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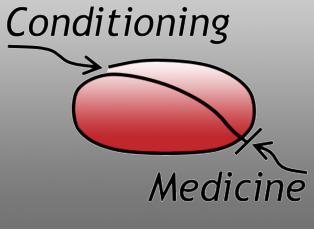

REVIEW ARTICLE | OPEN ACCESS

Cardioprotection with Ischemic Conditioning: The Diabetes Dilemma

Joseph M. Wider[1], Karin Przyklenk[2]

Ischemic conditioning paradigms used to reduce infarct size are largely based on data obtained from preclinical models that are devoid of the risk factors and comorbidities typically seen in patients with coronary artery disease. In this review, we focus on diabetes mellitus, an established risk factor for cardiovascular disease, and summarize our current understanding of the impact of type-2 and type-1 diabetes on conditioning-induced cardioprotection.

Keywords: Ischemic preconditioning, postconditioning, remote conditioning, diabetes, heart, infarct size

Introduction

A wealth of preclinical evidence has established that ischemic conditioning – encompassing the phenomena of preconditioning, postconditioning, and remote conditioning – is profoundly cardioprotective, evoking a significant infarct-sparing effect in models ranging from cardiomyocytes in culture to isolated buffer-perfused hearts to *in vivo* models of myocardial ischemia-reperfusion (I-R) (Hausenloy et al., 2016; Przyklenk, 2013). These data have provided the impetus for the launch of Phase II and Phase III trials that seek to translate the concept of conditioning-induced cardioprotection to patients with cardiovascular disease (Heusch, 2013; Heusch et al., 2016; Ovize et al., 2013). However, in contrast to the consensus among preclinical studies that ischemic conditioning reduces infarct size, the outcomes of clinical trials completed to date have been variable (ranging from positive to neutral to *deleterious*). Thus progress toward clinical translation has aptly been described as "*somewhere between frustrating and disappointing*" (Schevchuck et al., 2013).

Various explanations have been raised to explain the apparent incongruity between the efficacy of ischemic conditioning in preclinical and clinical studies (Garratt et al., 2016; Heusch et al., 2016; Heusch et al., 2017; Przyklenk et al., 2017). However, one issue that we believe merits scrutiny and discussion is the clinical relevance of the preclinical models that have been utilized. In this regard, it is noteworthy that the overwhelming majority of preclinical studies have used healthy juvenile or adult animal cohorts that are devoid of the constellation of clinically relevant risk factors and comorbidities seen in patients with coronary artery disease (Ferdinandy et al., 2014; Heusch, 2017; McCafferty et al., 2014; Miki et al., 2012; Przyklenk, 2011; Przyklenk, 2013; Przyklenk, 2015). The importance of this issue extends beyond simple choices in study design: i.e., there is a growing body of literature suggesting that these risk factors and comorbidities (including, most notably, diabetes, aging, hypertension, and hypercholesterolemia) are accompanied by dysregulation of multiple components of the signal transduction pathways that play requisite mechanistic roles in reducing infarct size with ischemic conditioning (Ferdinandy et al., 2014; Pipicz et al., 2018; Przyklenk, 2011; Przyklenk, 2013; Przyklenk, 2015; Saeid et al., 2018; Varga et al., 2015).

In the current review, we focus specifically on diabetes mellitus, an established risk factor for cardiovascular disease that affects ~8.5% of adults worldwide and is associated with a significant ~3-fold higher risk of acute myocardial infarction (WHO, 2018; Wider et al., 2014). Our goal is to provide a state-of-the-art summary of our present understanding of the impact of type-2 and type-1 diabetes on conditioning-induced cardioprotection.

Efficacy of ischemic conditioning in animal models of diabetes: a preclinical consensus?

Studies on ischemic conditioning in the context of diabetes have used various established animal models. Type-1 diabetes has been induced in rodents, rabbits, and in large animal (canine) models by single or repeated injection of the cytotoxic glucose analogues streptozotocin and alloxan. Although the mechanisms of toxicity are distinct, diabetogenic doses of streptozotocin and alloxan cause necrosis of insulin-producing beta cells, resulting

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in sustained hyperglycemia and insulinopenia within 48 hours (Lenzen, 2008). For protocols that have focused on ischemic conditioning in type-2 diabetes, rodent models in which key genes have been mutated (in particular, the leptin gene or its receptor) or wild-type mice fed high-fat and high-glucose diets have largely been used. In these models, hyperglycemia is caused by insulin resistance and is associated with additional metabolic derangements (including symptoms of metabolic syndrome such as hyperlipidemia), which may affect the response of heart ischemic conditioning or ischemia-reperfusion (I-R) injury *per se* (Fuentes-Antras et al., 2015).

Effect of experimental diabetes on sensitivity to myocardial I-R

Infarct size and clinical outcome are decidedly worse in the type-1 and type-2 diabetic population (Alegria et al., 2007; Chowdhry et al., 2007; Frustaci et al., 2000; Go et al., 2014; Haffner et al., 1998; Krempf et al., 2010; Marso et al., 2007; Mukamal et al., 2001; Murcia et al., 2004; Zia et al., 2014). In apparent contrast, the cardiac consequences of diabetes and hyperglycemia are less clear in animal models: diabetes has been reported to exacerbate the sensitivity to I-R, and increase myocardial infarct size, to render the heart resistant to I-R injury, or to have no effect (Liu et al., 1993; Miki et al., 2012; Paulson, 1997; Wider et al., 2018). This variation in outcomes may be explained by differences in experimental conditions including: i) the duration and severity of diabetes; ii) the glycemic index; iii) the presence or absence of dyslipidemia and obesity; as well as iv) the severity and duration of ischemia (Paulson, 1997; Whittington et al., 2012).

