schulte JS, Hamdani N, Linke WA et al. (2016) Sphingosine-1-phosphate receptor 1 regulates cardiac function by modulating Ca²⁺ sensitivity and Na⁺/H⁺ exchange and mediates protection by ischemic preconditioning. *J Am Heart Assoc* **5**:e003393.
- Khan SU, Arshad A, Riaz IB, Talluri S, Nasir F, and Kaluski E (2018) Meta-analysis of the safety and efficacy of the oral anticoagulant agents (apixaban, rivaroxaban, dabigatran) in patients with acute coronary syndrome. *Am J Cardiol* **121**:301–307.
- Kharbada RK, Peters M, Walton B, Kattenhorn M, Mullen M, Klein N, Vallance P, Deanfield J, and MacAllister R (2001) Ischemic preconditioning prevents endothelial injury and systemic neutrophil activation during ischemia-reperfusion in humans in vivo. *Circulation* **103**:1624–1630.
- Khodeer DM, Zaitone SA, Farag NE, and Moustafa YM (2016) Cardioprotective effect of pioglitazone in diabetic and non-diabetic rats subjected to acute myocardial infarction involves suppression of AGE-RAGE axis and inhibition of apoptosis. *Can J Physiol Pharmacol* **94**:463–476.
- Kim EK, Hahn JY, Song YB, Lee SC, Choi JH, Choi SH, Lee SH, Choe YH, and Gwon HC (2015) Effect of ischemic postconditioning on myocardial salvage in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: cardiac magnetic resonance substudy of the POST randomized trial. *Int J Cardiovasc Imaging* **31**:629–637.
- Kim EK, Park TK, Yang JH, Song YB, Choi JH, Choi SH, Chun WJ, Choe YH, Gwon HC, and Hahn JY (2017) Ticagrelor versus clopidogrel on myocardial infarct size in patients undergoing primary percutaneous coronary intervention. *J Am Coll Cardiol* **69**:2098–2099.
- Kim HS, Cho JE, Hwang KC, Shim YH, Lee JH, and Kwak YL (2010) Diabetes mellitus mitigates cardioprotective effects of remifentanyl preconditioning in ischemia-reperfused rat heart in association with anti-apoptotic pathways of survival. *Eur J Pharmacol* **628**:132–139.
- Kim SC, Stice JP, Chen L, Jung JS, Gupta S, Wang Y, Baumgarten G, Trial J, and Knowlton AA (2009) Extracellular heat shock protein 60, cardiac myocytes, and apoptosis. *Circ Res* **105**:1186–1195.
- Kim SJ, Zhang X, Xu X, Chen A, González JB, Koul S, Vijayan K, Crystal GJ, Vatner SF, and Hintze TH (2007) Evidence for enhanced eNOS function in coronary microvessels during the second window of protection. *Am J Physiol Heart Circ Physiol* **292**:H2152–H2158.
- Kim TK, Nam K, Cho YJ, Choi S, Row HS, and Jeon Y (2020) Effect of remote ischaemic conditioning on coagulation function as measured by whole blood impedance aggregometry and rotational thromboelastometry in off-pump coronary artery bypass surgery: a randomised controlled trial. *Thromb Res* **187**:72–78.
- Kim YD, Cha MJ, Kim J, Lee DH, Lee HS, Nam CM, Nam HS, and Heo JH (2011) Ischaemic cardiovascular mortality in patients with non-valvular atrial fibrillation according to CHADS₂ score. *Thromb Haemostasis* **105**:712–720.
- Kim YM, Guzik TJ, Zhang YH, Zhang MH, Kattach H, Ratnatunga C, Pillai R, Channon KM, and Casadei B (2005) A myocardial Nox2 containing NAD(P)H

- oxidase contributes to oxidative stress in human atrial fibrillation. *Circ Res* **97**:629–636.
- Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wehseider K, Boriani G, Brandes A et al. (2012) Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options—a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference. *Europace* **14**:8–27.
- Kiss A, Tratsiakovich Y, Nonon AT, Fedotovskaya O, Lanner JT, Andersson DC, Yang J, and Pernow J (2014) The role of arginase and rho kinase in cardioprotection from remote ischemic preconditioning in non-diabetic and diabetic rat in vivo. *PLoS One* **9**:e104731.
- Kleinbongard P, Amanakis G, Skyschally A, and Heusch G (2018) Reflection of Cardioprotection by Remote Ischemic Preconditioning in Attenuated ST-Segment Elevation During Ongoing Coronary Occlusion in Pigs. *Circ Res* **122**:1102–1108.
- Kleinbongard P, Andreadou I, and Vilahur G (2021) The platelet paradox of injury versus protection in myocardial infarction—has it been overlooked? *Basic Res Cardiol* **116**:37.
- Kleinbongard P, Böse D, Baars T, Möhlenkamp S, Konorza T, Schöner S, Elter-Schulz M, Eggebrecht H, Degen H, Haude M et al. (2011) Vasoconstrictor potential of coronary aspirate from patients undergoing stenting of saphenous vein aortocoronary bypass grafts and its pharmacological attenuation. *Circ Res* **108**:344–352.
- Kleinbongard P, Bøtker HE, Ovize M, Hausenloy DJ, and Heusch G (2020) Comorbidities and co-medications as confounders of cardioprotection—does it matter in the clinical setting? *Br J Pharmacol* **177**:5252–5269.
- Kleinbongard P and Heusch G (2022) A fresh look at coronary microembolization. *Nat Rev Cardiol* **19**:265–280.
- Kleinbongard P, Lieder HR, Skyschally A, Alloosh M, Gödecke A, Rahmann S, Sturek M, and Heusch G (2022a) Non-responsiveness to cardioprotection by ischaemic preconditioning in Ossabaw minipigs with genetic predisposition to, but without the phenotype of the metabolic syndrome. *Basic Res Cardiol* **117**:58.
- Kleinbongard P, Lieder H, Skyschally A, and Heusch G (2022b) No sex-related differences in infarct size, no-reflow and protection by ischaemic preconditioning in Göttingen minipigs. *Cardiovasc Res* cvac062 DOI: 10.1093/cvr/cvac062.
- Kleinbongard P, Neuhäuser M, Thielmann M, Kottenberg E, Peters J, Jakob H, and Heusch G (2016) Confounders of cardioprotection by remote ischemic preconditioning in patients undergoing coronary artery bypass grafting. *Cardiology* **133**:128–133.
- Kleinbongard P, Skyschally A, Gent S, Pesch M, and Heusch G (2017) STAT3 as a common signal of ischemic conditioning: a lesson on “rigor and reproducibility” in preclinical studies on cardioprotection. *Basic Res Cardiol* **113**:3.
- Kleinbongard P, Skyschally A, and Heusch G (2017) Cardioprotection by remote ischemic conditioning and its signal transduction. *Pflügers Arch* **469**:159–181.
- Kleinbongard P, Thielmann M, Jakob H, Peters J, Heusch G, and Kottenberg E (2013) Nitroglycerin does not interfere with protection by remote ischemic preconditioning in patients with surgical coronary revascularization under isoflurane anesthesia. *Cardiovasc Drugs Ther* **27**:359–361.
- Kleveland O, Kunszt G, Bratlie M, Ueland T, Broch K, Holte E, Michelsen AE, Bendz B, Amundsen BH, Espevik T et al. (2016) Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial. *Eur Heart J* **37**:2406–2413.
- Kloner RA, Ganote CE, and Jennings RB (1974) The “no-reflow” phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* **54**:1496–1508.
- Kloner RA and Jennings RB (2001) Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2. *Circulation* **104**:3158–3167.
- Kloner RA, Shook T, Antman EM, Cannon CP, Przyklenk K, Yoo K, McCabe CH, Braunwald E; TIMI-9B Investigators (1998) Prospective temporal analysis of the onset of preinfarction angina versus outcome: an ancillary study in TIMI-9B. *Circulation* **97**:1042–1045.
- Kobayashi S, Xu X, Chen K, and Liang Q (2012) Suppression of autophagy is protective in high glucose-induced cardiomyocyte injury. *Autophagy* **8**:577–592.
- Kong P, Christia P, and Frangogiannis NG (2014) The pathogenesis of cardiac fibrosis. *Cell Mol Life Sci* **71**:549–574.
- Koo EH, Park YC, Lim SH, and Kim HZ (2006) Amiodarone offsets the cardioprotective effects of ischaemic preconditioning against ischaemia/reperfusion injury. *J Int Med Res* **34**:140–151.
- Korantzopoulos P, Letsas KP, Tse G, Fragakis N, Goudis CA, and Liu T (2018) Inflammation and atrial fibrillation: a comprehensive review. *J Arrhythm* **34**:394–401.
- Kottenberg E, Thielmann M, Bergmann L, Heine T, Jakob H, Heusch G, and Peters J (2012) Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol—a clinical trial. *Acta Anaesthesiol Scand* **56**:30–38.
- Kottenberg E, Thielmann M, Kleinbongard P, Frey UH, Heine T, Jakob H, Heusch G, and Peters J (2014) Myocardial protection by remote ischaemic preconditioning is abolished in sulphonylurea-treated diabetics undergoing coronary revascularisation. *Acta Anaesthesiol Scand* **58**:453–462.
- Kouassi Nzougheh J, Bocca C, Simard G, Prunier-Mirebeau D, Chao de la Barca JM, Bonneau D, Procaccio V, Prunier F, Lenaers G, and Reynier P (2017) A nontargeted UHPLC-HRMS metabolomics pipeline for metabolite identification: application to cardiac remote ischemic preconditioning. *Anal Chem* **89**:2138–2146.
- Kreutzer FP, Meinecke A, Schmidt K, Fiedler J, and Thum T (2022) Alternative strategies in cardiac preclinical research and new clinical trial formats. *Cardiovasc Res* **118**:746–762.
- Kristensen KE, Knage CC, Nyhegn LH, Mulder BA, Rienstra M, Van Gelder IC, and Brandes A (2020) Subclinical atherosclerosis is associated with incident atrial fibrillation: a systematic review and meta-analysis. *Europace* **22**:991–1000.
- Kristiansen SB, Pælestik KB, Johnsen J, Jespersen NR, Pryds K, Hjørtbak MV, Jensen RV, and Bøtker HE (2019) Impact of hyperglycemia on myocardial ischemia-reperfusion susceptibility and ischemic preconditioning in hearts from rats with type 2 diabetes. *Cardiovasc Diabetol* **18**:66.
- Krug A, and Korb G; Du Mesnil de Rochemont (1966) Blood supply of the myocardium after temporary coronary occlusion. *Circ Res* **19**:57–62.
- Kumar A, Singh H, and Shariff M (2019) Remote ischemic preconditioning and its role in the prevention of new onset atrial fibrillation post-cardiac surgery: A meta-analysis of randomized control trials. *J Arrhythm* **35**:789–794.
- Kunuthur SP, Mocanu MM, Hemmings BA, Hausenloy DJ, and Yellon DM (2012) The Akt1 isoform is an essential mediator of ischaemic preconditioning. *J Cell Mol Med* **16**:1739–1749.
- Kupai K, Csonka C, Fekete V, Odendaal L, van Rooyen J, Marais W, Csont T, and Ferdinandy P (2009) Cholesterol diet-induced hyperlipidemia impairs the cardioprotective effect of postconditioning: role of peroxynitrite. *Am J Physiol Heart Circ Physiol* **297**:H1729–H1735.
- Kupat D, Wichels R, Horstkotte J, Krombach F, Habazettl H, and Boekstegers P (2002) Molecular mechanisms of platelet-mediated leukocyte recruitment during myocardial reperfusion. *J Leukoc Biol* **72**:455–461.
- Kurzelewski M, Czarnowska E, Maczewski M, and Beresewicz A (1999) Effect of ischemic preconditioning on endothelial dysfunction and granulocyte adhesion in isolated guinea-pig hearts subjected to ischemia/reperfusion. *J Physiol Pharmacol* **50**:617–628.
- Kwok MK and Schooling CM (2021) Mendelian randomization study on atrial fibrillation and cardiovascular disease subtypes. *Sci Rep* **11**:18682.
- Kyrou D, Kolibianakis EM, Fatemi HM, Camus M, Tournaye H, Tarlatzis BC, and Devroey P (2011) High exposure to progesterone between the end of menstruation and the day of triggering final oocyte maturation is associated with a decreased probability of pregnancy in patients treated by in vitro fertilization and intracytoplasmic sperm injection. *Fertil Steril* **96**:884–888.
- Lagranha CJ, Deschamps A, Aponte A, Steenbergen C, and Murphy E (2010) Sex differences in the phosphorylation of mitochondrial proteins result in reduced production of reactive oxygen species and cardioprotection in females. *Circ Res* **106**:1681–1691.
- Lahnwong S, Palee S, Apajai N, Sriwichaiin S, Kerdphoo S, Jaiwongkam T, Chattipakorn SC, and Chattipakorn N (2020) Acute dapagliflozin administration exerts cardioprotective effects in rats with cardiac ischemia/reperfusion injury. *Cardiovasc Diabetol* **19**:91.
- Lange M, Redel A, Lotz C, Smul TM, Blomeyer C, Frank A, Stumpner J, Roewer N, and Kehl F (2009) Desflurane-induced postconditioning is mediated by beta-adrenergic signaling: role of beta 1- and beta 2-adrenergic receptors, protein kinase A, and calcium/calmodulin-dependent protein kinase II. *Anesthesiology* **110**:516–528.
- Lanza GA, Stazi A, Villano A, Torrini F, Milo M, Laurito M, Flego D, Aurigemma C, Liuzzo G, and Crea F (2016) Effect of remote ischemic preconditioning on platelet activation induced by coronary procedures. *Am J Cardiol* **117**:359–365.
- Lassen TR, Hjørtbak MV, Hauerslev M, Tonnesen PT, Kristiansen SB, Jensen RV, and Bøtker HE (2021) Influence of strain, age, origin, and anesthesia on the cardioprotective efficacy by local and remote ischemic conditioning in an ex vivo rat model. *Physiol Rep* **9**:e14810.
- Lassen TR, Just J, Hjørtbak MV, Jespersen NR, Stenz KT, Gu T, Yan Y, Su J, Hansen J, Bæk R et al. (2021) Cardioprotection by remote ischemic conditioning is transferable by plasma and mediated by extracellular vesicles. *Basic Res Cardiol* **116**:16.
- Lauridsen T, Feidenhansl R, and Pinholt EM (2018) Virtual histology uncertainty in synchrotron x-ray micro-computed tomography evaluation. *J Craniomaxillofac Surg* **46**:1569–1575.
- Lecour S (2009) Multiple protective pathways against reperfusion injury: a SAFE path without Aktion? *J Mol Cell Cardiol* **46**:607–609.
