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Themed Issue: Risk factors, comorbidities, and comedications in cardioprotection

REVIEW ARTICLE

Cardioprotection in right heart failure

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Ischaemic and pharmacological conditioning of the left ventricle is mediated by the activation of signalling cascades, which finally converge at the mitochondria and reduce ischaemia/reperfusion (I/R) injury. Whereas the molecular mechanisms of conditioning in the left ventricle are well characterized, cardioprotection of the right ventricle is principally feasible but less established. Similar to what is known for the left ventricle, a dysregulation in signalling pathways seems to play a role in I/R injury of the healthy and failing right ventricle and in the ability/inability of the right ventricle to respond to a conditioning stimulus. The maintenance of mitochondrial function seems to be crucial in both ventricles to reduce I/R injury. As far as currently known, similar molecular mechanisms mediate ischaemic and pharmacological preconditioning in the left and right ventricles. However, the two ventricles seem to respond differently towards exercise-induced preconditioning.

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1 | MYOCARDIAL ISCHAEMIA/REPERFUSION INJURY AND CARDIOPROTECTIVE STRATEGIES

In order to prevent cardiomyocyte death due to extended ischaemia, blood flow has to be restored to the ischaemic tissue. Whereas reperfusion of the ischaemic myocardium is necessary to salvage the myocardium, reperfusion itself causes additional tissue damage. However, the application of conditioning strategies allows to reduce myocardial infarct size after ischaemia/reperfusion (I/R). Conditioning describes the infarct size reduction by short, non-lethal periods of I/R, which are performed at different points in time respective to the sustained I/R. In ischaemic preconditioning (IPC), the short phases of I/R are conducted before, in ischemic perconditioning during and in ischaemic postconditioning after the sustained period of ischaemia. In remote IPC, other tissues than the heart, for example skeletal muscle undergo I/R and thereby myocardialinfarct size is decreased (Davidson et al., 2019; Hausenloy & Yellon, 2011; Hausenloy & Yellon, 2016; Heusch, 2015). Whereas IPC, ischaemic postconditioning and remote conditioning confer robust protection against I/R injury in laboratory settings, the translation of these manoeuvres to the clinical situation has been limited potentially by including all patients (even those with low risk) and the presence of co-morbidities and comedications which might interfere with the signalling cascades involved in the cardioprotective strategies. Thus, there is a need to develop novel cardioprotective strategies on the basis of new targets and

Abbreviations: 5-HD, 5-hydroxydecanoate; AMPK, AMP-activated protein kinase; CsA, cyclosporin A; Cx43, connexin 43; Drp1, dynamin-related protein 1; GLP-1, glucagon-like peptide 1; GSK3β, glycogen synthase kinase 3 β; IPC, ischaemic preconditioning; I/R, ischaemia/reperfusion; LC3A/B, microtubule-associated protein 1 light chain 3A/B; LV, left ventricle; mitoK$_{ATP}$ channels, mitochondrial ATP-dependent potassium channels; MPTP, mitochondrial permeability transition pore; NOX, NADPH oxidase; PAB, pulmonary artery banding; RISK, reperfusion injury salvage kinase; RV, right ventricle; SAFE, survival activating factor enhancement; UCP2, uncoupling protein 2.

multitarget therapies (Davidson et al., 2019; Ferdinandy, Hausenloy, Heusch, Baxter, & Schulz, 2014; Hausenloy et al., 2017).

Intensive research has been performed to elucidate the signalling pathways, which become activated upon a conditioning stimulus (for a review, see Davidson et al., 2019; Heusch, 2015). In principle, the factors contributing to conditioning are divided into triggers, intracellular mediators and so-called end-effectors. The signalling proteins can be classified into different pathways. The best characterized ones involve NO/PKG, the reperfusion injury salvage kinase (RISK) and the survival activating factor enhancement (SAFE) pathways. Mitochondria contribute to cardioprotection as they function as common endpoints of the signal transduction cascades activated by cardioprotective manoeuvres, however they also represent a source of I/R-induced myocardial damage.

Most of the studies analysing the effectiveness of conditioning focus on the left ventricle (LV). However, inferior LV infarction may also affect the right ventricle (RV) (Gadsboll et al., 1987) and involvement of the RV is associated with increased morbidity and mortality (Assali et al., 2007; Mehta et al., 2001). The analysis of the mechanisms contributing to I/R injury shows that among other factors, ischaemic calcium overload, a burst of reactive oxygen species (ROS) at reperfusion and a first pro-inflammatory response after myocardial infarction followed by a later anti-inflammatory reaction, contributes to the final size of myocardial infarction (Andreadou et al., 2019; Boengler, Lochnit, & Schulz, 2018). Accordingly, these mechanisms may be targeted in order to reduce I/R injury both in LV and RV tissues.

On the other hand, acute RV ischaemia also impacts on LV function as shown in pigs *in vivo* where RV ischaemia impairs LV contractility and relaxation (Brookes et al., 1999; Danton et al., 2001). In addition, permanent ligation of the right coronary artery in mice induces RV dysfunction and impairs LV diastolic function (Sicard et al., 2019).