The big picture: ischemic conditioning in preclinical models of diabetes

Despite the aforementioned variations in experimental design among models and the accompanying differences in the consequences of I-R in control cohorts, there is a growing preclinical consensus that the efficacy of ischemic conditioning (including preconditioning, postconditioning, and remote conditioning) is diminished in the setting of diabetes. Of the 32 studies published to date that have measured infarct size (the acknowledged gold standard for the assessment of cardioprotection [Botker et al., 2018; Lindsey et al., 2018]), 27 (84%) reported that the infarct-sparing effect of ischemic conditioning was partially or completely attenuated in models of type-1 and type-2 diabetes (Badalzadeh et al., 2012; Bouhidel et al., 2008; Drenger et al., 2011; Fan et al., 2012; Galagudza et al., 2007; Hausenloy et al., 2013; Hjortbak et al., 2018; Ji et al., 2013; Katakam et al., 2007; Kersten et al., 2000; Kiss et al., 2014; Kristiansen et al., 2004; Lacerda et al., 2012; Liu et al., 2013; Liu et al., 1993; Liu et al., 2018; Nieszner et al., 2002; Oosterlinck et al., 2013; Potier et al., 2013; Przyklenk et al., 2011; Shi-ting, 2010; Tsang et al., 2005; Vinokur et al., 2013; Wagner et al., 2008; Wang et al., 2018; Whittington et al., 2013; Wider et al., 2018; Xue et al., 2016; Yadav et al., 2010; Zhou et al., 2017; Zhu et al., 2012; Zhu et al., 2011); summarized in Tables 1-3. Moreover, among these, only one preclinical study concluded that type-2 diabetes did not alter the efficacy of ischemic conditioning in reducing infarct size (Hjortbak et al., 2018).

Taken together, these preclinical data provide three additional and overarching insights into ischemic conditioning in diabetic models. First, the concept of an attenuation in the efficacy of ischemic conditioning was a consistent finding, irrespective of the species and model that was used (Tables 1-3), thereby suggesting that cardiac sensitivity to metabolic dysregulation is a common and consistent theme (Miki et al., 2012; Wider et al., 2014). Second, diabetes may not abrogate the infarct-sparing effect of ischemic conditioning but, rather, may increase the threshold required to achieve protection: i.e., a stronger stimulus (increased number of ischemic conditioning cycles) may be required to reach the protective threshold. For example, there are three reports that one cycle of ischemic preconditioning had no protective effect, whereas amplification

Table 1. Summary of Published Preclinical Studies: Ischemic Preconditioning

Author	Year	Species		Protective?	Mechanistic Insights?
Type-1 diabetes *			***Duration***		
Liu	1993	Rat: Wistar	11-12 months	**YES**	
Kersten	2000	Dog	3 weeks	**NO**	
Nieszner	2002	Rabbit: New Zealand White	4-5 weeks	**NO**	Impaired mito-K_{ATP} channel opening
Galagudza	2007	Rat: Wistar	6 weeks	**Attenuated**	
Shi-Ting	2010	Rat: Sprague Dawley	4 and 8 weeks	**Attenuated**	Efficacy attenuated with increased duration of diabetes
Yadav	2010	Rat: Wistar	6 weeks	**Attenuated**	Resistance to GSK-3 inhibition.
Vinokur	2013	Rat: Sprague Dawley	4 weeks	**NO**	Ferritin loss after preconditioning
Ji	2013	Rat: Sprague Dawley		**NO**	Impaired Akt phosphorylation and GLUT4 translocation
Liu	2018	Rat: Sprague Dawley	8 weeks	**NO**	Impaired Akt phosphorylation; overactive autophagy
Type-2 diabetes			***Age***		
Kristiansen	2004	Rat: Zucker Fatty	16 weeks	**NO**	
Kristiansen	2004	Rat: Goto-Kakizaki	16 weeks	**NO**	
Tsang	2005	Rat: Goto-Kakizaki		**Attenuated**	Efficacy attenuated; impaired Akt phosphorylation Amplified preconditioning stimulus required to achieve protection.
Katakam	2007	Rat: Zucker Obese	10-12 weeks	**NO**	Zucker Obese rats are normoglycemic.
Hausenloy	2013	Rat: Goto-Kakizaki		**Attenuated**	Efficacy attenuated; amplified preconditioning stimulus required to achieve protection. Co-administration of glimepimide restored protection, possibly by activation of Akt
Whittington	2013	Rat: Goto-Kakizaki	3,8,12,18 months	**Attenuated**	Impaired Akt phosphorylation; amplified stimulus was protective in 3 and 8 month old rats; complete loss in efficacy at $\geq$ 12 months
Hjortbak	2018	Rat: Zucker Fatty	6, 12, 24 weeks	**YES**	

* induced by injection of streptozotocin or alloxan.
Abbreviations: KATP = mitochondrial ATP-sensitive potassium channel; GLUT4 = glucose transporter type 4; GSK-3β = glycogen synthase kinase-3β.

to three cycles of brief I-R reduced infarct size in Goto-Kakizaki rats, a non-obese model of diabetes (Hausenloy et al., 2013; Tsang et al., 2005; Whittington et al., 2013). Finally, and perhaps not surprisingly, there is an apparent temporal or aging component to the diabetes-associated loss in efficacy of ischemic conditioning. This concept is illustrated by evidence that ischemic preconditioning effectively reduced infarct size in 3- to 8-month old Goto-Kakizaki rats but had no benefit after 12 months of age (Whittington et al., 2013). Furthermore, in the small number of studies that reported a persistent benefit of ischemic conditioning in the setting of diabetes, all utilized animals in the very early stage of type-1 diabetes; i.e., diabetic cohorts had been injected with streptozotocin 5-10 days before the ischemic event (Lacerda et al., 2012; Zhu et al., 2011). These results provide further support for the concept that the effect of diabetes on infarct size reduction with ischemic conditioning is dependent on the duration of the disease.

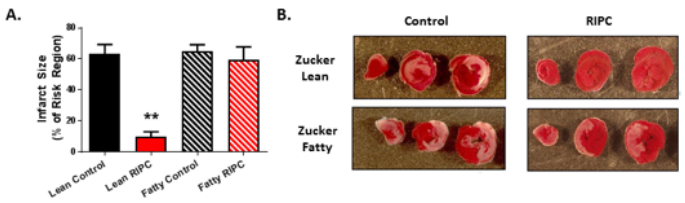

Figure 1. (A) Infarct size, expressed as a % of the myocardium at risk (mean ± SEM), for Zucker Lean and Zucker Fatty rats randomized to receive remote ischemic preconditioning (RIPC) or a time-matched control period. **p<0.01 versus the Zucker Lean control group. (B) Images of heart slices obtained from one control and one RIPC-treated rat from the Zucker Lean and Zucker Fatty cohorts. Heart slices were incubated in triphenyltetrazolium chloride; using this method, viable myocardium stains red while areas of necrosis remain unstained and thus appear pale. Reprinted with permission from Wider et al., 2018.