- Lecour S, Andreadou I, Bøtker HE, Davidson SM, Heusch G, Ruiz-Meana M, Schulz R, Zuurbier CJ, Ferdinandy P, and Hausenloy DJ; on behalf of the European Union-CARDIOPROTECTION COST Action CA16225 (2021) Improving Preclinical Assessment of Cardioprotective Therapies (IMPACT) criteria: guidelines of the EU-CARDIOPROTECTION COST Action. *Basic Res Cardiol* **116**:52.
- Ledvenyiova V, Panca D, Matejiková J, Ferko M, Bernatova I, and Ravingerova T (2013) Impact of age and sex on response to ischemic preconditioning in the rat heart: differential role of the PI3K-AKT pathway. *Can J Physiol Pharmacol* **91**:640–647.
- Lee TM, Chang NC, and Lin SZ (2017) Dapagliflozin, a selective SGLT2 inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic Biol Med* **104**:298–310.
- Leeser MA, Stoddard MF, Dawn B, Jasti VG, Masden R, and Bolli R (2001) Delayed preconditioning-mimetic action of nitroglycerin in patients undergoing coronary angioplasty. *Circulation* **103**:2935–2941.
- Lefer DJ (2002) Do neutrophils contribute to myocardial reperfusion injury? *Basic Res Cardiol* **97**:263–267.
- Lefer DJ and Bolli R (2011) Development of an NIH consortium for preclinical ASSESSment of CARDioprotective therapies (CAESAR): a paradigm shift in studies of infarct size limitation. *J Cardiovasc Pharmacol Ther* **16**:332–339.
- Lemoine S, Tritapepe L, Hanouz JL, and Puddu PE (2016) The mechanisms of cardio-protective effects of desflurane and sevoflurane at the time of reperfusion: anaesthetic post-conditioning potentially translatable to humans? *Br J Anaesth* **116**:456–475.
- Lerman A, Holmes DR, Herrmann J, and Gersh BJ (2007) Microcirculatory dysfunction in ST-elevation myocardial infarction: cause, consequence, or both? *Eur Heart J* **28**:788–797.
- Lesnfsky EJ, Tandler B, Ye J, Slabe TJ, Turkaly J, and Hoppel CL (1997) Myocardial ischemia decreases oxidative phosphorylation through cytochrome oxidase in subsarcolemmal mitochondria. *Am J Physiol* **273**:H1544–H1554.
- Letavernier E, Zafrani L, Perez J, Letavernier B, Haymann JP, and Baud L (2012) The role of calpains in myocardial remodelling and heart failure. *Cardiovasc Res* **96**:38–45.

- Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM et al. (2016) 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. *J Am Coll Cardiol* **67**:1235–1250.
- Li J, Rohailla S, Gelber N, Rutka J, Sabah N, Gladstone RA, Wei C, Hu P, Kharbanda RK, and Redington AN (2014) MicroRNA-144 is a circulating effector of remote ischemic preconditioning. *Basic Res Cardiol* **109**:423.
- Li N and Brundel BJ (2020) Inflammasomes and proteostasis: novel molecular mechanisms associated with atrial fibrillation. *Circ Res* **127**:73–90.
- Li Q, Zhao YG, Wang Z, Jiang HP, Liu WB, and Cao BF (2018) Effects of first high-dose atorvastatin loading in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention. *Am J Ther* **25**:e291–e298.
- Li W, Wu N, Shu W, Jia D, and Jia P (2015) Pharmacological preconditioning and postconditioning with nicorandil attenuates ischemia/reperfusion-induced myocardial necrosis and apoptosis in hypercholesterolemic rats. *Exp Ther Med* **10**:2197–2205.
- Li YW, Li YM, Hon Y, Wan QL, He RL, Wang ZZ, and Zhao CH (2017) AT1 receptor modulator attenuates the hypercholesterolemia-induced impairment of the myocardial ischemic post-conditioning benefits. *Korean Circ J* **47**:182–192.
- Liang F and Wang Y (2021) Coronary heart disease and atrial fibrillation: a vicious cycle. *Am J Physiol Heart Circ Physiol* **320**:H1–H12.
- Liberale L, Badimon L, Montecucco F, Lüscher TF, Libby P, and Camici GG (2022) Inflammation, aging, and cardiovascular disease: JACC review topic of the week. *J Am Coll Cardiol* **79**:837–847.
- Lieder H, Breithardt G, and Heusch G (2018) Fatal attraction—a brief pathophysiology of the interaction between atrial fibrillation and myocardial ischemia. *Int J Cardiol* **254**:132–135.
- Lieder HR, Irmert A, Kamler M, Heusch G, and Kleinbongard P (2019) Sex is no determinant of cardioprotection by ischemic preconditioning in rats, but ischemic/reperfused tissue mass is for remote ischemic preconditioning. *Physiol Rep* **7**:e14146.
- Lieder HR, Kleinbongard P, Skyschally A, Hagelschuer H, Chilian WM, and Heusch G (2018) Vago-splenic axis in signal transduction of remote ischemic preconditioning in pigs and rats. *Circ Res* **123**:1152–1163.
- Lim SY, Yellon DM, and Hausenloy DJ (2010) The neural and humoral pathways in remote limb ischemic preconditioning. *Basic Res Cardiol* **105**:651–655.
- Lim VG, Bell RM, Arjun S, Kolatsi-Joannou M, Long DA, and Yellon DM (2019) SGLT2 inhibitor, canagliflozin, attenuates myocardial infarction in the diabetic and nondiabetic heart. *JACC Basic Transl Sci* **4**:15–26.
- Lim WY, Messow CM, and Berry C (2012) Cyclosporin variably and inconsistently reduces infarct size in experimental models of reperfused myocardial infarction: a systematic review and meta-analysis. *Br J Pharmacol* **165**:2034–2043.
- Lincoff AM, Wolksi K, Nicholls SJ, and Nissen SE (2007) Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* **298**:1180–1188.
- Liu GS, Thornton J, Van Winkle DM, Stanley AW, Olsson RA, and Downey JM (1991) Protection against infarction afforded by preconditioning is mediated by A1 adenosine receptors in rabbit heart. *Circulation* **84**:350–356.
- Liu Y, Gao WD, O'Rourke B, and Marban E (1996) Synergistic modulation of ATP-sensitive K⁺ currents by protein kinase C and adenosine. Implications for ischemic preconditioning. *Circ Res* **78**:443–454.
- Liu Y, Tsuchida A, Cohen MV, and Downey JM (1995) Pretreatment with angiotensin II activates protein kinase C and limits myocardial infarction in isolated rabbit hearts. *J Mol Cell Cardiol* **27**:883–892.
- Liu Y, Ytrehus K, and Downey JM (1994) Evidence that translocation of protein kinase C is a key event during ischemic preconditioning of rabbit myocardium. *J Mol Cell Cardiol* **26**:661–668.
- Liu Z, Finet JE, Wolfram JA, Anderson ME, Ai X, and Donahue JK (2019) Calcium/calmodulin-dependent protein kinase II causes atrial structural remodeling associated with atrial fibrillation and heart failure. *Heart Rhythm* **16**:1080–1088.
- Liu Z, Zhao L, Hong D, and Gao J (2016) Remote ischaemic preconditioning reduces myocardial ischaemic reperfusion injury in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Acta Cardiol* **71**:596–603.
- Llach A, Molina CE, Prat-Vidal C, Fernandes J, Casadó V, Ciruela F, Lluís C, Franco R, Cinca J, and Hove-Madsen L (2011) Abnormal calcium handling in atrial fibrillation is linked to up-regulation of adenosine A2A receptors. *Eur Heart J* **32**:721–729.
- Lobo-Gonzalez M, Galán-Arriola C, Rossello X, González-Del-Hoyo M, Vilchez JP, Higuero-Verdejo MI, Garcia-Ruiz JM, López-Martín GJ, Sánchez-González J, Oliver E et al. (2020) Metoprolol blunts the time-dependent progression of infarct size. *Basic Res Cardiol* **115**:55.
- Lochner A, Genade S, Genis A, Marais E, and Salie R (2020) Long-chain free fatty acids inhibit ischemic preconditioning of the isolated rat heart. *Mol Cell Biochem* **473**:1111–1132.
- Lochner A, Pentz A, Williams K, Tromp E, and Harper IS (1996) Substrate effects on sarcolemmal permeability in the normoxic and hypoxic perfused rat heart. *Basic Res Cardiol* **91**:64–78.
- Lønborg J, Kelbæk H, Vejstrup N, Bøtker HE, Kim WY, Holmvang L, Jørgensen E, Helqvist S, Saunamäki K, Terkelsen CJ et al. (2012) Exenatide reduces final infarct size in patients with ST-segment-elevation myocardial infarction and short-duration of ischemia. *Circ Cardiovasc Interv* **5**:288–295.
- Lønborg J, Kelbæk H, Vejstrup N, Bøtker HE, Kim WY, Holmvang L, Jørgensen E, Helqvist S, Saunamäki K, Thuesen L et al. (2012) Influence of pre-infarction angina, collateral flow, and pre-procedural TIMI flow on myocardial salvage index by cardiac magnetic resonance in patients with ST-segment elevation myocardial infarction. *Eur Heart J Cardiovasc Imaging* **13**:433–443.
- Lønborg J, Vejstrup N, Kelbæk H, Bøtker HE, Kim WY, Mathiasen AB, Jørgensen E, Helqvist S, Saunamäki K, Clemmensen P et al. (2012) Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J* **33**:1491–1499.
- López-Farré AJ, Rodríguez-Sierra P, Modrego J, Segura A, Martín-Palacios N, Saiz AM, Zamorano-León JJ, Duarte J, Serrano J, and Moñux G (2014) Effects of factor Xa on the expression of proteins in femoral arteries from type 2 diabetic patients. *Br J Clin Pharmacol* **78**:1366–1377.
- Lorgis L, Gudjoncik A, Richard C, Mock L, Buffet P, Brunel P, Janin-Manificat L, Beer JC, Brunet D, Touzery C et al. (2012) Pre-infarction angina and outcomes in non-ST-segment elevation myocardial infarction: data from the RICO survey. *PLoS One* **7**:e48513.
- Lou Z, Wu W, Chen R, Xia J, Shi H, Ge H, Xue J, Wang H, Lin Z, Chu M et al. (2021) Microarray analysis reveals a potential role of lncRNA expression in remote ischemic preconditioning in myocardial ischemia-reperfusion injury. *Am J Transl Res* **13**:234–252.
- Loubeyre C, Morice MC, Lefèvre T, Piéchaud JF, Louvard Y, and Dumas P (2002) A randomized comparison of direct stenting with conventional stent implantation in selected patients with acute myocardial infarction. *J Am Coll Cardiol* **39**:15–21.
- Loukogeorgakis SP, Williams R, Panagiotidou AT, Kolvekar SK, Donald A, Cole TJ, Yellon DM, Deanfield JE, and MacAllister RJ (2007) Transient limb ischemia induces remote preconditioning and remote postconditioning in humans by a K(ATP)-channel dependent mechanism. *Circulation* **116**:1386–1395.
- Lu C, Ren D, Wang X, Ha T, Liu L, Lee EJ, Hu J, Kalbfleisch J, Gao X, Kao R et al. (2014) Toll-like receptor 3 plays a role in myocardial infarction and ischemia/reperfusion injury. *Biochim Biophys Acta* **1842**:22–31.
- Lu J and Pan SS (2017) Elevated C-type natriuretic peptide elicits exercise preconditioning-induced cardioprotection against myocardial injury probably via the up-regulation of NPR-B. *J Physiol Sci* **67**:475–487.
- Lu X, Bi YW, and Chen KB (2015) Olmesartan restores the protective effect of remote ischemic preconditioning against myocardial ischemia/reperfusion injury in spontaneously hypertensive rats. *Clinics (São Paulo)* **70**:500–507.
- Lu X, Bi YW, Chen KB, and Wang HY (2015) Protective effect of olmesartan against cardiac ischemia/reperfusion injury in spontaneously hypertensive rats. *Exp Ther Med* **9**:2081–2087.
- Lucchinetti E, Lou PH, Gandhi M, Clanachan AS, and Zaugg M (2018) Differential effects of anesthetics and opioid receptor activation on cardioprotection elicited by reactive oxygen species-mediated postconditioning in Sprague-Dawley rat hearts. *Anesth Analg* **126**:1739–1746.
- Luo H, Li X, Li T, Zhao L, He J, Zha L, Qi Q, and Yu Z (2019) microRNA-423-3p exosomes derived from cardiac fibroblasts mediates the cardioprotective effects of ischaemic post-conditioning. *Cardiovasc Res* **115**:1189–1204.
- Luo J, Xu S, Li H, Gong M, Li Z, Liu B, Qin X, Shi B, and Wei Y (2021) Long-term impact of the burden of new-onset atrial fibrillation in patients with acute myocardial infarction: results from the NOAFCAMI-SH registry. *Europace* **23**:196–204.
- Luo J, Xu S, Li H, Li Z, Liu B, Qin X, Gong M, Shi B, and Wei Y (2020) Long-term impact of new-onset atrial fibrillation complicating acute myocardial infarction on heart failure. *ESC Heart Fail* **7**:2762–2772.
- Luo W, Li B, Chen R, Huang R, and Lin G (2008) Effect of ischemic postconditioning in adult valve replacement. *Eur J Cardiothorac Surg* **33**:203–208.
- Luongo TS, Lambert JP, Yuan A, Zhang X, Gross P, Song J, Shanmughapriya S, Gao E, Jain M, Houser SR et al. (2015) The mitochondrial calcium uniporter matches energetic supply with cardiac workload during stress and modulates permeability transition. *Cell Rep* **12**:23–34.
- Ma L, Kong F, Ge H, Liu J, Gong F, Xu L, Hu B, and Sun R (2014) Ventricular hypertrophy blocked delayed anesthetic cardioprotection in rats by alteration of iNOS/COX-2 signaling. *Sci Rep* **4**:7071.
- Ma LL, Kong FJ, Guo JJ, Zhu JB, Shi HT, Li Y, Sun RH, and Ge JB (2017) Hypercholesterolemia abrogates remote ischemic preconditioning-induced cardioprotection: role of reperfusion injury salvage kinase signals. *Shock* **47**:363–369.
- Ma LL, Zhang FJ, Kong FJ, Qian LB, Ma H, Wang JA, and Yan M (2013) Hypertrophied myocardium is refractory to sevoflurane-induced protection with alteration of reperfusion injury salvage kinase/glycogen synthase kinase 3 β signals. *Shock* **40**:217–221.
- MacAllister R, Clayton T, Knight R, Robertson S, Nicholas J, Motwani M, and Veighey K (2015) *RE*remote preconditioning for Protection Against Ischaemia-Reperfusion in renal transplantation (REPAIR): a multicentre, multinational, double-blind, factorial designed randomised controlled trial, NIHR Journals Library, Southampton (UK).