A deeper dive: effect of diabetes on preconditioning-, postconditioning-, and remote preconditioning-induced infarct size reduction

Ischemic preconditioning is the archetype among the conditioning paradigms and thus, is the benchmark and gold standard of conditioning-induced cardioprotection. Of the 15 studies that assessed the efficacy of ischemic preconditioning in diabetic models, 13 (87%) concluded that the infarct-sparing effect of ischemic preconditioning is attenuated or eliminated: (Galagudza et al., 2007; Hausenloy et al., 2013; Hjortbak et al., 2018; Ji et al., 2013; Katakam et al., 2007; Kersten et al., 2000; Kristiansen et al., 2004; Liu et al., 1993; Liu et al., 2018; Nieszner et al., 2002; Shi-ting, 2010; Tsang et al., 2005; Vinokur et al., 2013; Whittington et al., 2013; Yadav et al., 2010; Zhu et al., 2011); see Table 1.

Investigations into the molecular mechanisms that may contribute to the diabetes-associated loss in efficacy of ischemic preconditioning have, in most studies, focused on possible defects in elements of the so-called reperfusion injury salvage kinase (RISK) and survival activating factor enhancement (SAFE) pathways – i.e., the two pathways, in addition to nitric oxide/protein kinase G (NO/PKG) signaling, that are considered to play pivotal roles in conditioning-induced cardioprotection (Hausenloy et al., 2016; Heusch, 2015; Przyklenk, 2013). In this regard, impaired phosphorylation of Akt was identified in both diabetic Goto-Kakizaki rats and streptozotocin-induced diabetes in Sprague Dawley rats (Ji et al., 2013; Tsang et al., 2005), whereas glycogen synthase kinase-3β (GSK-3β), the inhibition of which is involved as a distal component in the RISK pathway, is reportedly activated in diabetic myocardium (Eldar-Finkelman et al., 1999; Gross et al., 2004). Interestingly, while ischemic preconditioning was not protective in streptozotocin-induced diabetic rats, direct pharmacologic inhibition of GSK-3β reduced infarct size, supporting the concept that the defect in cardioprotective signaling is upstream of GSK-3β (Yadav et al., 2010). Finally, the loss in efficacy of ischemic preconditioning in the setting of diabetes has also been attributed to defects in mitochondrial-associated mechanisms of protection (including impaired activation of mitochondrial KATP channels and aberrant hexokinase translocation (Gurel et al., 2013; Hassouna et al., 2006; Katakam et al., 2007)), as well as a diabetes-associated upregulation of autophagy (Liu et al., 2018).

Similarly, the majority of preclinical studies that have used *ischemic postconditioning* as the protective stimulus found that cardioprotection was lost or attenuated in diabetic models (12 of 13 studies; 92%: see Table 2). As with preconditioning, dysregulation of one or more components of the RISK, SAFE, and NO/PKG pathways in diabetic models has been implicated to contribute to the compromised cardioprotection, with defects in a diverse array of candidates, including Akt, GSK-3β, extracellular signal-regulated kinase (ERK), p70s6 kinase, and 5' adenosine monophosphate-activated protein kinase (AMPK) (Bouhidel et al., 2008; Fan et al., 2012; Liu et al., 2013; Przyklenk et al., 2011; Wagner et al., 2008), as well as signal transducer and activator of transcription 3 (STAT3) and NO synthase (Badalzadeh et al., 2012; Drenger et al., 2011; Fan et al., 2012) having been identified. An additional, novel culprit may be phosphatase and tensin homolog (PTEN), a negative regulator of phosphoinositide 3-kinase/Akt signaling. There is evidence that, in diabetic myocardium, PTEN is resistant to deactivation by ischemic postconditioning (thereby exerting a molecular brake on the upregulation of cardioprotective signaling) – a defect that purportedly can be mitigated (and cardioprotection restored) by pharmacologic inhibition of PTEN (Xue et al., 2016). Lastly, aberrations in autophagy have also been implicated. However, contrary to the aforementioned upregulation in autophagy in hearts from rats with streptozotocin-induced diabetes (Liu et al., 2018), others have concluded, using the same model, that: i) autophagy is repressed in the setting of diabetes, and ii) the infarct-sparing effect of postconditioning is re-established in response to genetic and pharmacologic upregulation of autophagy (Zhou et al., 2017). The reasons for this discrepancy are unclear, but may reflect the complexities of this still poorly understood phenomenon, particularly under pathophysiologic conditions of stress and cardioprotection (Dong et al., 2010; Przyklenk et al., 2012).

Remarkably, there are at present only four published studies that have investigated infarct size reduction with *remote preconditioning* in preclinical models of diabetes. Among these, two have reported persistent and significant cardioprotection, while the remaining two studies found a loss in efficacy (Table 3).

Our group provided the first and only study to date conducted in the setting of type-2 diabetes (Wider et al., 2018), Using 10-12 week old Zucker Fatty rats (an early stage time point characterized by modest elevations in non-fasting blood glucose), our results revealed that remote preconditioning, initiated by the standard stimulus of four 5-minute episodes of bilateral hindlimb ischemia, failed to reduce infarct size (Figure 1). This loss in protection did not correlate with plasma glucose concentration, thereby suggesting that the defect was not caused by hyperglycemia *per se* (Wider et al., 2018). Rather, focusing on the hallmark of remote conditioning (that is, the communication of the cardioprotective signal from the site of the remote conditioning stimulus to the at-risk myocardium (Hausenloy et al., 2016; Pickard et al., 2015; Przyklenk,