- Maddock HL, Siedlecka SM, and Yellon DM (2004) Myocardial protection from either ischaemic preconditioning or nicorandil is not blocked by gliclazide. *Cardiovasc Drugs Ther* **18**:113–119.
- Madias JE (2015) Sustained blood pressure lowering effect of twice daily remote ischemic conditioning sessions in a normotensive/prehypertensive subject. *Int J Cardiol* **182**:392–394.
- Makkos A, Ágg B, Petrovich B, Varga ZV, Görbe A, and Ferdinandy P (2021) Systematic review and network analysis of microRNAs involved in cardioprotection against myocardial ischemia/reperfusion injury and infarction: involvement of redox signalling. *Free Radic Biol Med* **172**:237–251.
- Manciet LH, Poole DC, McDonagh PF, Copeland JG, and Mathieu-Costello O (1994) Microvascular compression during myocardial ischemia: mechanistic basis for no-reflow phenomenon. *Am J Physiol* **266**:H1541–H1550.
- Marenzi G, Cosentino N, Cortinovis S, Milazzo V, Rubino M, Cabiati A, De Metrio M, Moltrasio M, Lauri G, Campodonico J et al. (2015) Myocardial infarct size in patients on long-term statin therapy undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Am J Cardiol* **116**:1791–1797.

- Martins-Marques T, Hausenloy DJ, Sluijter JPG, Leybaert L, and Girao H (2021) Intercellular communication in the heart: therapeutic opportunities for cardiac ischemia. *Trends Mol Med* **27**:248–262.
- Massalha E, Oren D, Goitein O, Brodov Y, Fardman A, Younis A, Berkovitch A, Raibman-Spector S, Konen E, Maor E et al. (2022) Post-ST-segment-elevation myocardial infarction platelet reactivity is associated with the extent of microvascular obstruction and infarct size as determined by cardiac magnetic resonance imaging. *J Am Heart Assoc* **11**:e020973.
- Mayr M, Liem D, Zhang J, Li X, Avliyakov NK, Yang JI, Young G, Vondriska TM, Ladroue C, Madhu B et al. (2009) Proteomic and metabolomic analysis of cardioprotection: interplay between protein kinase C epsilon and delta in regulating glucose metabolism of murine hearts. *J Mol Cell Cardiol* **46**:268–277.
- Mazo T, D'Annunzio V, Donato M, Perez V, Zaobornyj T, and Gelpi RJ (2019) Dyslipidemia in ischemia/reperfusion injury. *Adv Exp Med Biol* **1127**:117–130.
- McDonald MA, Braga JR, Li J, Manlhiot C, Ross HJ, and Redington AN (2014) A randomized pilot trial of remote ischemic preconditioning in heart failure with reduced ejection fraction. *PLoS One* **9**:e105361.
- Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruno N, Fox KA et al.; ATLAS ACS 2–TIMI 51 Investigators (2012) Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* **366**:9–19.
- Mendieta G, Ben-Aicha S, Casani L, Badimon L, Sabate M, and Vilahur G (2019) Molecular pathways involved in the cardioprotective effects of intravenous statin administration during ischemia. *Basic Res Cardiol* **115**:2.
- Mendieta G, Ben-Aicha S, Gutiérrez M, Casani L, Arzanauskaitė M, Carreras F, Sabate M, Badimon L, and Vilahur G (2020) Intravenous statin administration during myocardial infarction compared with oral post-infarct administration. *J Am Coll Cardiol* **75**:1386–1402.
- Meng R, Asmaro K, Meng L, Liu Y, Ma C, Xi C, Li G, Ren C, Luo Y, Ling F et al. (2012) Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology* **79**:1853–1861.
- Merkle S, Frantz S, Schön MP, Bauersachs J, Buitrago M, Frost RJ, Schmitteckert EM, Lohse MJ, and Engelhardt S (2007) A role for caspase-1 in heart failure. *Circ Res* **100**:645–653.
- Mewton N, Thibault H, Roubille F, Lairez O, Rioufol G, Sportouch C, Sanchez I, Bergerot C, Cung TT, Finet G et al. (2013) Postconditioning attenuates no-reflow in STEMI patients. *Basic Res Cardiol* **108**:383.
- Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, Coburn M, Schaele G, Böning A, Niemann B et al.; RIPHeart Study Collaborators (2015) A multicenter trial of remote ischemic preconditioning for heart surgery. *N Engl J Med* **373**:1397–1407.
- MIAMI Trial Research Group (1985) Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. *Eur Heart J* **6**:199–226.
- Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, and He J (2016) Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation* **134**:441–450.
- Miro-Casas E, Ruiz-Meana M, Agullo E, Stahlhofen S, Rodriguez-Sinovas A, Cabestrero A, Jorge I, Torre I, Vazquez J, Boengler K et al. (2009) Connexin43 in cardiomyocyte mitochondria contributes to mitochondrial potassium uptake. *Cardiovasc Res* **83**:747–756.
- Mitchell MB, Meng X, Ao L, Brown JM, Harken AH, and Banerjee A (1995) Preconditioning of isolated rat heart is mediated by protein kinase C. *Circ Res* **76**:73–81.
- Mittal D, Taliyan R, Sharma PL, and Yadav HN (2016) Effect of pioglitazone on the abrogated cardioprotective effect of ischemic preconditioning in hyperlipidemic rat heart. *Indian J Pharmacol* **48**:59–63.
- Mocanu MM, Maddock HL, Baxter GF, Lawrence CL, Standen NB, and Yellon DM (2001) Glimperide, a novel sulfonylurea, does not abolish myocardial protection afforded by either ischemic preconditioning or diazoxide. *Circulation* **103**:3111–3116.
- Mokhtari B, Aboli-Shadbad M, Alihemmati A, Javadi A, and Badalzadeh R (2022) Alpha-lipoic acid preconditioning plus ischemic postconditioning provides additional protection against myocardial reperfusion injury of diabetic rats: modulation of autophagy and mitochondrial function. *Mol Biol Rep* **49**:1773–1782.
- Mølgaard S, Faricelli B, Salomonsson M, Engström T, and Treiman M (2016) Increased myocardial vulnerability to ischemia-reperfusion injury in the presence of left ventricular hypertrophy. *J Hypertens* **34**:513–523, discussion 523.
- Mujović N, Dobrev D, Marinković M, Russo V, and Potpara TS (2020) The role of amiodarone in contemporary management of complex cardiac arrhythmias. *Pharmacol Res* **151**:104521.
- Murphy PG, Myers DS, Davies MJ, Webster NR, and Jones JG (1992) The antioxidant potential of propofol (2,6-diisopropylphenol). *Br J Anaesth* **68**:613–618.
- Nadtochiy SM, Wang YT, Nehrke K, Munger J, and Brookes PS (2018) Cardioprotection by nicotinamide mononucleotide (NMN): involvement of glycolysis and acidic pH. *J Mol Cell Cardiol* **121**:155–162.
- Nakanishi N, Kaikita K, Ishii M, Oimatsu Y, Mitsuse T, Ito M, Yamanaga K, Fujisue K, Kanazawa H, Sueta D et al. (2020) Cardioprotective effects of rivaroxaban on cardiac remodeling after experimental myocardial infarction in mice. *Circ Rep* **2**:158–166.
- Nattel S, Heijman J, Zhou L, and Dobrev D (2020) Molecular basis of atrial fibrillation pathophysiology and therapy: a translational perspective. *Circ Res* **127**:51–72.
- Nawada R, Murakami T, Iwase T, Nagai K, Morita Y, Kouchi I, Akao M, and Sasayama S (1997) Inhibition of sarcolemmal Na⁺-K⁺-ATPase activity reduces the infarct size-limiting effect of preconditioning in rabbit hearts. *Circulation* **96**:599–604.
- Nederlof R, Denis S, Lauzier B, Rosiers CD, Laakso M, Hagen J, Argmann C, Wanders R, Houtkooper RH, Hollmann MW et al. (2017) Acute detachment of hexokinase II from mitochondria modestly increases oxygen consumption of the intact mouse heart. *Metabolism* **72**:66–74.
- Nepper-Christensen L, Høfsten DE, Helqvist S, Lassen JF, Tilsted HH, Holmvang L, Pedersen F, Joshi F, Sørensen R, Bang L et al. (2020) Interaction of ischaemic postconditioning and thrombectomy in patients with ST-elevation myocardial infarction. *Heart* **106**:24–32.
- Nepper-Christensen L, Lønborg J, Ahtarovski KA, Høfsten DE, Kyhl K, Ghotbi AA, Schoos MM, Göransson C, Bertelsen L, Køber L et al. (2017) Left ventricular hypertrophy is associated with increased infarct size and decreased myocardial salvage in patients With ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *J Am Heart Assoc* **6**:e004823.
- Newton K, Dugger DL, Maltzman A, Greve JM, Hedehus M, Martin-McNulty B, Carano RA, Cao TC, van Bruggen N, Bernstein L et al. (2016) RIPK3 deficiency or catalytically inactive RIPK1 provides greater benefit than MLKL deficiency in mouse models of inflammation and tissue injury. *Cell Death Differ* **23**:1565–1576.
- Niccoli G, Scalone G, Cosentino N, Fabretti A, Mirizzi AM, Gramegna M, Panebianco M, Roberto M, and Crea F (2014) Protective effect of pre-infarction angina on microvascular obstruction after primary percutaneous coronary intervention is blunted in humans by cardiovascular risk factors. *Circ J* **78**:1935–1941.
- Nichol G, Strickland W, Shavelle D, Maehara A, Ben-Yehuda O, Genereux P, Dressler O, Parvataneni R, Nichols M, McPherson J et al.; VELOCITY Investigators (2015) Prospective, multicenter, randomized, controlled pilot trial of peritoneal hypothermia in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* **8**:e001965.
- Nikolaou PE, Efentakis P, Abu Qourah F, Femmino S, Makridakis M, Kanaki Z, Varela A, Tsoumani M, Davos CH, Dimitriou CA et al. (2021) Chronic Empagliflozin Treatment Reduces Myocardial Infarct Size in Nondiabetic Mice Through STAT-3-Mediated Protection on Microvascular Endothelial Cells and Reduction of Oxidative Stress. *Antioxid Redox Signal* **34**:551–571.
- Nishida K, Qi XY, Wakili R, Comtois P, Chartier D, Harada M, Iwasaki YK, Romeo P, Maguy A, Dobrev D et al. (2011) Mechanisms of atrial tachyarrhythmias associated with coronary artery occlusion in a chronic canine model. *Circulation* **123**:137–146.
- Nishino Y, Miura T, Miki T, Sakamoto J, Nakamura Y, Ikeda Y, Kobayashi H, and Shimamoto K (2004) Ischemic preconditioning activates AMPK in a PKC-dependent manner and induces GLUT4 up-regulation in the late phase of cardioprotection. *Cardiovasc Res* **61**:610–619.
- Noc M, Laanmets P, Neskovic AN, Petrović M, Stanetić B, Aradi D, Kiss RG, Ungi I, Merkely B, Hudec M et al. (2021) A multicentre, prospective, randomised controlled trial to assess the safety and effectiveness of cooling as an adjunctive therapy to percutaneous intervention in patients with acute myocardial infarction: the COOL AMI EU Pivotal Trial. *EuroIntervention* **17**:466–473.
- Núñez C, Victor VM, Tur R, Alvarez-Barrientos A, Moncada S, Esplugues JV, and D'Ocoñ P (2005) Discrepancies between nitroglycerin and NO-releasing drugs on mitochondrial oxygen consumption, vasoactivity, and the release of NO. *Circ Res* **97**:1063–1069.
- Nwabuo CC and Vasan RS (2020) Pathophysiology of hypertensive heart disease: beyond left ventricular hypertrophy. *Curr Hypertens Rep* **22**:11.
- Oei GT, Huhn R, Heinen A, Hollmann MW, Schlack WS, Preckel B, and Weber NC (2012) Helium-induced cardioprotection of healthy and hypertensive rat myocardium in vivo. *Eur J Pharmacol* **684**:125–131.
- Oeing CU, Jun S, Mishra S, Dunkerly-Eyring BL, Chen A, Grajeda MI, Tahir UA, Gerszten RE, Paolucci N, Ranek MJ et al. (2021) MTORC1-regulated metabolism controlled by TSC2 limits cardiac reperfusion injury. *Circ Res* **128**:639–651.
- Olenchock BA, Moslehi J, Baik AH, Davidson SM, Williams J, Gibson WJ, Chakraborty AA, Pierce KA, Miller CM, Hanse EA et al. (2016) EGLN1 inhibition and rerouting of α -ketoglutarate suffice for remote ischemic protection. *Cell* **164**:884–895.
- Olschewski A, Bräu ME, Olschewski H, Hempelmann G, and Vogel W (1996) ATP-dependent potassium channel in rat cardiomyocytes is blocked by lidocaine. Possible impact on the antiarrhythmic action of lidocaine. *Circulation* **93**:656–659.
- Ong SB, Kwek XY, Katwadi K, Hernandez-Resendiz S, Crespo-Avilan GE, Ismail NI, Lin YH, Yap EP, Lim SY, Ja KPMM et al. (2019) Targeting mitochondrial fission using Mdivi-1 in a clinically relevant large animal model of acute myocardial infarction: a pilot study. *Int J Mol Sci* **20**:3972.
- Onody A, Zvara A, Hackler L Jr, Vigh L, Ferdinandy P, and Puskás LG (2003) Effect of classic preconditioning on the gene expression pattern of rat hearts: a DNA microarray study. *FEBS Lett* **536**:35–40.
- Opacic D, van Bragt KA, Nasrallah HM, Schotten U, and Verheule S (2016) Atrial metabolism and tissue perfusion as determinants of electrical and structural remodelling in atrial fibrillation. *Cardiovasc Res* **109**:527–541.
- Otaka N, Shibata R, Ohashi K, Uemura Y, Kambara T, Enomoto T, Ogawa H, Ito M, Kawamishi H, Maruyama S et al. (2018) Myonectin is an exercise-induced myokine that protects the heart from ischemia-reperfusion injury. *Circ Res* **123**:1326–1338.
- Ottani F, Latini R, Staszewsky L, La Vecchia L, Locuratolo N, Sicuro M, Masson S, Barlera S, Milani V, Lombardi M et al.; CYCLE Investigators (2016) Cyclosporine A in reperfusion myocardial infarction: the multicenter, controlled, open-label CYCLE Trial. *J Am Coll Cardiol* **67**:365–374.
- Oyama J, Blais Jr C, Liu X, Pu M, Kobzik L, Kelly RA, and Bourcier T (2004) Reduced myocardial ischemia-reperfusion injury in toll-like receptor 4-deficient mice. *Circulation* **109**:784–789.