Table 2. Summary of Published Preclinical Studies: Postconditioning

Author	Year	Species		Protective?	Mechanistic Insight?
Type-1 diabetes *			***Duration***		
Dregner	2011	Rat: Sprague Dawley	4-5 weeks	**NO**	Inhibited p-STAT3 nuclear translocation
Przyklenk	2011	Mouse: C57	2 weeks	**NO**	Impaired ERK phosphorylation
Lacerda	2012	Mouse	5, 10 days	**YES**	
Fan	2012	Rat: Wistar **	4 weeks	**NO**	Impaired eNOS, Akt phosphorylation
Badalzadeh	2012	Rat: Wistar	8 weeks	**NO**	Impaired NO synthesis
Liu	2013	Rat: Sprague Dawley	12 weeks	**NO**	Impaired Akt phosphorylation, increased PTEN
Potier	2013	Mouse: C57	4-5 weeks	**NO**	
Xue	2016	Rat: Sprague Dawley	8 weeks	**NO**	Impaired Akt, STAT3 and GSK-3β phosphorylation; impaired inhibition of PTEN
Zhou	2017	Rat: Sprague Dawley	8 weeks	**NO**	Defect in AMPK/mTOR-mediated activation of autophagy
Type-2 diabetes			***Age***		
Wagner	2008	Rat: WOKW	28 weeks	**NO**	Impaired ERK, GSK-3-β phosphorylation
Bouhidel	2008	Mouse: *ob/ob*	8-10 weeks	**NO**	Impaired Akt, ERK, p70S6 kinase, AMPK phosphorylation
Przyklenk	2011	Mouse: *db/db*	12-14 weeks	**NO**	Impaired ERK phosphorylation
Zhu	2012	Mouse: *db/db*	10-12 weeks	**NO**	Differential expression of F1-ATPaseγ, Echs1 and HSP20
Oosterlinck	2013	Mouse: *ob/ob*	24 weeks	**Attenuated**	

* induced by injection of streptozotocin; ** injection of streptozotocin + high fat diet.
Abbreviations: AMPK =5' adenosine monophosphate-activated protein kinase; Echs1 = enoyl coenzyme A hydratate, short chain 1; eNOS = endothelial nitric oxide synthase; ERK = extracellular signal-regulated kinase; GSK-3β = glycogen synthase kinase-3β; HSP20 = heat shock protein 20; mTOR = mammalian target of rapamycin; NO = nitric oxide; PTEN = signal transducer and activator of transcription 3; STAT3 = signal transducer and activator of transcription 3.

2013)), we found evidence that the production or transfer of humoral blood-borne protective factor(s) in response to the preconditioning stimulus was impaired in Zucker Fatty rats when compared with matched normoglycemic Zucker Lean cohorts. Specifically, serum harvested from Zucker Lean rats following hindlimb ischemia and applied to cultured HL-1 cardiomyocytes rendered the cells resistant to a subsequent episode of hypoxia-reoxygenation, whereas serum from Zucker Fatty rats either had no cytoprotective effect or, for a specific sub-fraction of serum, exacerbated HL-1 cell death (Wider et al., 2018). Despite an exploratory proteomic analysis (Wider et al., 2018), the identity of the protective humoral factor(s) released in normoglycemic rats in response to the remote preconditioning stimulus and the identity of the toxic circulating factor(s) released in the diabetic Zucker Fatty rats remain unknown. Interestingly, one previous study used a similar experimental strategy but, in this case, collected plasma from diabetic human subjects following a remote conditioning stimulus and assessed its cardioprotective efficacy in isolated buffer-perfused rabbit hearts subjected to global I-R. Diabetes was associated with a defect in the humoral transfer of a protective trigger, but this defect was limited to a subset of diabetic patients displaying peripheral neuropathy (Jensen et al., 2012) – a factor that, in all likelihood, did not contribute to our observations made using Zucker Fatty rats treated before the development of neuropathy in our model (Oltman et al., 2005).

Among the remaining three studies, all of which used the rat model of streptozotocin-induced type-1 diabetes, outcomes have been mixed. One study reported that the reduction in infarct size with remote preconditioning was diminished 4-5 weeks after induction of diabetes, citing a defect in the generation of cardioprotective NO (Kiss et al., 2014). Conversely, in rats in which remote ischemic conditioning was commenced 8 weeks after streptozotocin injection, significant protective was still observed; however, an atypical stimulus – hindlimb ischemia applied repeatedly (daily for 3 days) was used (Wang et al., 2018). These results are consistent with the concept that an amplified (in this case, repeated) conditioning stimuli may be capable of achieving a protective threshold in diabetic myocardium, either by augmenting conventional cardioprotective signaling or via mechanisms that differ from acute kinase phosphorylation. Although the paradigm of repeated remote preconditioning is a recent development and, thus, its mechanisms are not well-understood (Thijssen et al., 2016), evidence suggests that repeated stimulus influences vascular function, myocardial gene expression, circulating factors, and effectors that are distinct from the acute standard stimulus (Epps et al., 2016; Luca et al., 2013; Wang et al., 2018; Yamaguchi et al., 2015). The fourth study also reported persistent cardioprotection using an amplified preconditioning stimulus (Zhu et al., 2011), however, as animals in this latter protocol were subjected to the conditioning stimulus only 1 week after induction of diabetes, the efficacy of conditioning-induced cardioprotection may not yet have been compromised.

Clues into clinical relevance?

Taken together, and despite the substantial heterogeneity in experimental design and mechanistic endpoints among the small number of published reports, the majority of preclinical studies have concluded that the infarct-sparing effect of ischemic conditioning is attenuated or lost in genetic and drug-induced models of diabetes (Tables 1-3; Figure 1). Nonetheless, it must be acknowledged that these data were obtained in models that do not fully mimic the scope and often years-long duration of the disease in patients. Thus, the obvious question is: are the aforementioned observations of a diabetes-associated defect in conditioning-induced cardioprotection clinically relevant?

A handful of Phase II trials took the proactive step, presumably based in part on these emerging preclinical concerns, and prospectively excluded diabetic patients from enrollment (Heusch et al., 2012; Kottenberg et al., 2012; Thielmann et al., 2010; Venugopal et al., 2009) – a practice that has also been applied to studies of ischemic conditioning in other organs (Venugopal et al., 2010). In terms of more direct evidence, there are clinical data, albeit limited, that appear to corroborate the preclinical outcomes. For example, prospective subset analyses of larger Phase II studies revealed that preinfarct angina (considered a proxy for ischemic preconditioning) failed to limit infarct size (assessed by cardiac enzyme release) in the

Table 3. Summary of Published Preclinical Studies: Remote Preconditioning

Author	Year	Species		Protective?	Mechanistic insight?
Type-1 diabetes *			***Duration***		
Zhu	2011	Rat: Wistar	1 week	**YES**	Maintained superoxide dismutase activation, xanthine oxidase deactivation
Kiss	2014	Rat: Sprague Dawley	4-5 weeks	**NO**	Impaired eNOS phosphorylation, arginase activity, ROCK activity
Wang	2018	Rat: Sprague Dawley	8 weeks	**YES**	Maintained PKC-ε deactivation; Akt, STAT3 activation
Type-2 diabetes			***Age***		
Wider	2018	Rat: Zucker Fatty	10-12 weeks	**NO**	Impaired humoral communication of protective signal

* induced by injection of streptozotocin.
Abbreviations: eNOS = endothelial nitric oxide synthase; PKC-ε = protein kinase C-ε; ROCK = rho-associated coiled containing protein kinase; STAT3 = signal transducer and activator of transcription 3.

cohort with type-2 diabetes, while there was a trend toward exacerbation of infarct size with postconditioning in diabetic subjects (Ishihara et al., 2001; Yetgin et al., 2014). Similarly, remote preconditioning was reportedly ineffective in attenuating cardiac enzyme release in diabetic patients undergoing surgical Rcoronary revascularization (Kottenberg et al., 2014), whereas in the setting of elective percutaneous coronary intervention (PCI), the incidence of peri-procedural myocardial infarction was either unchanged (rather than decreased: (Xu et al., 2014)) or exacerbated (Carrasco-Chinchilla et al., 2013) in patients with diabetes. Finally, as an interesting corollary in apparent support of preclinical reports that cardioprotection can be re-established by direct pharmacologic activation of key signaling elements, intracoronary administration of adenosine during PCI has been shown to act as an effective 'conditioning-mimetic' in diabetic patients (Shehata, 2014). However, and of potential importance: despite the aforementioned outcomes, a meta-analysis assessing the aggregate data from five trials concluded that there was no diabetes-associated loss in efficacy of remote preconditioning in patients undergoing elective PCI (D'Ascenzo et al., 2014).

Limitations, conclusions, and future directions

It could be argued that studies conducted using preclinical models of type-2 and type-1 diabetes (and, in fact, all preclinical models) are too simplistic, and will not be helpful in advancing the clinical translation of ischemic conditioning. The preclinical models clearly do not duplicate the complexities of patients with cardiovascular disease – elements of complexity that include both the presence, in some cohorts, of multiple comorbidities, as well as the potential confounding effects of the pharmacologic therapies administered as a standard of care for the clinical management of these diseases. Indeed, this latter concept is supported by evidence that anti-platelet drugs, statins, nitrates, and opiates may, in themselves, evoke significant cardioprotection and mimic or re-initiate the infarct-sparing effect of ischemic conditioning (Ferdinandy et al., 2014; Heusch, 2013; Przyklenk, 2011; Przyklenk, 2015). Moreover, there is evidence that, in surgical studies, the choice of anesthetic regimen (and, in particular, the use of propofol) can profoundly affect outcomes and conclusions regarding cardioprotection (Behmenburg et al., 2018; Garratt et al., 2016; Heusch et al., 2016; Heusch et al., 2017), most notably in diabetic populations (Ansley et al., 2016). Nonetheless, despite these limitations, the majority of studies conducted in our simplistic preclinical models of diabetes have found a loss in efficacy of conditioning-induced cardioprotection – an observation that has largely been corroborated in clinical studies and, we believe, warrants continued prospective investigation.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

Alegria JR, Miller TD, Gibbons RJ, Yi QL, Yusuf S, Collaborative Organization of RheothRx Evaluation Trial I (2007). Infarct size, ejection fraction, and mortality in diabetic patients with acute myocardial infarction treated with thrombolytic therapy. Am Heart J 154:743-750.

Ansley DM, Raedschelders K, Choi PT, Wang B, Cook RC, Chen DD (2016). Propofol cardioprotection for on-pump aortocoronary bypass surgery in patients with type 2 diabetes mellitus (PRO-TECT II): a phase 2 randomized-controlled trial. Can J Anaesth 63:442-453.

Badalzadeh R, Mohammadi M, Najafi M, Ahmadiasl N, Farajnia S, Ebrahimi H (2012). The additive effects of ischemic postconditioning and cyclosporine-A on nitric oxide activity and functions of diabetic myocardium injured by ischemia/reperfusion. J Cardiovasc Pharmacol Ther 17:181-189.

Behmenburg F, van Caster P, Bunte S, Brandenburger T, Heinen A, Hollmann MW, et al. (2018). Impact of Anesthetic Regimen on Remote Ischemic Preconditioning in the Rat Heart *In Vivo*. Anesth Analg 126:1377-1380.

Botker HE, Hausenloy D, Andreadou I, Antonucci S, Boengler K, Davidson SM, et al. (2018). Practical guidelines for rigor and reproducibility in preclinical and clinical studies on cardioprotection. Basic Res Cardiol 113:39.

Bouhidel O, Pons S, Souktani R, Zini R, Berdeaux A, Ghaleb B (2008). Myocardial ischemic postconditioning against ischemia-reperfusion is impaired in ob/ob mice. Am J Physiol Heart Circ Physiol 295:H1580-1586.

Carrasco-Chinchilla F, Munoz-Garcia AJ, Dominguez-Franco A, Millan-Vazquez G, Guerrero-Molina A, Ortiz-Garcia C, et al. (2013). Remote ischaemic postconditioning: does it protect against ischaemic damage in percutaneous coronary revascularisation? Randomised placebo-controlled clinical trial. Heart 99:1431-1437.

Chowdhry MF, Vohra HA, Galinanes M (2007). Diabetes increases apoptosis and necrosis in both ischemic and nonischemic human myocardium: role of caspases and poly-adenosine diphosphate-ribose polymerase. J Thorac Cardiovasc Surg 134:124-131,131 e121-123.

D'Ascenzo F, Moretti C, Omede P, Cerrato E, Cavallero E, Er F, et al. (2014). Cardiac remote ischaemic preconditioning reduces periprocedural myocardial infarction for patients undergoing percutaneous coronary interventions: a meta-analysis of randomised clinical trials. EuroIntervention 9:1463-1471.