- Pælestik KB, Jespersen NR, Jensen RV, Johnsen J, Bøtker HE, and Kristiansen SB (2017) Effects of hypoglycemia on myocardial susceptibility to ischemia-reperfusion injury and preconditioning in hearts from rats with and without type 2 diabetes. *Cardiovasc Diabetol* **16**:148.
- Pagliari P and Penna C (2017) Hypertension, hypertrophy, and reperfusion injury. *J Cardiovasc Med (Hagerstown)* **18**:131–135.
- Palee S, McSweeney CM, Manecheote C, Moisesuc DM, Jaiwongkam T, Kerdphoo S, Chattipakorn SC, and Chattipakorn N (2019) PCSK9 inhibitor improves

- cardiac function and reduces infarct size in rats with ischaemia/reperfusion injury: benefits beyond lipid-lowering effects. *J Cell Mol Med* **23**:7310–7319.
- Parini P, Altucci L, Balligand JL, Baumbach J, Ferdinandy P, Filetti S, Maron BA, Petrillo E, Silverman EK, Barabasi AL et al.; International Network Medicine Consortium (2020) The network medicine imperative and the need for an international network medicine consortium. *Am J Med* **133**:e451–e454.
- Park H, Otani H, Oishi C, Fujikawa M, Yamashita K, Okazaki T, Sato D, Ueyama T, Iwasaka J, Yamamoto Y et al. (2011) Efficacy of intracoronary administration of a short-acting β -blocker landiolol during reperfusion in pigs. *Int J Cardiol* **146**:347–353.
- Parry TL, Starnes JW, O'Neal SK, Bain JR, Muehlbauer MJ, Honcoop A, Iwai A, Christopher P, Patterson C, and Willis MS (2018) Untargeted metabolomics analysis of ischemia-reperfusion-injured hearts ex vivo from sedentary and exercise-trained rats. *Metabolomics* **14**:8.
- Pasdos P, Parker JE, and Halestrap AP (2012) Extent of mitochondrial hexokinase II dissociation during ischemia correlates with mitochondrial cytochrome c release, reactive oxygen species production, and infarct size on reperfusion. *J Am Heart Assoc* **2**:e005645.
- Pasupathy S, Tavella R, Grover S, Raman B, Procter NEK, Du YT, Mahadavan G, Stafford I, Heresztyn T, Holmes A et al. (2017) Early use of N-acetylcysteine with nitrate therapy in patients undergoing primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction reduces myocardial infarct size (the NACIAM Trial [N-acetylcysteine in acute myocardial infarction]). *Circulation* **136**:894–903.
- Patti G, Chello M, Pasceri V, Colonna D, Nusca A, Miglionico M, D'Ambrosio A, Covino E, and Di Sciascio G (2006) Protection from procedural myocardial injury by atorvastatin is associated with lower levels of adhesion molecules after percutaneous coronary intervention: results from the ARMYDA-CAMs (Atorvastatin for Reduction of Myocardial Damage during Angioplasty-Cell Adhesion Molecules) substudy. *J Am Coll Cardiol* **48**:1560–1566.
- Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, Sardella G, Montinaro A, and Di Sciascio G (2007) Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol* **49**:1272–1278.
- Pearce L, Davidson SM, and Yellon DM (2021) Does remote ischaemic conditioning reduce inflammation? A focus on innate immunity and cytokine response. *Basic Res Cardiol* **116**:12.
- Pearson PJ, Schaff HV, and Vanhoutte PM (1990) Long-term impairment of endothelium-dependent relaxations to aggregating platelets after reperfusion injury in canine coronary arteries. *Circulation* **81**:1921–1927.
- Peng H, Want LL, and Aroda VR (2016) Safety and tolerability of glucagon-like peptide-1 receptor agonists utilizing data from the exenatide clinical trial development program. *Curr Diab Rep* **16**:44.
- Penna C, Aragno M, Cento AS, Femminò S, Russo I, Bello FD, Chiazza F, Collotta D, Alves GF, Bertinaria M et al. (2020) Ticagrelor conditioning effects are not additive to cardioprotection induced by direct NLRP3 inflammasome inhibition: role of RISK, NLRP3, and redox cascades. *Oxid Med Cell Longev* **2020**:9219825.
- Penna C, Rastaldo R, Mancardi D, Raimondo S, Cappello S, Gattullo D, Losano G, and Pagliaro P (2006) Post-conditioning induced cardioprotection requires signaling through a redox-sensitive mechanism, mitochondrial ATP-sensitive K⁺ channel and protein kinase C activation. *Basic Res Cardiol* **101**:180–189.
- Penna C, Sorge M, Tullio F, Comità S, Femminò S, Brancaccio M, and Pagliaro P (2022) A TRICk to improve the effectiveness of RIC: role of limb temperature in enhancing the effectiveness of remote ischemic conditioning. *Biology (Basel)* **11**:146.
- Penna C, Tullio F, Merlino A, Moro F, Raimondo S, Rastaldo R, Perrelli MG, Mancardi D, and Pagliaro P (2009) Postconditioning cardioprotection against infarct size and post-ischemic systolic dysfunction is influenced by gender. *Basic Res Cardiol* **104**:390–402.
- Penna C, Tullio F, Moro F, Folino A, Merlino A, and Pagliaro P (2010) Effects of a protocol of ischemic postconditioning and/or captopril in hearts of normotensive and hypertensive rats. *Basic Res Cardiol* **105**:181–192.
- Perez V, D Annunzio V, Mazo T, Marchini T, Caceres L, Evelson P, and Gelpi RJ (2016) Ischemic postconditioning confers cardioprotection and prevents reduction of Trx-1 in young mice, but not in middle-aged and old mice. *Mol Cell Biochem* **415**:67–76.
- Perrino C, Barabási AL, Condorelli G, Davidson SM, De Windt L, Dimmeler S, Engel FB, Hausenloy DJ, Hill JA, Van Laake LW et al. (2017) Epigenomic and transcriptomic approaches in the post-genomic era: path to novel targets for diagnosis and therapy of the ischaemic heart? Position paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart. *Cardiovasc Res* **113**:725–736.
- Perrino C, Ferdinandy P, Bøtker HE, Brundel BJJM, Collins P, Davidson SM, den Ruijter HM, Engel FB, Gerds E, Girao H et al. (2021) Improving translational research in sex-specific effects of comorbidities and risk factors in ischaemic heart disease and cardioprotection: position paper and recommendations of the ESC Working Group on Cellular Biology of the Heart. *Cardiovasc Res* **117**:367–385.
- Peter T, Norris RM, Clarke ED, Heng MK, Singh BN, Williams B, Howell DR, and Ambler PK (1978) Reduction of enzyme levels by propranolol after acute myocardial infarction. *Circulation* **57**:1091–1095.
- Petermichl W, Eglmeier K, Hesse H, Gruber M, Graf B, Bredthauer A, and Redel A (2021) Remote and anesthetic-induced myocardial preconditioning is preserved in atherosclerotic LDL receptor^{-/-} mice in vivo. *Cardiovasc Ther* **2021**:5596590.
- Pham PT, Fukuda D, Yagi S, Kusunose K, Yamada H, Soeki T, Shimabukuro M, and Sata M (2019) Rivaroxaban, a specific FXa inhibitor, improved endothelium-dependent relaxation of aortic segments in diabetic mice. *Sci Rep* **9**:11206.
- Pierre SV, Yang C, Yuan Z, Seminerio J, Mouas C, Garlid KD, Dos-Santos P, and Xie Z (2007) Ouabain triggers preconditioning through activation of the Na⁺/K⁺-ATPase signaling cascade in rat hearts. *Cardiovasc Res* **73**:488–496.
- Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, Elbelghiti R, Cung TT, Bonnefoy E, Angoulvant D et al. (2008) Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med* **359**:473–481.
- Piper HM, Garcia-Dorado D, and Ovize M (1998) A fresh look at reperfusion injury. *Cardiovasc Res* **38**:291–300.
- Pitcher JM, Nagy RD, Tsai BM, Wang M, Kher A, and Meldrum DR (2005) Is the preconditioning threshold different in females? *J Surg Res* **125**:168–172.
- Pizarro G, Fernández-Friera L, Fuster V, Fernández-Jiménez R, García-Ruiz JM, García-Álvarez A, Mateos A, Barreiro MV, Escalera N, Rodríguez MD et al. (2014) Long-term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction: results from the METOCARD-CNIC trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction). *J Am Coll Cardiol* **63**:2356–2362.
- Podesser BK and Kiss A (2022) Editorial comments on “Effects of ischaemic postconditioning in aortic valve replacement: a multicenter randomized controlled trial.” *Eur J Cardiothorac Surg* **61**:1153–1154.
- Podlesnikar T, Pizarro G, Fernández-Jiménez R, Montero-Cabezas JM, Greif N, Sánchez-González J, Bucciarelli-Ducci C, Marsan NA, Fras Z, Bax JJ et al. (2020) Left ventricular functional recovery of infarcted and remote myocardium after ST-segment elevation myocardial infarction (METOCARD-CNIC randomized clinical trial substudy). *J Cardiovasc Magn Reson* **22**:44.
- Posa A, Pavo N, Hemetsberger R, Csonka C, Csont T, Ferdinandy P, Petrási Z, Varga C, Pavo JJ, Laszlo Jr F et al. (2010) Protective effect of ischaemic preconditioning on ischaemia/reperfusion-induced microvascular obstruction determined by on-line measurements of coronary pressure and blood flow in pigs. *Thromb Haemost* **103**:450–460.
- Povlsen JA, Løfgren B, Dalgas C, Birkler RL, Johannsen M, Støttrup NB, and Bøtker HE (2013) Protection against myocardial ischemia-reperfusion injury at onset of type 2 diabetes in Zucker diabetic fatty rats is associated with altered glucose oxidation. *PLoS One* **8**:e64093.
- Prag HA, Aksejtijevic D, Dannhorn A, Giles AV, Mulvey JF, Sauchanka O, Du L, Bates G, Reinhold J, Kula-Alwar D et al. (2022) Ischemia-Selective Cardioprotection by Malonate for Ischemia/Reperfusion Injury. *Circ Res* **131**:528–541.
- Prakash A, Crespo-Avilan GE, Hernandez-Resendiz S, Ong SG, and Hausenloy DJ (2020) Extracellular vesicles - mediating and delivering cardioprotection in acute myocardial infarction and heart failure. *Cond Med* **3**:227–238.
- Prumier F, Angoulvant D, Saint Etienne C, Vermes E, Gilard M, Piot C, Roubille F, Elbaz M, Ovize M, Bière L et al. (2014) The RIPOST-MI study, assessing remote ischemic preconditioning alone or in combination with local ischemic postconditioning in ST-segment elevation myocardial infarction. *Basic Res Cardiol* **109**:400.
- Pryds K, Nielsen RR, Jorsal A, Hansen MS, Ringgaard S, Refsgaard J, Kim WY, Petersen AK, Bøtker HE, and Schmidt MR (2017) Effect of long-term remote ischemic conditioning in patients with chronic ischemic heart failure. *Basic Res Cardiol* **112**:67.
- Przyklenk K, Maynard M, Darling CE, and Whittaker P (2008) Aging mouse hearts are refractory to infarct size reduction with post-conditioning. *J Am Coll Cardiol* **51**:1393–1398.
- Przyklenk K, Maynard M, Greiner DL, and Whittaker P (2011) Cardioprotection with postconditioning: loss of efficacy in murine models of type-2 and type-1 diabetes. *Antioxid Redox Signal* **14**:781–790.
- Qian J, Ren X, Wang X, Zhang P, Jones WK, Molkentin JD, Fan GC, and Kranias EG (2009) Blockade of Hsp20 phosphorylation exacerbates cardiac ischemia/reperfusion injury by suppressed autophagy and increased cell death. *Circ Res* **105**:1223–1231.
- Querio G, Geddo F, Antoniotti S, Gallo MP, and Penna C (2021) Sex and response to cardioprotective conditioning maneuvers. *Front Physiol* **12**:667961.
- Quindry JC and Franklin BA (2021) Exercise preconditioning as a cardioprotective phenotype. *Am J Cardiol* **148**:8–15.
- Rahman FA, Abdullah SS, Manan ZWZA, Tan LT, Neoh CF, Ming LC, Chan KG, Lee LH, Goh BH, Salmasi S et al. (2018) Efficacy and safety of cyclosporine in acute myocardial infarction: a systematic review and meta-analysis. *Front Pharmacol* **9**:238.
- Rahman IA, Mascaro JG, Steeds RP, Frenneaux MP, Nightingale P, Gosling P, Townsend P, Townend JN, Green D, and Bonser RS (2010) Remote ischemic preconditioning in human coronary artery bypass surgery: from promise to disappointment? *Circulation* **122**(11, Suppl):S53–S59.
- Rahmi RM, Uchida AH, Rezende PC, Lima EG, Garzillo CL, Favaro D, Strunz CM, Takiuti M, Girardi P, Hueb W et al. (2013) Effect of hypoglycemic agents on ischemic preconditioning in patients with type 2 diabetes and symptomatic coronary artery disease. *Diabetes Care* **36**:1654–1659.
- Raivio P, Kuitunen A, Suojäranta-Ylinen R, Lassila R, and Petäjä J (2006) Thrombin generation during reperfusion after coronary artery bypass surgery associates with postoperative myocardial damage. *J Thromb Haemost* **4**:1523–1529.
- Raivio P, Lassila R, and Petäjä J (2009) Thrombin in myocardial ischemia-reperfusion during cardiac surgery. *Ann Thorac Surg* **88**:318–325.
- Ramos GC, van den Berg A, Nunes-Silva V, Weirather J, Peters L, Burkard M, Friedrich M, Pinnecker J, Abeßer M, Heinze KG et al. (2017) Myocardial aging as a T-cell-mediated phenomenon. *Proc Natl Acad Sci USA* **114**:E2420–E2429.
- Rassaf T, Totzcek M, Hendgen-Cotta UB, Shiva S, Heusch G, and Kelm M (2014) Circulating nitrite contributes to cardioprotection by remote ischemic preconditioning. *Circ Res* **114**:1601–1610.
- Reilly SN, Jayaram R, Nahar K, Antoniadis C, Verheule S, Channon KM, Alp NJ, Schotten U, and Casadei B (2011) Atrial sources of reactive oxygen species vary with the duration and substrate of atrial fibrillation: implications for the antiarrhythmic effect of statins. *Circulation* **124**:1107–1117.

- Reinstadler SJ, Stiermaier T, Eitel C, Metzler B, de Waha S, Fuernau G, Desch S, Thiele H, and Eitel I (2017) Relationship between diabetes and ischaemic injury among patients with revascularized ST-elevation myocardial infarction. *Diabetes Obes Metab* **19**:1706–1713.
- Reinstadler SJ, Stiermaier T, Reindl M, Feistritz HJ, Fuernau G, Eitel C, Desch S, Klug G, Thiele H, Metzler B et al. (2019) Intramyocardial haemorrhage and prognosis after ST-elevation myocardial infarction. *Eur Heart J Cardiovasc Imaging* **20**:138–146.
- Reiter R, Henry TD, and Traverse JH (2013) Preinfarction angina reduces infarct size in ST-elevation myocardial infarction treated with percutaneous coronary intervention. *Circ Cardiovasc Interv* **6**:52–58.
- Renguet E, Ginion A, Gélinas R, Bultot L, Auquier J, Robillard Frayne I, Daneault C, Vanoverschelde JL, Des Rosiers C, Hue L et al. (2017) Metabolism and acetylation contribute to leucine-mediated inhibition of cardiac glucose uptake. *Am J Physiol Heart Circ Physiol* **313**:H432–H445.
- Rezkalla SH and Kloner RA (2004) Ischemic preconditioning and preinfarction angina in the clinical arena. *Nat Clin Pract Cardiovasc Med* **1**:96–102.
- Riess ML, Elorbany R, Wehrauch D, Stowe DF, and Camara AKS (2020) PPAR γ -independent side effects of thiazolidinediones on mitochondrial redox state in rat isolated hearts. *Cells* **9**:252.
- Ritschel VN, Seljeflot I, Arnesen H, Halvorsen S, Weiss T, Eritsland J, and Andersen GO (2013) IL-6 signalling in patients with acute ST-elevation myocardial infarction. *Results Immunol* **4**:8–13.
- Rochetaing A, Barbé C, and Kreher P (2001) Beneficial effects of amiodarone and dronedarone (SR 33589b), when applied during low-flow ischemia, on arrhythmia and functional parameters assessed during reperfusion in isolated rat hearts. *J Cardiovasc Pharmacol* **38**:500–511.
- Rodriguez-Sinovas A, Boengler K, Cabestrero A, Gres P, Morente M, Ruiz-Meana M, Konietzka I, Miró E, Totzeck A, Heusch G et al. (2006) Translocation of connexin 43 to the inner mitochondrial membrane of cardiomyocytes through the heat shock protein 90-dependent TOM pathway and its importance for cardioprotection. *Circ Res* **99**:93–101.
- Roolvink V, Ibáñez B, Ottervanger JP, Pizarro G, van Royen N, Mateos A, Dambrink JE, Escalera N, Lipsic E, Albarán A et al.; EARLY-BAMI Investigators (2016) Early intravenous beta-blockers in patients with ST-segment elevation myocardial infarction before primary percutaneous coronary intervention. *J Am Coll Cardiol* **67**:2705–2715.
- Rork TH, Wallace KL, Kennedy DP, Marshall MA, Lankford AR, and Linden J (2008) Adenosine A2A receptor activation reduces infarct size in the isolated, perfused mouse heart by inhibiting resident cardiac mast cell degranulation. *Am J Physiol Heart Circ Physiol* **295**:H1825–H1833.
- Rossello X, Piñero A, Fernández-Jiménez R, Sánchez-González J, Pizarro G, Galán-Arriola C, Lobo-González M, Vilchez JP, García-Prieto J, García-Ruiz JM et al. (2018) Mirabegron, a clinically approved β_3 adrenergic receptor agonist, does not reduce infarct size in a swine model of reperfused myocardial infarction. *J Cardiovasc Transl Res* **11**:310–318.
- Rossello X, Riquelme JA, He Z, Taferner S, Vanhaesebroeck B, Davidson SM, and Yellon DM (2017) The role of PI3K α isoform in cardioprotection. *Basic Res Cardiol* **112**:66.
- Rossello X, Rodriguez-Sinovas A, Vilahur G, Crisóstomo V, Jorge I, Zaragoza C, Zamorano JL, Bermejo J, Ordoñez A, Boscá L et al. (2019) CIBER-CLAP (CIBERCV Cardioprotection Large Animal Platform): a multicenter preclinical network for testing reproducibility in cardiovascular interventions. *Sci Rep* **9**:20290.
- Roth S, Torregroza C, Feige K, Preckel B, Hollmann MW, Weber NC, and Huhn R (2021) Pharmacological conditioning of the heart: an update on experimental developments and clinical implications. *Int J Mol Sci* **22**:2519.
- Roubille F, Laire O, Mewton N, Rioufol G, Ranc S, Sanchez I, Cung TT, Elbaz M, Piot C, and Ovize M (2012) Cardioprotection by clopidogrel in acute ST-elevated myocardial infarction patients: a retrospective analysis. *Basic Res Cardiol* **107**:275.
- Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T, and Otterstad JE (2017) Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: a systematic review and meta-analysis. *Eur J Prev Cardiol* **24**:1555–1566.
- Ruggeri ZM (2002) Platelets in atherothrombosis. *Nat Med* **8**:1227–1234.
- Ruiz-Meana M, Boengler K, Garcia-Dorado D, Hausenloy DJ, Kaambre T, Kararigas G, Perrino C, Schulz R, and Ytrehus K (2020) Ageing, sex, and cardioprotection. *Br J Pharmacol* **177**:5270–5286.
- Ruiz-Meana M, Bou-Teen D, Ferdinandy P, Gyongyosi M, Pesce M, Perrino C, Schulz R, Sluijter JPG, Tocchetti CG, Thum T et al. (2020) Cardiomyocyte ageing and cardioprotection: consensus document from the ESC working groups cell biology of the heart and myocardial function. *Cardiovasc Res* **116**:1835–1849.
- Ruiz-Meana M, Minguet M, Bou-Teen D, Miro-Casas E, Castans C, Castellano J, Bonzon-Kulichenko E, Igual A, Rodriguez-Lecoq R, Vázquez J et al. (2019) Ryanodine receptor glycation favors mitochondrial damage in the senescent heart. *Circulation* **139**:949–964.
- Ruiz-Meana M, Núñez E, Miro-Casas E, Martínez-Acedo P, Barba I, Rodriguez-Sinovas A, Inerte J, Fernandez-Sanz C, Hernandez V, Vázquez J et al. (2014) Ischemic preconditioning protects cardiomyocyte mitochondria through mechanisms independent of cytosol. *J Mol Cell Cardiol* **68**:79–88.
- Russell JS, Griffith TA, Helman T, Du Toit EF, Peart JN, and Headrick JP (2019) Chronic type 2 but not type 1 diabetes impairs myocardial ischaemic tolerance and preconditioning in C57Bl/6 mice. *Exp Physiol* **104**:1868–1880.
- Russo I, Penna C, Musso T, Popara J, Alloatti G, Cavalot F, and Pagliaro P (2017) Platelets, diabetes and myocardial ischemia/reperfusion injury. *Cardiovasc Diabetol* **16**:71.
- Ryden L, Tadokoro H, Sjöquist PO, Regardh C, Kobayashi S, Corday E, and Drury JK (1991) Pharmacokinetic analysis of coronary venous retroinfusion: a comparison with anterograde coronary artery drug administration using metoprolol as a tracer. *J Am Coll Cardiol* **18**:603–612.
- Sabbah M, Nepper-Christensen L, Køber L, Høfsten DE, Ahtarovski KA, Göransson C, Kyhl K, Ghotbi AA, Schoos MM, Sadjadieh G et al. (2020) Infarct size following loading with Ticagrelor/Prasugrel versus Clopidogrel in ST-segment elevation myocardial infarction. *Int J Cardiol* **314**:7–12.
- Saito S, Thuc LC, Teshima Y, Nakada C, Nishio S, Kondo H, Fukui A, Abe I, Ebata Y, Saikawa T et al. (2016) Glucose fluctuations aggravate cardiac susceptibility to ischemia/reperfusion injury by modulating MicroRNAs expression. *Circ J* **80**:186–195.
- Salie R, Moolman JA, and Lochner A (2011) The role of β -adrenergic receptors in the cardioprotective effects of beta-preconditioning (β PC). *Cardiovasc Drugs Ther* **25**:31–46.
- Sandanger I, Gao E, Ranheim T, Bliksøen M, Kaasbøll OJ, Alfsnes K, Nymo SH, Rashidi A, Ohm IK, Attramadal H et al. (2016) NLRP3 inflammasome activation during myocardial ischemia reperfusion is cardioprotective. *Biochem Biophys Res Commun* **469**:1012–1020.
- Sandanger I, Ranheim T, Vinge LE, Bliksøen M, Alfsnes K, Finsen AV, Dahl CP, Askevold ET, Florholmen G, Christensen G et al. (2013) The NLRP3 inflammasome is up-regulated in cardiac fibroblasts and mediates myocardial ischaemia-reperfusion injury. *Cardiovasc Res* **99**:164–174.
- Santana MNS, Souza DS, Miguel-Dos-Santos R, Rabelo TK, Vasconcelos CML, Navia-Pelaez JM, Jesus ICG, Silva-Neto JAD, Louton-Santos S, Capettini LDSA et al. (2018) Resistance exercise mediates remote ischemic preconditioning by limiting cardiac eNOS uncoupling. *J Mol Cell Cardiol* **125**:61–72.
- Sárközy M, Márványkóvi FM, Szűcs G, Kovács ZZA, Szabó MR, Gáspár R, Siska A, Kóvári B, Csérni G, Földesi I et al. (2021) Ischemic preconditioning protects the heart against ischemia-reperfusion injury in chronic kidney disease in both males and females. *Biol Sex Differ* **12**:49.
- Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJJ, Pratley RE et al. (2021) Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *The Lancet Diabetes & Endocrinology* **9**:653–662.
- Sawa Y, Ichikawa H, Kagisaki K, Ohata T, and Matsuda H (1998) Interleukin-6 derived from hypoxic myocytes promotes neutrophil-mediated reperfusion injury in myocardium. *J Thorac Cardiovasc Surg* **116**:511–517.
- Saxena P, Aggarwal S, Misso NL, Passage J, Newman MA, Thompson PJ, d'Udekem Y, Praporski S, and Konstantinov IE (2013) Remote ischaemic preconditioning down-regulates kinin receptor expression in neutrophils of patients undergoing heart surgery. *Interact Cardiovasc Thorac Surg* **17**:653–658.
- Sayour AA, Korkmaz-İcöz S, Loganathan S, Ruppert M, Sayour VN, Oláh A, Benke K, Brune M, Benkő R, Horváth EM et al. (2019) Acute canagliflozin treatment protects against in vivo myocardial ischemia-reperfusion injury in non-diabetic male rats and enhances endothelium-dependent vasorelaxation. *J Transl Med* **17**:127.
- Scalone G, Aurigemma C, Tomai F, Corvo P, Battipaglia I, Lanza GA, and Crea F (2013) Effect of pre-infarction angina on platelet reactivity in acute myocardial infarction. *Int J Cardiol* **167**:51–56.
- Scarsini R, Terentes-Prinzios D, Shmuganathan M, Kotronias RA, Borlotti A, Marin F, Langrish J, Lucking A, Ribichini F, Oxford Acute Myocardial Infarction S et al. (2022) Pressure-controlled intermittent coronary sinus occlusion improves the vasodilatory microvascular capacity and reduces myocardial injury in patients with STEMI. *Catheter Cardiovasc Interv* **99**:329–339.
- Schaller S, Paradis S, Ngh GA, Assaly R, Buisson B, Drouot C, Ostuni MA, Lacapere JJ, Bassissi F, Bordet T et al. (2010) TRO40303, a new cardioprotective compound, inhibits mitochondrial permeability transition. *J Pharmacol Exp Ther* **333**:696–706.
- Schmidt M, Horváth-Puhó E, Pedersen L, Sørensen HT, and Bøtker HE (2015) Time-dependent effect of preinfarction angina pectoris and intermittent claudication on mortality following myocardial infarction: a Danish nationwide cohort study. *Int J Cardiol* **187**:462–469.
- Schulman D, Latchman DS, and Yellon DM (2002) Urocortin protects the heart from reperfusion injury via upregulation of p42/p44 MAPK signaling pathway. *Am J Physiol Heart Circ Physiol* **283**:H1481–H1488.
- Schulz R and Heusch G (2022) Targeted Mito- and Cardioprotection by Malonate. *Circ Res* **131**:542–544.
- Schulz R, Gres P, and Heusch G (2001) Role of endogenous opioids in ischemic preconditioning but not in short-term hibernation in pigs. *Am J Physiol Heart Circ Physiol* **280**:H2175–H2181.
- Schulz R, Post H, Vahlhaus C, and Heusch G (1998) Ischemic preconditioning in pigs: a graded phenomenon: its relation to adenosine and bradykinin. *Circulation* **98**:1022–1029.
- Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederic R, Wiviott SD, Hoffman EB et al.; SAVOR-TIMI 53 Steering Committee and Investigators (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* **369**:1317–1326.
- Seefeldt JM, Lassen TR, Hjortbak MV, Jespersen NR, Kvist F, Hansen J, and Bøtker HE (2021) Cardioprotective effects of empagliflozin after ischemia and reperfusion in rats. *Sci Rep* **11**:9544.
- Sgarra L, Leo V, Addabbo F, Iacobazzi D, Carratù MR, Montagnani M, and Potenza MA (2014) Intermittent losartan administration triggers cardiac post-conditioning in isolated rat hearts: role of BK2 receptors. *PLoS One* **9**:e88542.
- Shah M, He Z, Rauf A, Beikoghli Kalkhoran S, Heiestad CM, Stenslökken KO, Parish CR, Soehnlein O, Arjun S, Davidson SM et al. (2022) Extracellular histones are a target in myocardial ischaemia-reperfusion injury. *Cardiovasc Res* **118**:1115–1125.
- Shan X, Liu Z, Wulashian M, and Ma S (2019) Edoxaban improves atrial fibrillation and thromboembolism through regulation of the Wnt- β -induced PI3K/ATK-activated protein C system. *Exp Ther Med* **17**:3509–3517.

- Shanmuganathan S, Hausenloy DJ, Duchon MR, and Yellon DM (2005) Mitochondrial permeability transition pore as a target for cardioprotection in the human heart. *Am J Physiol Heart Circ Physiol* **289**:H237–H242.
- Shi G, Yang X, Pan M, Sun J, Ke H, Zhang C, and Geng H (2018) Apixaban attenuates ischemia-induced myocardial fibrosis by inhibition of Gq/PLC signaling. *Biochem Biophys Res Commun* **500**:550–556.
- Shi H, Gao Y, Dong Z, Yang J, Gao R, Li X, Zhang S, Ma L, Sun X, Wang Z et al. (2021) GSDMD-mediated cardiomyocyte pyroptosis promotes myocardial IR injury. *Circ Res* **129**:383–396.
- Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, Zhuang Y, Cai T, Wang F, and Shao F (2015) Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature* **526**:660–665.
- Shibata T, Kawakami S, Noguchi T, Tanaka T, Asaumi Y, Kanaya T, Nagai T, Nakao K, Fujino M, Nagatsuka K et al. (2015) Prevalence, clinical features, and prognosis of acute myocardial infarction attributable to coronary artery embolism. *Circulation* **132**:241–250.
- Shimizu M, Saxena P, Konstantinov IE, Cherepanov V, Cheung MM, Wearden P, Zhangdong H, Schmidt M, Downey GP, and Redington AN (2010) Remote ischemic preconditioning decreases adhesion and selectively modifies functional responses of human neutrophils. *J Surg Res* **158**:155–161.
- Siddiqi N, Neil C, Bruce M, MacLennan G, Cotton S, Papadopoulos S, Feelisch M, Bunce N, Lim PO, Hildick-Smith D et al.; NIAMI investigators (2014) Intravenous sodium nitrite in acute ST-elevation myocardial infarction: a randomized controlled trial (NIAMI). *Eur Heart J* **35**:1255–1262.
- Skyschally A, Amanakis G, Neuhäuser M, Kleinbongard P, and Heusch G (2017) Impact of electrical defibrillation on infarct size and no-reflow in pigs subjected to myocardial ischemia-reperfusion without and with ischemic conditioning. *Am J Physiol Heart Circ Physiol* **313**:H871–H878.
- Skyschally A, Gres P, Heusch P, Martin C, Haude M, Erbel R, Schulz R, and Heusch G (2005) Preinfarction angina: no interference of coronary microembolization with acute ischemic preconditioning. *J Mol Cell Cardiol* **39**:355–361.
- Skyschally A, Gres P, Hoffmann S, Haude M, Erbel R, Schulz R, and Heusch G (2007) Bidirectional role of tumor necrosis factor- α in coronary microembolization: progressive contractile dysfunction versus delayed protection against infarction. *Circ Res* **100**:140–146.
- Skyschally A and Heusch G (2011) Reduction of myocardial infarct size by dronedarone in pigs—a pleiotropic action? *Cardiovasc Drugs Ther* **25**:197–201.
- Skyschally A, Kleinbongard P, Lieder H, Gedik N, Stoian L, Amanakis G, Elbers E, and Heusch G (2018) Humoral transfer and intramyocardial signal transduction of protection by remote ischemic preconditioning in pigs, rats, and mice. *Am J Physiol Heart Circ Physiol* **315**:H159–H172.
- Skyschally A, Schulz R, Gres P, Konietzka I, Martin C, Haude M, Erbel R, and Heusch G (2004) Coronary microembolization does not induce acute preconditioning against infarction in pigs—the role of adenosine. *Cardiovasc Res* **63**:313–322.
- Skyschally A, Schulz R, and Heusch G (2010) Cyclosporine A at reperfusion reduces infarct size in pigs. *Cardiovasc Drugs Ther* **24**:85–87.
- Skyschally A, van Caster P, Boengler K, Gres P, Musiolik J, Schilawa D, Schulz R, and Heusch G (2009) Ischemic preconditioning in pigs: no causal role for RISK activation. *Circ Res* **104**:15–18.
- Skyschally A, Walter B, and Heusch G (2013) Coronary microembolization during early reperfusion: infarct extension, but protection by ischaemic preconditioning. *Eur Heart J* **34**:3314–3321.
- Slagsvold KH, Rognum O, Høydal M, Wisløff U, and Wahba A (2014) Remote ischemic preconditioning preserves mitochondrial function and influences myocardial microRNA expression in atrial myocardium during coronary bypass surgery. *Circ Res* **114**:851–859.
- Sloth AD, Schmidt MR, Munk K, Kharbanda RK, Redington AN, Schmidt M, Pedersen L, Sørensen HT, Bøtker HE; CONDI Investigators (2014) Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. *Eur Heart J* **35**:168–175.
- Sloth AD, Schmidt MR, Munk K, Schmidt M, Pedersen L, Sørensen HT, Bøtker HE; Investigators C; CONDI Investigators (2015) Impact of cardiovascular risk factors and medication use on the efficacy of remote ischaemic conditioning: post hoc subgroup analysis of a randomised controlled trial. *BMJ Open* **5**: e006923.
- Sluijter JPG, Davidson SM, Boulanger CM, Buzás EI, De Kleijn DPV, Engel FB, Giricz Z, Hausenloy DJ, Kishore R, Lecour S et al. (2018) Extracellular vesicles in diagnostics and therapy of the ischaemic heart: Position Paper from the Working Group on Cellular Biology of the Heart of the European Society of Cardiology. *Cardiovasc Res* **114**:19–34.
- Smeel KM, Southworth R, Wu R, Xie C, Nederlof R, Warley A, Nelson JK, van Horssen P, van den Wijngaard JP, Heikkinen S et al. (2011) Disruption of hexokinase II-mitochondrial binding blocks ischemic preconditioning and causes rapid cardiac necrosis. *Circ Res* **108**:1165–1169.
- Smit KF, Weber NC, Hollmann MW, and Preckel B (2015) Noble gases as cardioprotectants - translatability and mechanism. *Br J Pharmacol* **172**:2062–2073.
- Smith CC, Davidson SM, Lim SY, Simpkin JC, Hothersall JS, and Yellon DM (2007) Necrostatin: a potentially novel cardioprotective agent? *Cardiovasc Drugs Ther* **21**:227–233.
- Soattin L, Lubberding AF, Bentzen BH, Christ T, and Jespersen T (2020) Inhibition of adenosine pathway alters atrial electrophysiology and prevents atrial fibrillation. *Front Physiol* **11**:493.
- Sobot NM, Sobot TS, Jeremic JN, Bolevich SB, Bolevich SS, Mitrovic SL, Fisenko VP, Inic SG, Samanovic ADM, Rankovic MR et al. (2022) Minocycline as heart conditioning agent in experimental type 2 diabetes mellitus - an antibacterial drug in heart protection. *Naunyn-Schmiedeberg's Arch Pharmacol* **395**:429–444.
- Sodi-Pallares D, Testelli MR, Fishleder BL, Bisteni A, Medrano GA, Friedland C, and De Micheli A (1962) Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. A preliminary clinical report. *Am J Cardiol* **9**:166–181.
- Soliman EZ, Ambrosius WT, Cushman WC, Zhang ZM, Bates JT, Neyra JA, Carson TY, Tamariz L, Ghazi L, Cho ME et al.; SPRINT Research Study Group (2017) Effect of intensive blood pressure lowering on left ventricular hypertrophy in patients with hypertension: SPRINT (Systolic Blood Pressure Intervention Trial). *Circulation* **136**:440–450.
- Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, Loehr L, Cushman M, and Alonso A (2015) Atrial fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* **131**:1843–1850.
- Soliman EZ and Prineas RJ (2017) Antihypertensive therapies and left ventricular hypertrophy. *Curr Hypertens Rep* **19**:79.
- Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G et al. (2014) Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med* **174**:e107–114.
- Song X, Li G, Vaage J, and Valen G (2003) Effects of sex, gonadectomy, and oestrogen substitution on ischaemic preconditioning and ischaemia-reperfusion injury in mice. *Acta Physiol Scand* **177**:459–466.
- Song Y, Song JW, Lee S, Jun JH, Kwak YL, and Shim JK (2017) Effects of remote ischemic preconditioning in patients with concentric myocardial hypertrophy: a randomized, controlled trial with molecular insights. *Int J Cardiol* **249**:36–41.
- Sonne DP, Engström T, and Treiman M (2008) Protective effects of GLP-1 analogues exendin-4 and GLP-1(9-36) amide against ischemia-reperfusion injury in rat heart. *Regul Pept* **146**:243–249.
- Spannauer A, Traxler D, Lukovic D, Zlabinger K, Winkler J, Gugerell A, Ferdinandy P, Hausenloy DJ, Pavo N, Emmert MY et al. (2019) Effect of ischemic preconditioning and postconditioning on exosome-rich fraction microRNA levels, in relation with electrophysiological parameters and ventricular arrhythmia in experimental closed-chest reperfused myocardial infarction. *Int J Mol Sci* **20**:2140.
- Speckly-Dick ME, Baxter GF, and Yellon DM (1994) Ischaemic preconditioning protects hypertrophied myocardium. *Cardiovasc Res* **28**:1025–1029.
- Staat P, Rioufol C, Piot C, Cottin Y, Cung TT, L'Huillier I, Aupetit JF, Bonnefoy E, Finet G, André-Fouët X et al. (2005) Postconditioning the human heart. *Circulation* **112**:2143–2148.
- Stiermaier T, Jensen JO, Rommel KP, de Waha-Thiele S, Fuernau G, Desch S, Thiele H, and Eitel I (2019) Combined intrahospital remote ischemic preconditioning and postconditioning improves clinical outcome in ST-elevation myocardial infarction. *Circ Res* **124**:1482–1491.
- Stiermaier T, Pöss J, Eitel C, de Waha S, Fuernau G, Desch S, Thiele H, and Eitel I (2018) Impact of left ventricular hypertrophy on myocardial injury in patients with ST-segment elevation myocardial infarction. *Clin Res Cardiol* **107**:1013–1020.
- Stiermaier T, Schaefer P, Meyer-Saraei R, Saad M, de Waha-Thiele S, Pöss J, Fuernau G, Graf T, Kurz T, Frydrychowicz A et al. (2021) Impact of morphine treatment with and without metoclopramide coadministration on myocardial and microvascular injury in acute myocardial infarction: insights from the randomized MonAMI Trial. *J Am Heart Assoc* **10**:e018881.
- Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL et al. (2016) Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. *J Am Coll Cardiol* **67**:1674–1683.
- Su H, Ji L, Xing W, Zhang W, Zhou H, Qian X, Wang X, Gao F, Sun X, and Zhang H (2013) Acute hyperglycaemia enhances oxidative stress and aggravates myocardial ischaemia/reperfusion injury: role of thioredoxin-interacting protein. *J Cell Mol Med* **17**:181–191.
- Suleiman MS, Hancock M, Shukla R, Rajakaruna C, and Angelini GD (2011) Cardioplegic strategies to protect the hypertrophic heart during cardiac surgery. *Perfusion* **26** (Suppl 1):48–56.
- Sun J, Nguyen T, Aponte AM, Menazza S, Kohr MJ, Roth DM, Patel HH, Murphy E, and Steenbergen C (2015) Ischaemic preconditioning preferentially increases protein S-nitrosylation in subsarcolemmal mitochondria. *Cardiovasc Res* **106**:227–236.
- Sun L, Shukair S, Naik TJ, Moazed F, and Ardehali H (2008) Glucose phosphorylation and mitochondrial binding are required for the protective effects of hexokinases I and II. *Mol Cell Biol* **28**:1007–1017.
- Sun T, Zhang HJ, Krittanawong C, Wang S, Tao Y, Li Z, Yin Q, Zhang D, Wang Q, Huang J et al. (2017) Acute atorvastatin treatment restores the cardioprotective effects of ischemic preconditioning in hyperlipidemic rats. *Oncotarget* **8**:55187–55193.
- Szabó MR, Gáspár R, Pipicz M, Zsindely N, Diószegi P, Sárközy M, Bodai L, and Csont T (2020) Hypercholesterolemia Interferes with Induction of miR-125b-1-3p in Preconditioned Hearts. *Int J Mol Sci* **21**:3744.
- Szobi A, Farkasová-Ledvényiová V, Lichý M, Muráriková M, Čarnická S, Ravingerová T, and Adameová A (2018) Cardioprotection of ischaemic preconditioning is associated with inhibition of translocation of MLKL within the plasma membrane. *J Cell Mol Med* **22**:4183–4196.
- Szobi A, Gonçalvesová E, Varga ZV, Leszek P, Kuśmierczyk M, Hulman M, Kyselović J, Ferdinandy P, and Adameová A (2017) Analysis of necroptotic proteins in failing human hearts. *J Transl Med* **15**:86.
- Tada H, Thompson CI, Recchia FA, Loke KE, Ochoa M, Smith CJ, Shesely EG, Kaley G, and Hintze TH (2000) Myocardial glucose uptake is regulated by nitric oxide via endothelial nitric oxide synthase in Langendorff mouse heart. *Circ Res* **86**:270–274.
- Takahashi M (2022) NLRP3 inflammasome as a key driver of vascular disease. *Cardiovasc Res* **118**:372–385.
- Talukder MA, Yang F, Shimokawa H, and Zweier JL (2010) eNOS is required for acute in vivo ischemic preconditioning of the heart: effects of ischemic duration and sex. *Am J Physiol Heart Circ Physiol* **299**:H437–H445.
- Tanjak P, Sa-Nguanmoo P, Sivasinprasasn S, Thummasorn S, Siri-Angkul N, Chattipakorn SC, and Chattipakorn N (2018) Cardioprotection of dapagliflozin and vildagliptin in rats with cardiac ischemia-reperfusion injury. *J Endocrinol* **236**:69–84.

- Tarantini G, Favaretto E, Marra MP, Frigo AC, Napodano M, Cacciavillani L, Giovagnoni A, Renda P, De Biasio V, Plebani M et al. (2012) Postconditioning during coronary angioplasty in acute myocardial infarction: the POST-AMI trial. *Int J Cardiol* **162**:33–38.
- Taylor D, Bhandari S, and Seymour AM (2015) Mitochondrial dysfunction in uremic cardiomyopathy. *Am J Physiol Renal Physiol* **308**:F579–F587.
- Techiryan G, Weil BR, Palka BA, and Cauty JM Jr (2018) Effect of Intracoronary Metformin on Myocardial Infarct Size in Swine. *Circ Res* **123**:986–995.
- Ten Cate H, Guzik TJ, Eikelboom J, and Spronk HMH (2021) Pleiotropic actions of factor Xa inhibition in cardiovascular prevention: mechanistic insights and implications for anti-thrombotic treatment. *Cardiovasc Res* **117**:2030–2044.
- Testori C, Beitzke D, Mangold A, Sterz F, Loewe C, Weiser C, Scherz T, Herkner H, and Lang I (2019) Out-of-hospital initiation of hypothermia in ST-segment elevation myocardial infarction: a randomised trial. *Heart* **105**:531–537.
- Thibault H, Piot C, Staat P, Bontemps L, Sportouch C, Rioufol G, Cung TT, Bonnefoy E, Angoulvant D, Aupetit JF et al. (2008) Long-term benefit of postconditioning. *Circulation* **117**:1037–1044.
- Thielmann M, Kottenberg E, Kleinbongard P, Wendt D, Gedik N, Pasa S, Price V, Tsagakis K, Neuhauser M, Peters J et al. (2013) Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. *Lancet* **382**:597–604.