Dong Y, Undyala VV, Gottlieb RA, Mentzer RM, Jr., Przyklenk K (2010). Autophagy: definition, molecular machinery, and potential role in myocardial ischemia-reperfusion

injury. J Cardiovasc Pharmacol Ther 15:220-230.
Drenger B, Ostrovsky IA, Barak M, Nechemia-Arbely Y, Ziv E, Axelrod JH (2011). Diabetes blockade of sevoflurane postconditioning is not restored by insulin in the rat heart: phosphorylated signal transducer and activator of transcription 3- and phosphatidylinositol 3-kinase-mediated inhibition. Anesthesiology 114:1364-1372.
Eldar-Finkelman H, Schreyer SA, Shinohara MM, LeBoeuf RC, Krebs EG (1999). Increased glycogen synthase kinase-3 activity in diabetes- and obesity-prone C57BL/6J mice. Diabetes 48:1662-1666.
Epps J, Dieberg G, 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.
Fan Y, Yang S, Zhang X, Cao Y, Huang Y (2012). Comparison of cardioprotective efficacy resulting from a combination of atorvastatin and ischaemic post-conditioning in diabetic and non-diabetic rats. Clin Exp Pharmacol Physiol 39:938-943.
Ferdinandy P, Hausenloy DJ, Heusch G, Baxter GF, 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.
Frustaci A, Kajstura J, Chimenti C, Jakoniuk I, Leri A, Maseri A, et al. (2000). Myocardial cell death in human diabetes. Circ Res 87:1123-1132.
Fuentes-Antras J, Picatoste B, Gomez-Hernandez A, Egido J, Tunon J, Lorenzo O (2015). Updating experimental models of diabetic cardiomyopathy. J Diabetes Res 2015:656795.
Galagudza MM, Nekrasova MK, Syrenskii AV, Nifontov EM (2007). Resistance of the myocardium to ischemia and the efficacy of ischemic preconditioning in experimental diabetes mellitus. Neurosci Behav Physiol 37:489-493.
Garratt KN, Whittaker P, Przyklenk K (2016). Remote Ischemic Conditioning and the Long Road to Clinical Translation: Lessons Learned From ERICCA and RIPHeart. Circ Res 118:1052-1054.
Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. (2014). Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 129:e28-e292.
Gross ER, Hsu AK, Gross GJ (2004). Opioid-induced cardioprotection occurs via glycogen synthase kinase beta inhibition during reperfusion in intact rat hearts. Circ Res 94:960-966.
Gurel E, Ustunova S, Kapucu A, Yilmazer N, Eerbeek O, Nederlof R, et al. (2013). Hexokinase cellular trafficking in ischemia-reperfusion and ischemic preconditioning is altered in type I diabetic heart. Mol Biol Rep 40:4153-4160.
Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M (1998). Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229-234.
Hassouna A, Loubani M, Matata BM, Fowler A, Standen NB, Galinanes M (2006). Mitochondrial dysfunction as the cause of the failure to precondition the diabetic human myocardium. Cardiovasc Res 69:450-458.
Hausenloy DJ, Wynne AM, Mocanu MM, Yellon DM (2013). Glimepiride treatment facilitates ischemic preconditioning in the diabetic heart. J Cardiovasc Pharmacol Ther 18:263-269.
Hausenloy DJ, Barrabes JA, Botker HE, Davidson SM, Di Lisa F, Downey J, et al. (2016). Ischaemic conditioning and targeting reperfusion injury: a 30 year voyage of discovery. Basic Res Cardiol 111:70.
Heusch G (2013). Cardioprotection: chances and challenges of its translation to the clinic. Lancet 381:166-175.
Heusch G (2015). Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. Circ Res 116:674-699.
Heusch G (2017). Critical Issues for the Translation of Cardioprotection. Circ Res 120:477-1486.
Heusch G, 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.
Heusch G, 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, Musiolik J, Kottenberg E, Peters J, Jakob H, Thielmann M (2012). STAT5 activation and cardioprotection by remote ischemic preconditioning in humans: short communication. Circ Res 110:111-115.
Hjortbak MV, Hjort J, Povlsen JA, Jensen RV, Stottrup NB, Laursen MR, et al. (2018). Influence of diabetes mellitus duration on the efficacy of ischemic preconditioning in a Zucker diabetic fatty rat model. PLoS One 13: e0192981.
Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, et al. (2001). Diabetes mellitus prevents ischemic preconditioning in patients with a first acute anterior wall myocardial infarction. J Am Coll Cardiol 38:1007-1011.
Jensen RV, Stottrup NB, Kristiansen SB, Botker 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.
Ji L, Zhang X, Liu W, Huang Q, Yang W, Fu F, et al. (2013). AMPK-regulated and Akt-dependent enhancement of glucose uptake is essential in ischemic preconditioning-alleviated reperfusion injury. PLoS One 8:e69910.
Katakam PV, Jordan JE, Snipes JA, Tulbert CD, Miller AW, Busija DW (2007). Myocardial preconditioning against ischemia-reperfusion injury is abolished in Zucker obese rats with insulin resistance. Am J Physiol Regul Integr Comp Physiol 292:R920-926.
Kersten JR, Toller WG, Gross ER, Pagel PS, Warltier DC (2000). Diabetes abolishes ischemic preconditioning: role of glucose, insulin, and osmolality. Am J Physiol Heart Circ Physiol 278:H1218-1224.
Kiss A, Tratsiakovich Y, Gonon AT, Fedotovskaya O, Lanner JT, Andersson DC, et al. (2014). The role of arginase and rho kinase in cardioprotection from remote ischemic perconditioning in non-diabetic and diabetic rat *in vivo*. PLoS One 9:e104731.
Kottenberg E, Thielmann M, Bergmann L, Heine T, Jakob H, Heusch G, et al. (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, et al. (2014). Myocardial protection by remote ischaemic pre-conditioning is abolished in sulphonylurea-treated diabetics undergoing coronary revascularisation. Acta Anaesthesiol Scand 58:453-462.
Krempf M, Parhofer KG, Steg PG, Bhatt DL, Ohman EM, Rother J, et al. (2010). Cardiovascular event rates in diabetic and nondiabetic individuals with and without established atherothrombosis (from the REduction of Atherothrombosis for Continued Health [REACH]