- Thuny F, Lairez O, Roubille F, Mewton N, Rioufol G, Sportouch C, Sanchez I, Bergerot C, Thibault H, Cung TT et al. (2012) Post-conditioning reduces infarct size and edema in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* **59**:2175–2181.
- Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, and White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction (2018) Fourth universal definition of myocardial infarction (2018). *Circulation* **138**:e618–e651.
- Timmers L, Henriques JP, de Kleijn DP, Devries JH, Kemperman H, Steendijk P, Verlaan CW, Kerver M, Piek JJ, Doevendans PA et al. (2009) Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury. *J Am Coll Cardiol* **53**:501–510.
- Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, Gale CP, Maggioni AP, Petersen SE, Huculeci R et al.; Atlas Writing Group, European Society of Cardiology (2022) European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J* **43**:716–799.
- Toggart EJ, Nellis SH, and Liedtke AJ (1987) The efficacy of intermittent coronary sinus occlusion in the absence of coronary artery collaterals. *Circulation* **76**:667–677.
- Toldo S, Marchetti C, Mauro AG, Chojnacki J, Mezzaroma E, Carbone S, Zhang S, Van Tassel B, Salloum FN, and Abbate A (2016) Inhibition of the NLRP3 inflammasome limits the inflammatory injury following myocardial ischemia-reperfusion in the mouse. *Int J Cardiol* **209**:215–220.
- Torregroza C, Raupach A, Feige K, Weber NC, Hollmann MW, and Huhn R (2020) Perioperative cardioprotection: general mechanisms and pharmacological approaches. *Anesth Analg* **131**:1765–1780.
- Traverse JH, Swingen CM, Henry TD, Fox J, Wang YL, Chavez IJ, Lips DL, Lesser JR, Pedersen WR, Burke NM et al. (2019) NHLBI-sponsored randomized trial of postconditioning during primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Circ Res* **124**:769–778.
- Tsang A, Hausenloy DJ, Mocanu MM, Carr RD, and Yellon DM (2005) Preconditioning the diabetic heart: the importance of Akt phosphorylation. *Diabetes* **54**:2360–2364.
- Tsibulnikov SY, Maslov LN, Gorbunov AS, Voronkov NS, Boshchenko AA, Popov SV, Prokudina ES, Singh N, and Downey JM (2019) A review of humoral factors in remote preconditioning of the heart. *J Cardiovasc Pharmacol Ther* **24**:403–421.
- Tsuchida A, Liu Y, Liu GS, Cohen MV, and Downey JM (1994) Alpha 1-adrenergic agonists precondition rabbit ischemic myocardium independent of adenosine by direct activation of protein kinase C. *Circ Res* **75**:576–585.
- Turcato S, Turnbull L, Wang GY, Honbo N, Simpson PC, Karliner JS, and Baker AJ (2006) Ischemic preconditioning depends on age and gender. *Basic Res Cardiol* **101**:235–243.
- Tyagi S, Singh N, Viridi JK, and Jaggi AS (2019) Diabetes abolish cardioprotective effects of remote ischemic conditioning: evidences and possible mechanisms. *J Physiol Biochem* **75**:19–28.
- Uthman L, Nederlof R, Eerbeek O, Baartscheer A, Schumacher C, Buchholtz N, Hollmann MW, Coronel R, Weber NC, and Zuurbier CJ (2019) Delayed ischaemic contracture onset by empagliflozin associates with NHE1 inhibition and is dependent on insulin in isolated mouse hearts. *Cardiovasc Res* **115**:1533–1545.
- Vahlhaus C, Schulz R, Post H, Onallah R, and Heusch G (1996) No prevention of ischemic preconditioning by the protein kinase C inhibitor staurosporine in swine. *Circ Res* **79**:407–414.
- Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L et al.; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies (2018) 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* **39**:213–260.
- Valls-Lacalle L, Barba I, Miró-Casas E, Alburquerque-Béjar JJ, Ruiz-Meana M, Fuertes-Agudo M, Rodríguez-Sinovas A, and García-Dorado D (2016) Succinate dehydrogenase inhibition with malonate during reperfusion reduces infarct size by preventing mitochondrial permeability transition. *Cardiovasc Res* **109**:374–384.
- Valls-Lacalle L, Barba I, Miró-Casas E, Ruiz-Meana M, Rodríguez-Sinovas A, and García-Dorado D (2018) Selective inhibition of succinate dehydrogenase in reperfused myocardium with intracoronary malonate reduces infarct size. *Sci Rep* **8**:2442.
- van der Bijl P, Abou R, Goedemans L, Gersh BJ, Holmes Jr DR, Ajmone Marsan N, Delgado V, and Bax JJ (2020) Left ventricular post-infarct remodeling: implications for systolic function improvement and outcomes in the modern era. *JACC Heart Fail* **8**:131–140.
- van der Pals J, Koul S, Andersson P, Göteborg M, Ubachs JF, Kanski M, Arheden H, Olivecrona GK, Larsson B, and Erlinge D (2010) Treatment with the C5a receptor antagonist ADC-1004 reduces myocardial infarction in a porcine ischemia-reperfusion model. *BMC Cardiovasc Disord* **10**:45.
- van Gorp RH, Dijkgraaf I, Bröker V, Bauwens M, Leenders P, Jennen D, Dweck MR, Bucorius J, Briedé JJ, van Ryn J et al. (2021) Off-target effects of oral anticoagulants—vascular effects of vitamin K antagonist and non-vitamin K antagonist oral anticoagulant dabigatran etexilate. *J Thromb Haemost* **19**:1348–1363.
- van Hout GP, Bosch L, Ellenbroek GH, de Haan JJ, van Solinge WW, Cooper MA, Arslan F, de Jager SC, Robertson AA, Pasterkamp G et al. (2017) The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction. *Eur Heart J* **38**:828–836.
- Van Wagoner DR (2021) Right atrial blood supply and complexity of induced atrial fibrillation: what's left? *Int J Cardiol Heart Vasc* **34**:100816.
- Vanezis AP, Arnold JR, Rodrigo G, Lai FY, Debiec R, Nazir S, Khan JN, Ng LL, Chitkara K, Coghlan JG et al. (2018) Daily remote ischaemic conditioning following acute myocardial infarction: a randomised controlled trial. *Heart* **104**:1955–1962.
- Varga ZV, Ágg B, and Ferdinandy P (2018) miR-125b is a protectomiR: a rising star for acute cardioprotection. *J Mol Cell Cardiol* **115**:51–53.
- Varga ZV, Giricz Z, Bencsik P, Madonna R, Gyongyosi M, Schulz R, Mayr M, Thum T, Puskas LG, and Ferdinandy P (2015) Functional genomics of cardioprotection by ischemic conditioning and the influence of comorbid conditions: implications in target identification. *Curr Drug Targets* **16**:904–911.
- Varga ZV, Kupai K, Szücs G, Gáspár R, Pálóczi J, Faragó N, Zvara A, Puskás LG, Rázga Z, Tiszlavicz L et al. (2013) MicroRNA-25-dependent up-regulation of NADPH oxidase 4 (NOX4) mediates hypercholesterolemia-induced oxidative/nitrative stress and subsequent dysfunction in the heart. *J Mol Cell Cardiol* **62**:111–121.
- Varga ZV, Zvara A, Faragó N, Kocsis GF, Pipicz M, Gáspár R, Bencsik P, Görbe A, Csonka C, Puskás LG et al. (2014) MicroRNAs associated with ischemia-reperfusion injury and cardioprotection by ischemic pre- and postconditioning: protectomiRs. *Am J Physiol Heart Circ Physiol* **307**:H216–H227.
- Varjabedian L, Bourji M, Pourafkari L, and Nader ND (2018) Cardioprotection by metformin: beneficial effects beyond glucose reduction. *Am J Cardiovasc Drugs* **18**:181–193.
- Vermond RA, Van Gelder IC, Crijns HJ, and Rienstra M (2015) Does myocardial infarction beget atrial fibrillation and atrial fibrillation beget myocardial infarction? *Circulation* **131**:1824–1826.
- Verouhis D, Sörensson P, Gourine A, Henareh L, Persson J, Saleh N, Settergren M, Sundqvist M, Tornvall P, Witt N et al. (2016) Effect of remote ischemic conditioning on infarct size in patients with anterior ST-elevation myocardial infarction. *Am Heart J* **181**:66–73.
- Vicencio JM, Yellon DM, Sivaraman V, Das D, Boi-Doku C, Arjun S, Zheng Y, Riquelme JA, Kearney J, Sharma V et al. (2015) Plasma exosomes protect the myocardium from ischemia-reperfusion injury. *J Am Coll Cardiol* **65**:1525–1536.
- Vilahrur G and Badimon L (2014) Ischemia/reperfusion activates myocardial innate immune response: the key role of the toll-like receptor. *Front Physiol* **5**:496.
- von Elverfeldt D, Maier A, Duerschmied D, Braig M, Witsch T, Wang X, Mauler M, Neudorfer I, Menza M, Idzko M et al. (2014) Dual-contrast molecular imaging allows noninvasive characterization of myocardial ischemia/reperfusion injury after coronary vessel occlusion in mice by magnetic resonance imaging. *Circulation* **130**:676–687.
- Wagner C, Ebner B, Tillack D, Strasser RH, and Weinbrenner C (2013) Cardioprotection by ischemic postconditioning is abrogated in hypertrophied myocardium of spontaneously hypertensive rats. *J Cardiovasc Pharmacol* **61**:35–41.
- Wallbridge DR, Schulz R, Braun C, Post H, and Heusch G (1996) No attenuation of ischaemic preconditioning by the calcium antagonist nisoldipine. *J Mol Cell Cardiol* **28**:1801–1810.
- Walsh SR, Tang TY, Kullar P, Jenkins DP, Dutka DP, and Gaunt ME (2008) Ischaemic preconditioning during cardiac surgery: systematic review and meta-analysis of perioperative outcomes in randomised clinical trials. *Eur J Cardiothorac Surg* **34**:985–994.
- Wang C, Chiari PC, Weihrach D, Krolkowski JG, Warltier DC, Kersten JR, Pratt PF Jr, and Pagel PS (2006) Gender-specificity of delayed preconditioning by isoflurane in rabbits: potential role of endothelial nitric oxide synthase. *Anesth Analg* **103**:274–280 table of contents.
- Wang H, Shi X, Cheng L, Han J, and Mu J (2021) Hydrogen sulfide restores cardioprotective effects of remote ischemic preconditioning in aged rats via HIF-1 α /Nrf2 signaling pathway. *Korean J Physiol Pharmacol* **25**:239–249.
- Wang J, Wang Y, Wang J, Gao J, Tong C, Manithody C, Li J, and Rezaie AR (2013) Antithrombin is protective against myocardial ischemia and reperfusion injury. *J Thromb Haemost* **11**:1020–1028.
- Wang M, Crisostomo PR, Markel TA, Wang Y, and Meldrum DR (2008) Mechanisms of sex differences in TNFR2-mediated cardioprotection. *Circulation* **118**(14, Suppl):S38–S45.
- Wang M, Zhang W, Crisostomo P, Markel T, Meldrum KK, Fu XY, and Meldrum DR (2007) Sex differences in endothelial STAT3 mediate sex differences in myocardial inflammation. *Am J Physiol Endocrinol Metab* **293**:E872–E877.
- Wang P, Downey JM, and Cohen MV (1996) Mast cell degranulation does not contribute to ischemic preconditioning in isolated rabbit hearts. *Basic Res Cardiol* **91**:458–467.
- Wang X, Chen X, Dobrev D, and Li N (2021) The crosstalk between cardiomyocyte calcium and inflammasome signaling pathways in atrial fibrillation. *Pflugers Arch* **473**:389–405.

- Wang X, Ha T, Zou J, Ren D, Liu L, Zhang X, Kalbfleisch J, Gao X, Williams D, and Li C (2014) MicroRNA-125b protects against myocardial ischemia/reperfusion injury via targeting p53-mediated apoptotic signaling and TRAF6. *Cardiovasc Res* **102**:385–395.
- Wang X, Xu Y, Li L, and Lu W (2021) Thrombin aggravates hypoxia/reoxygenation injury of cardiomyocytes by activating an autophagy pathway-mediated by SIRT1. *Med Sci Monit* **27**:e928480.
- Webster I, Salie R, Marais E, Fan WJ, Maarman G, Huisamen B, and Lochner A (2017) Myocardial susceptibility to ischemia/reperfusion in obesity: a re-evaluation of the effects of age. *BMC Physiol* **17**:3.
- Wei M, Xin P, Li S, Tao J, Li Y, Li J, Liu M, Li J, Zhu W, and Redington AN (2011) Repeated remote ischemic postconditioning protects against adverse left ventricular remodeling and improves survival in a rat model of myocardial infarction. *Circ Res* **108**:1220–1225.
- Weil J, Zolk O, Griepentrog J, Wenzel U, Zimmermann WH, and Eschenhagen T (2006) Alterations of the preproenkephalin system in cardiac hypertrophy and its role in atrioventricular conduction. *Cardiovasc Res* **69**:412–422.
- Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW et al. (2018) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* **71**:2199–2269.
- White HD, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Erglis A, Goodman SG, Hanotin C et al.; ODYSSEY OUTCOMES Investigators (2019) Effects of alirocumab on types of myocardial infarction: insights from the ODYSSEY OUTCOMES trial. *Eur Heart J* **40**:2801–2809.
- White SK, Frohlich GM, Sado DM, Maestrini V, Fontana M, Treibel TA, Tehrani S, Flett AS, Meier P, Ariti C et al. (2015) Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* **8** (1 Pt B):178–188.
- White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S et al.; EXAMINE Investigators (2013) Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* **369**:1327–1335.
- Whittington HJ, Harding I, Stephenson CI, Bell R, Hausenloy DJ, Mocanu MM, and Yellon DM (2013) Cardioprotection in the aging, diabetic heart: the loss of protective Akt signalling. *Cardiovasc Res* **99**:694–704.
- Wider J, Undyala VVR, Whittaker P, Woods J, Chen X, and Przyklenk K (2018) Remote ischemic preconditioning fails to reduce infarct size in the Zucker fatty rat model of type-2 diabetes: role of defective humoral communication. *Basic Res Cardiol* **113**:16.
- Wiersma M, van Marion DMS, Bouman EJ, Li J, Zhang D, Ramos KS, Lanters EAH, de Groot NMS, and Brundel BJJM (2020) Cell-free circulating mitochondrial DNA: a potential blood-based marker for atrial fibrillation. *Cells* **9**:1159.
- Wildhagen KC, Schrijver R, Beckers L, ten Cate H, Reutelingsperger CP, Lutgens E, and Nicolaes GA (2014) Effects of exogenous recombinant APC in mouse models of ischemia reperfusion injury and of atherosclerosis. *PLoS One* **9**:e101446.