Registry). Am J Cardiol 105:667-671.
Kristiansen SB, Lofgren B, Stottrup NB, Khatir D, Nielsen-Kudsk JE, Nielsen TT, et al. (2004). Ischaemic preconditioning does not protect the heart in obese and lean animal models of type 2 diabetes. Diabetologia 47:1716-1721.
Lacerda L, Opie LH, Lecour S (2012). Influence of tumour necrosis factor alpha on the outcome of ischaemic postconditioning in the presence of obesity and diabetes. Exp Diabetes Res 2012:502654.
Lenzen S (2008). The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia 51:216-226.
Lindsey ML, Bolli R, Canty JM, Jr., Du XJ, Frangogiannis NG, Frantz S, et al. (2018). Guidelines for experimental models of myocardial ischemia and infarction. Am J Physiol Heart Circ Physiol 314:H812-H838.
Liu M, Zhou B, Xia ZY, Zhao B, Lei SQ, Yang QJ, et al. (2013). Hyperglycemia-induced inhibition of DJ-1 expression compromised the effectiveness of ischemic postconditioning cardioprotection in rats. Oxid Med Cell Longev 2013:564902.
Liu Y, Thornton JD, Cohen MV, Downey JM, Schaffer SW (1993). Streptozotocin-induced non-insulin-dependent diabetes protects the heart from infarction. Circulation 88:1273-1278.
Liu YY, Sun C, Xue FS, Yang GZ, Li HX, Liu Q, et al. (2018). Effect of Autophagy Inhibition on the Protection of Ischemia Preconditioning against Myocardial Ischemia/Reperfusion Injury in Diabetic Rats. Chin Med J (Engl) 131:1702-1709.
Luca MC, Liuni A, McLaughlin K, Gori T, Parker JD (2013). Daily ischemic preconditioning provides sustained protection from ischemia-reperfusion induced endothelial dysfunction: a human study. J Am Heart Assoc 2:e000075.
Marso SP, Miller T, Rutherford BD, Gibbons RJ, Qureshi M, Kalynych A, et al. (2007). Comparison of myocardial reperfusion in patients undergoing percutaneous coronary intervention in ST-segment elevation acute myocardial infarction with versus without diabetes mellitus (from the EMERALD Trial). Am J Cardiol 100:206-210.
McCafferty K, Forbes S, Thiemermann C, Yaqoob MM (2014). The challenge of translating ischemic conditioning from animal models to humans: the role of comorbidities. Dis Model Mech 7:1321-1333.
Miki T, Itoh T, Sunaga D, Miura T (2012). Effects of diabetes on myocardial infarct size and cardioprotection by preconditioning and postconditioning. Cardiovasc Diabetol 11:67.
Mukamal KJ, Nesto RW, Cohen MC, Muller JE, Maclure M, Sherwood JB, et al. (2001). Impact of diabetes on long-term survival after acute myocardial infarction: comparability of risk with prior myocardial infarction. Diabetes Care 24:1422-1427.
Murcia AM, Hennekens CH, Lamas GA, Jimenez-Navarro M, Rouleau JL, Flaker GC, et al. (2004). Impact of diabetes on mortality in patients with myocardial infarction and left ventricular dysfunction. Arch Intern Med 164: 2273-2279.
Nieszner E, Posa I, Kocsis E, Pogatsa G, Preda I, Koltai MZ (2002). Influence of diabetic state and that of different sulfonylureas on the size of myocardial infarction with and without ischemic preconditioning in rabbits. Exp Clin Endocrinol Diabetes 110:212-218.
Oltman CL, Coppey LJ, Gellett JS, Davidson EP, Lund DD, Yorek MA (2005). Progression of vascular and neural dysfunction in sciatic nerves of Zucker diabetic fatty and Zucker rats. Am J Physiol Endocrinol Metab 289:E113-122.
Oosterlinck W, Dresselaers T, Geldhof V, Nevelsteen I, Janssens S, Himmelreich U, et al. (2013). Diabetes mellitus and the metabolic syndrome do not abolish, but might reduce, the cardioprotective effect of ischemic postconditioning. J Thorac Cardiovasc Surg 145:1595-1602.
Ovize M, Thibault H, Przyklenk K (2013). Myocardial conditioning: opportunities for clinical translation. Circ Res 113:439-450.
Paulson DJ (1997). The diabetic heart is more sensitive to ischemic injury. Cardiovasc Res 34:104-112.
Pickard JM, Botker HE, Crimi G, Davidson B, Davidson SM, Dutka D, et al. (2015). Remote ischemic conditioning: from experimental observation to clinical application: report from the 8th Biennial Hatter Cardiovascular Institute Workshop. Basic Res Cardiol 110:453.
Pipicz M, Demjan V, Sarkozy M, Csont T (2018). Effects of Cardiovascular Risk Factors on Cardiac STAT3. Int J Mol Sci 19(11).
Potier L, Waeckel L, Vincent MP, Chollet C, Gobeil F, Jr., Marre M, et al. (2013). Selective kinin receptor agonists as cardioprotective agents in myocardial ischemia and diabetes. J Pharmacol Exp Ther 346:23-30.
Przyklenk K (2011). Efficacy of cardioprotective 'conditioning' strategies in aging and diabetic cohorts: the co-morbidity conundrum. Drugs Aging 28:331-343.
Przyklenk K (2013). Reduction of myocardial infarct size with ischemic "conditioning": physiologic and technical considerations. Anesth Analg 117:891-901.
Przyklenk K (2015). Ischaemic conditioning: pitfalls on the path to clinical translation. Br J Pharmacol 172:1961-1973.
Przyklenk K, Whittaker P (2017). The Future of Remote Ischemic Conditioning. J Cardiovasc Pharmacol Ther 22:295-296.
Przyklenk K, Maynard M, Greiner DL, 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.
Przyklenk K, Dong Y, Undyala VV, Whittaker P (2012). Autophagy as a therapeutic target for ischaemia / reperfusion injury? Concepts, controversies, and challenges. Cardiovasc Res 94:197-205.
Saeid F, Aniseh J, Reza B, Manouchehr VS (2018). Signaling mediators modulated by cardioprotective interventions in healthy and diabetic myocardium with ischaemia-reperfusion injury. Eur J Prev Cardiol 2:1463-1481.
Schevchuck A, Laskey WK (2013). Ischemic conditioning as an adjunct to percutaneous coronary intervention. Circ Cardiovasc Interv 6:484-492.
Shehata M (2014). Cardioprotective effects of intracoronary adenosine in diabetic patients undergoing elective percutaneous coronary intervention. Minerva Cardioangiol 62:461-471.
Shi-ting W (2010). Study on tolerance to ischemia-reperfusion injury and protection of ischemic preconditioning of type 1 diabetes rat heart. Biomedicine & Aging Pathology 1:56-60.
Thielmann M, Kottenberg E, Boengler K, Raffelsieper C, Neuhaeuser M, Peters J, et al. (2010). Remote ischemic preconditioning reduces myocardial injury after coronary artery bypass surgery with crystalloid cardioplegic arrest. Basic Res Cardiol 105:657-664.
Thijssen DH, Maxwell J, Green DJ, Cable NT, Jones H (2016). Repeated ischaemic preconditioning: a novel therapeutic intervention and potential underlying mechanisms. Exp Physiol 101:677-692.
Tsang A, Hausenloy DJ, Mocanu MM, Carr RD, Yellon DM (2005). Preconditioning the diabetic heart: the importance