- Willeit K and Kiechl S (2014) Atherosclerosis and atrial fibrillation—two closely intertwined diseases. *Atherosclerosis* **233**:679–681.
- Wischmann P, Kuhn V, Suvorova T, Muessig JM, Fischer JW, Isakson BE, Haberkorn SM, Flögel U, Schrader J, Jung C et al. (2020) Anaemia is associated with severe RBC dysfunction and a reduced circulating NO pool: vascular and cardiac eNOS are crucial for the adaptation to anaemia. *Basic Res Cardiol* **115**:43.
- Wiviott SD, Giugliano RP, Morrow DA, De Ferrari GM, Lewis BS, Huber K, Kuder JF, Murphy SA, Forni DM, Kurtz CE et al. (2020) Effect of evolocumab on type and size of subsequent myocardial infarction: a prespecified analysis of the FOURIER randomized clinical trial. *JAMA Cardiol* **5**:787–793.
- Wiyosong CS, Bradley HA, Volmink J, Mayosi BM, and Opie LH (2017) Beta-blockers for hypertension. *Cochrane Database Syst Rev* **1**:CD002003.
- Wojeik B, Knapp M, and Gorski J (2018) Non-ischemic heart preconditioning. *J Physiol Pharmacol* **69** DOI: 10.26402/jpp.2018.2.03 [published ahead of print].
- Wolf A, Kutsche HS, Schreckenberg R, Weber M, Li L, Rohrbach S, Schulz R, and Schlüter KD (2020) Autocrine effects of PCSK9 on cardiomyocytes. *Basic Res Cardiol* **115**:65.
- Wolfrum S, Schneider K, Heidbreder M, Nienstedt J, Dominiak P, and Dendorfer A (2002) Remote preconditioning protects the heart by activating myocardial PKCepsilon-isoform. *Cardiovasc Res* **55**:583–589.
- Woo JS, Kim W, Ha SJ, Kim JB, Kim SJ, Kim WS, Seon HJ, and Kim KS (2013) Cardioprotective effects of exenatide in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of exenatide myocardial protection in revascularization study. *Arterioscler Thromb Vasc Biol* **33**:2252–2260.
- Wu N, Zhang X, Guan Y, Shu W, Jia P, and Jia D (2014) Hypercholesterolemia abrogates the cardioprotection of ischemic postconditioning in isolated rat heart: roles of glycogen synthase kinase-3 β and the mitochondrial permeability transition pore. *Cell Biochem Biophys* **69**:123–130.
- Wu X, Zhu H, Zhu S, Hao M, and Li Q (2017) lncRNA expression character associated with ischemic reperfusion injury. *Mol Med Rep* **16**:3745–3752.
- Wynne AM, Mocanu MM, and Yellon DM (2005) Pioglitazone mimics preconditioning in the isolated perfused rat heart: a role for the prosurvival kinases PI3K and P42/44MAPK. *J Cardiovasc Pharmacol* **46**:817–822.
- Xiao Y, Phelp P, Wang Q, Bakker D, Nederlof R, Hollmann MW, and Zuurbier CJ (2021) Cardioprotective properties of known agents in rat ischemia-reperfusion model under clinically relevant conditions: only the NAD precursor nicotinamide riboside reduces infarct size in presence of fentanyl, midazolam and cangrelor, but not propofol. *Front Cardiovasc Med* **8**:712478.
- Xie D, Zhao J, Guo R, Jiao L, Zhang Y, Lau WB, Lopez B, Christopher T, Gao E, Cao J et al. (2020) Sevoflurane pre-conditioning ameliorates diabetic myocardial ischemia/reperfusion injury via differential regulation of p38 and ERK. *Sci Rep* **10**:23.
- Xu S, Xia X, Liu Y, Chen F, Gu R, Bian X, Xu X, Jia C, Lu S, Gu Y et al. (2022) Remote cyclic compression ameliorates myocardial infarction injury in rats via AMPK-dependent pathway. *Microvasc Res* **141**:104313.
- Yamaguchi T, Izumi Y, Nakamura Y, Yamazaki T, Shiota M, Sano S, Tanaka M, Osada-Oka M, Shimada K, Miura K et al. (2015) Repeated remote ischemic conditioning attenuates left ventricular remodeling via exosome-mediated intercellular communication on chronic heart failure after myocardial infarction. *Int J Cardiol* **178**:239–246.
- Yamamoto T, Byun J, Zhai P, Ikeda Y, Oka S, and Sadoshima J (2014) Nicotinamide mononucleotide, an intermediate of NAD⁺ synthesis, protects the heart from ischemia and reperfusion. *PLoS One* **9**:e98972.
- Yan M, Chen C, Zhang F, and Chen G (2008) Lidocaine abolishes the myocardial protective effect of sevoflurane post-conditioning. *Acta Anaesthesiol Scand* **52**:111–116.
- Yang XM, Cui L, Alhammouri A, Downey JM, and Cohen MV (2013) Triple therapy greatly increases myocardial salvage during ischemia/reperfusion in the in situ rat heart. *Cardiovasc Drugs Ther* **27**:403–412.
- Yang XM, Liu Y, Cui L, Yang X, Liu Y, Tandon N, Kambayashi J, Downey JM, and Cohen MV (2013a) Platelet P2Y₁₂ blockers confer direct postconditioning-like protection in reperfused rabbit hearts. *J Cardiovasc Pharmacol Ther* **18**:251–262.
- Yang XM, Liu Y, Cui L, Yang X, Liu Y, Tandon N, Kambayashi J, Downey JM, and Cohen MV (2013b) Two classes of anti-platelet drugs reduce anatomical infarct size in monkey hearts. *Cardiovasc Drugs Ther* **27**:109–115.
- Yano T, Miki T, Tanno M, Kuno A, Itoh T, Takada A, Sato T, Kouzu H, Shimamoto K, and Miura T (2011) Hypertensive hypertrophied myocardium is vulnerable to infarction and refractory to erythropoietin-induced protection. *Hypertension* **57**:110–115.
- Yao C, Veleva T, Scott Jr L, Cao S, Li L, Chen G, Jeyabal P, Pan X, Alsina KM, Abu-Taha I et al. (2018) Enhanced cardiomyocyte NLRP3 inflammasome signaling promotes atrial fibrillation. *Circulation* **138**:2227–2242.
- Yasuda M, Takeuchi K, Hiruma M, Iida H, Tahara A, Itagane H, Toda I, Akioka K, Teragaki M, Oku H et al. (1990) The complement system in ischemic heart disease. *Circulation* **81**:156–163.
- Ye Y, Bajaj M, Yang HC, Perez-Polo JR, and Birnbaum Y (2017) SGLT-2 inhibition with dapagliflozin reduces the activation of the Nlrp3/ASC inflammasome and attenuates the development of diabetic cardiomyopathy in mice with type 2 diabetes. Further augmentation of the effects with saxagliptin, a DPP4 inhibitor. *Cardiovasc Drugs Ther* **31**:119–132.
- Ye Y, Perez-Polo JR, Aguilar D, and Birnbaum Y (2011) The potential effects of anti-diabetic medications on myocardial ischemia-reperfusion injury. *Basic Res Cardiol* **106**:925–952.
- Yellon DM and Davidson SM (2014) Exosomes: nanoparticles involved in cardioprotection? *Circ Res* **114**:325–332.
- Yellon DM, He Z, Khambata R, Ahluwalia A, and Davidson SM (2018) The GTN patch: a simple and effective new approach to cardioprotection? *Basic Res Cardiol* **113**:20.
- Yin Z, Burger N, Kula-Alwar D, Aksentijevic D, Bridges HR, Prag HA, Grba DN, Viscomi C, James AM, Mottahedin A et al. (2021) Structural basis for a complex I mutation that blocks pathological ROS production. *Nat Commun* **12**:707.
- Yuan Y, Pan SS, Wan DF, Lu J, and Huang Y (2018) H₂O₂ signaling-triggered PI3K mediates mitochondrial protection to participate in early cardioprotection by exercise preconditioning. *Oxid Med Cell Longev* **2018**:1916841.
- Yurista SR, Silljé HHW, Oberdorf-Maass SU, Schouten EM, Pavez Giani MG, Hillebrands JL, van Goor H, van Veldhuisen DJ, de Boer RA, and Westenbrink BD (2019) Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. *Eur J Heart Fail* **21**:862–873.
- Yusuf S, Sleight P, Rossi P, Ramsdale D, Peto R, Furze L, Sterry H, Pearson M, Motwani R, Parish S et al. (1983) Reduction in infarct size, arrhythmias and chest pain by early intravenous beta blockade in suspected acute myocardial infarction. *Circulation* **67**:132–141.
- Zalewski J, Claus P, Bogaert J, Driessche NV, Driesen RB, Galan DT, Sipido KR, Buszman P, Milewski K, and Van de Werf F (2015) Cyclosporine A reduces microvascular obstruction and preserves left ventricular function deterioration following myocardial ischemia and reperfusion. *Basic Res Cardiol* **110**:18.
- Zamorano-Leon JJ, Serna-Soto M, Moñux G, Freixer G, Zekri-Nechar K, Cabrero-Fernandez M, Segura A, Gonzalez-Cantalapiedra A, Serrano J, and Farré AL (2020) Factor Xa Inhibition by rivaroxaban modified mitochondrial-associated proteins in human abdominal aortic aneurysms. *Ann Vasc Surg* **67**:482–489.
- Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghiadu M, Lam CSP, Mehra MR, Neaton JD, Nessel CC et al.; COMMANDER HF Investigators (2018) Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med* **379**:1332–1342.
- Zaugg M and Lucchinetti E (2015) Remote ischemic preconditioning in cardiac surgery—ineffective and risky? *N Engl J Med* **373**:1470–1472.
- Zaugg M, Lucchinetti E, Behmanesh S, and Clanachan AS (2014) Anesthetic cardioprotection in clinical practice from proof-of-concept to clinical applications. *Curr Pharm Des* **20**:5706–5726.
- Zhang J, Huang L, Shi X, Yang L, Hua F, Ma J, Zhu W, Liu X, Xuan R, Shen Y et al. (2020) Metformin protects against myocardial ischemia-reperfusion injury and cell pyroptosis via AMPK/NLRP3 inflammasome pathway. *Aging (Albany NY)* **12**:24270–24287.
- Zhang J, Zhang X, Cui Y, Ferdous M, Cui L, and Zhao P (2018) Different postconditioning cycles affect prognosis of aged patients undergoing primary percutaneous coronary intervention. *Cardiol J* **25**:666–673.

- Zhang T, Zhang Y, Cui M, Jin L, Wang Y, Lv F, Liu Y, Zheng W, Shang H, Zhang J et al. (2016) CaMKII is a RIP3 substrate mediating ischemia- and oxidative stress-induced myocardial necroptosis. *Nat Med* **22**:175–182.
- Zhao JL, Yang YJ, Pei WD, Sun YH, Zhai M, Liu YX, and Gao RL (2008) Carvedilol reduces myocardial no-reflow by decreasing endothelin-1 via activation of the ATP-sensitive K⁺ channel. *Perfusion* **23**:111–115.
- Zhao JL, Yang YJ, You SJ, Cui CJ, and Gao RL (2007) Different effects of postconditioning on myocardial no-reflow in the normal and hypercholesterolemic mini-swines. *Microvasc Res* **73**:137–142.
- Zhao Z-Q, Corvera JS, Halkos ME, Kerendi F, Wang N-P, Guyton RA, and Vinten-Johansen J (2003) Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* **285**:H579–H588.
- Zheng Y and He JQ (2021) Common differentially expressed genes and pathways correlating both coronary artery disease and atrial fibrillation. *EXCLI J* **20**:126–141.
- Zhong Z, Liang S, Sanchez-Lopez E, He F, Shalapour S, Lin XJ, Wong J, Ding S, Seki E, Schnabl B et al. (2018) New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. *Nature* **560**:198–203.
- Zhou H, Hu S, Jin Q, Shi C, Zhang Y, Zhu P, Ma Q, Tian F, and Chen Y (2017) Mff-dependent mitochondrial fission contributes to the pathogenesis of cardiac microvasculature ischemia/reperfusion injury via induction of mROS-mediated cardiolipin oxidation and HK2/VDAC1 disassociation-involved mPTP opening. *J Am Heart Assoc* **6**:e005328.
- Zhou R, Yazdi AS, Menu P, and Tschopp J (2011) A role for mitochondria in NLRP3 inflammasome activation. *Nature* **469**:221–225.
- Zhu D, Hou J, Qian M, Jin D, Hao T, Pan Y, Wang H, Wu S, Liu S, Wang F et al. (2021) Nitrate-functionalized patch confers cardioprotection and improves heart repair after myocardial infarction via local nitric oxide delivery. *Nat Commun* **12**:4501.
- Ziegler M, Alt K, Paterson BM, Kanellakis P, Bobik A, Donnelly PS, Hagemeyer CE, and Peter K (2016) Highly Sensitive detection of minimal cardiac ischemia using positron emission tomography imaging of activated platelets. *Sci Rep* **6**:38161.
- Ziegler M, Wang X, and Peter K (2019) Platelets in cardiac ischaemia/reperfusion injury: a promising therapeutic target. *Cardiovasc Res* **115**:1178–1188.
- Zulfqar Z, Shah FA, Shafique S, Alattar A, Ali T, Alvi AM, Rashid S, and Li S (2020) Repurposing FDA approved drugs as JNK3 inhibitor for prevention of neuroinflammation induced by MCAO in rats. *J Inflamm Res* **13**:1185–1205.
- Zurbier CJ, Bertrand L, Beauloye CR, Andreadou I, Ruiz-Meana M, Jespersen NR, Kula-Alwar D, Prag HA, Eric Bøtker H, Dambrova M et al. (2020) Cardiac metabolism as a driver and therapeutic target of myocardial infarction. *J Cell Mol Med* **24**:5937–5954.
- Zurbier CJ, Heinen A, Koeman A, Stuijbergen R, Hakvoort TB, Weber NC, and Hollmann MW (2014) Cardioprotective efficacy depends critically on pharmacological dose, duration of ischaemia, health status of animals and choice of anaesthetic regimen: a case study with folic acid. *J Transl Med* **12**:325.
- Zurbier CJ and Ince C (2002) Post-ischaemic changes in the response time of oxygen consumption to demand in the isolated rat heart are mediated partly by calcium and glycolysis. *Pflugers Arch* **443**:908–916.
- Zurbier CJ, Jong WM, Eerbeek O, Koeman A, Pulskens WP, Butter LM, Leemans JC, and Hollmann MW (2012) Deletion of the innate immune NLRP3 receptor abolishes cardiac ischemic preconditioning and is associated with decreased IL-6/STAT3 signaling. *PLoS One* **7**:e40643.