of Akt phosphorylation. Diabetes 54:2360-2364.
Varga ZV, Giricz Z, Bencsik P, Madonna R, Gyongyosi M, Schulz R, et al. (2015). Functional Genomics of Cardioprotection by Ischemic Conditioning and the Influence of Comorbid Conditions: Implications in Target Identification. Curr Drug Targets 16:904-911.
Venugopal V, Laing CM, Ludman A, Yellon DM, Hausenloy D (2010). Effect of remote ischemic preconditioning on acute kidney injury in nondiabetic patients undergoing coronary artery bypass graft surgery: a secondary analysis of 2 small randomized trials. Am J Kidney Dis 56:1043-1049.
Venugopal V, Hausenloy DJ, Ludman A, Di Salvo C, Kolvekar S, Yap J, et al. (2009). Remote ischaemic preconditioning reduces myocardial injury in patients undergoing cardiac surgery with cold-blood cardioplegia: a randomised controlled trial. Heart 95:1567-1571.
Vinokur V, Berenshtein E, Bulvik B, Grinberg L, Eliashar R, Chevion M (2013). The bitter fate of the sweet heart: impairment of iron homeostasis in diabetic heart leads to failure in myocardial protection by preconditioning. PLoS One 8:e62948.
Wagner C, Kloeting I, Strasser RH, Weinbrenner C (2008). Cardioprotection by postconditioning is lost in WOKW rats with metabolic syndrome: role of glycogen synthase kinase 3 beta. J Cardiovasc Pharmacol 52:30-437.
Wang C, Li H, Wang S, Mao X, Yan D, Wong SS, et al. (2018). Repeated Non-Invasive Limb Ischemic Preconditioning Confers Cardioprotection Through PKC-/STAT3 Signaling in Diabetic Rats. Cell Physiol Biochem 45:2107-2121.
Whittington HJ, Babu GG, Mocanu MM, Yellon DM, Hausenloy DJ (2012). The diabetic heart: too sweet for its own good? Cardiol Res Pract 2012:845698
Whittington HJ, Harding I, Stephenson CI, Bell R, Hausenloy DJ, Mocanu MM, et al. (2013). Cardioprotection in the aging, diabetic heart: the loss of protective Akt signalling. Cardiovasc Res 99:694-704.
WHO (2018). World Health Organization Fact Sheet: https://www.who.int/news-room/fact-sheets/detail/diabetes.
Wider J, Przyklenk K (2014). Ischemic conditioning: the challenge of protecting the diabetic heart. Cardiovasc Diagn Ther 4:383-396.
Wider J, Undyala VVR, Whittaker P, Woods J, Chen X, 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 113:6.
Xu X, Zhou Y, Luo S, Zhang W, Zhao Y, Yu M, et al. (2014). Effect of remote ischemic preconditioning in the elderly patients with coronary artery disease with diabetes mellitus undergoing elective drug-eluting stent implantation. Angiology 65:660-666.
Xue R, Lei S, Xia ZY, Wu Y, Meng Q, Zhan L, et al. (2016). Selective inhibition of PTEN preserves ischaemic post-conditioning cardioprotection in STZ-induced Type 1 diabetic rats: role of the PI3K/Akt and JAK2/STAT3 pathways. Clin Sci (Lond) 130:77-392.
Yadav HN, Singh M, Sharma PL (2010). Involvement of GSK-3beta in attenuation of the cardioprotective effect of ischemic preconditioning in diabetic rat heart. Mol Cell Biochem 343:75-81.
Yamaguchi T, Izumi Y, Nakamura Y, Yamazaki T, Shiota M, Sano S, 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.
Yetgin T, Magro M, Manintveld OC, Nauta ST, Cheng JM, den Uil CA, et al. (2014). Impact of multiple balloon inflations during primary percutaneous coronary intervention on infarct size and long-term clinical outcomes in ST-segment elevation myocardial infarction: real-world postconditioning. Basic Res Cardiol 109:403.
Zhou B, Lei S, Xue R, Leng Y, Xia Z, Xia ZY (2017). DJ-1 overexpression restores ischaemic post-conditioning-mediated cardioprotection in diabetic rats: role of autophagy. Clin Sci (Lond) 131:1161-1178.
Zhu SG, Xi L, Kukreja RC (2012). Type 2 diabetic obese db/db mice are refractory to myocardial ischaemic post-conditioning *in vivo*: potential role for Hsp20, F1-ATPase delta and Echs1. J Cell Mol Med 16:950-958.
Zhu XH, Yuan HJ, Wu YN, Kang Y, Jiao JJ, Gao WZ, et al. (2011). Non-invasive limb ischemic pre-conditioning reduces oxidative stress and attenuates myocardium ischemia-reperfusion injury in diabetic rats. Free Radic Res 45:201-210.
Zia MI, Ghugre NR, Roifman I, Strauss BH, Walcarius R, Mohammed M, et al. (2014). Comparison of the frequencies of myocardial edema determined by cardiac magnetic resonance in diabetic versus nondiabetic patients having percutaneous coronary intervention for ST elevation myocardial infarction. Am J Cardiol 113:607-612.