When analysing I/R-induced damage of RV myocardium, differences between the RV and the LV have to be considered. For example, whereas LV myocardium originates from the primary heart field, RV myocardium derives from the secondary heart field, and such chamber-specific development is transcriptionally regulated (Srivastava & Olson, 2000). In addition, the RV is thinner—due to the coupling to a low-pressure circuit—and has a different shape than the LV. Due to lower pressures and wall stress, oxygen requirement of the RV is lower compared to that of the LV. The differences between the RV and the LV become important if the myocardium is subjected to stress conditions, specifically alterations in oxygen availability, with the RV being capable of increasingly extracting oxygen under haemodynamic stress (Crystal & Pagel, 2018; Hart, Bian, Gwirtz, Setty, & Downey, 2001). As a consequence, the RV is more resistant to ischaemia compared to the LV (Crystal & Pagel, 2018). Differences between LV and RV myocardium are shown in Figure 1.

In the present review, we focus on I/R injury and protection from it related to the RV and on the role of the diseased RV for LV I/R injury and cardioprotective strategies.

2 | ISCHAEMIA/REPERFUSION (I/R) INJURY AND ISCHAEMIC PRECONDITIONING (IPC) IN RIGHT VENTRICULAR TISSUE AND RIGHT HEART FAILURE

In the compensated phase of progressive pressure-overload hypertrophy, differences in the amounts of transcripts and proteins between left and right ventricular tissues are detected (Friehs et al., 2013). Already under baseline conditions, higher levels of proteins contributing to angiogenesis, autophagy and mitophagy are described in the rat LV compared to the RV. After I/R apoptosis is stimulated in both ventricles, the GATA-binding protein 4/Bcl-xL pathway is specifically decreased in the RV, thereby suggesting different apoptotic pathways in the LV and the RV undergoing I/R *in vitro* (Zungu-Edmondson & Suzuki, 2016).

When analysing the effectiveness of cardioprotective strategies such as IPC, the majority of studies focus on the LV. However, in 2012, Andersen and colleagues first characterized the effectiveness of IPC on the RV. In a model of global ischaemia in isolated rat hearts, IPC reduces

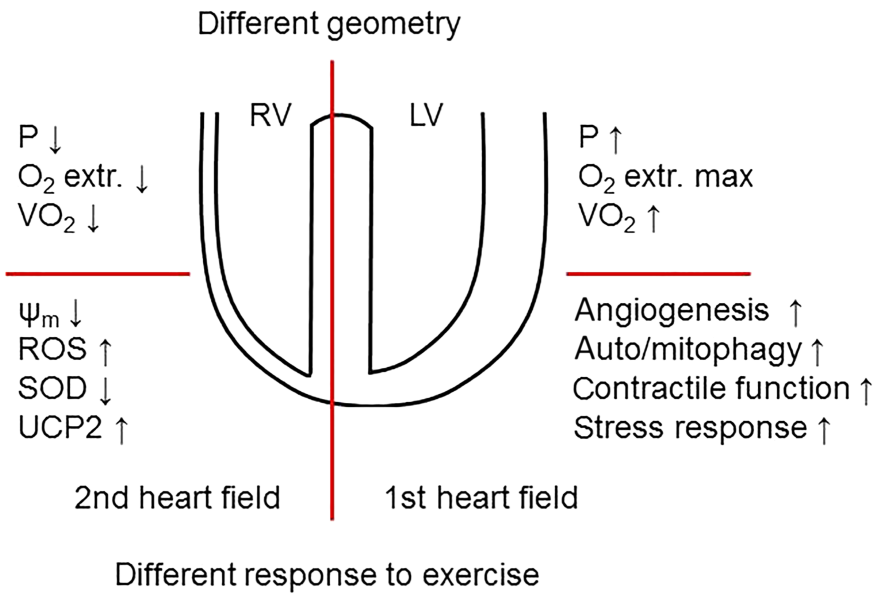

FIGURE 1 Differences between left and right ventricular myocardium (for details, see text). ↓, decreased; ↑, increased; ψm, mitochondrial membrane potential; O_2 extr., oxygen extraction; P, pressure; UCP2, uncoupling protein 2; VO_2, oxygen uptake

infarct size and improves the haemodynamic recovery of RV contractile function (Andersen, Povlsen, Botker, & Nielsen-Kudsk, 2012).

In porcine myocardium, both the PDE III-inhibitor **milrinone** and the calcium sensitizer levosimendan reduce RV I/R injury when applied during the ischaemic period (Hein et al., 2009), which extends the available data on LV pharmacological cardioprotection induced by these drugs (Bunte et al., 2018; du Toit, Genis, Opie, Pollesello, & Lochner, 2008; Sanada et al., 2001).

A recent study by Giblett et al. (2019) addresses the effect of glucagon-like peptide 1 (**GLP-1**) on stunning and ischaemic dysfunction of the RV induced by serial balloon occlusions of the right coronary artery. Here, GLP-1 exerts no protective effects, which is in contrast to the LV where GLP-1 is cardioprotective when administered either before or after the balloon occlusion (McCormick et al., 2015; Read et al., 2011). Therefore, the authors do not suggest GLP-1 as a useful therapy to reduce reversible ischaemic RV dysfunction.

IPC protects the healthy LV against I/R injury, however the cardioprotection is lost in aged and diseased myocardium (Davidson et al., 2019; Ferdinandy et al., 2014). Accordingly, the influence of RV hypertrophy and failure on the efficacy of IPC has been investigated. Subjecting rats to moderate or severe pulmonary trunk banding results in either compensated RV hypertrophy (moderate banding) or RV hypertrophy with failure (severe banding; Andersen, Povlsen, Botker, & Nielsen-Kudsk, 2013). Compared with sham-operated animals, RV infarct size after I/R *in vitro* is larger in hearts undergoing both moderate and severe banding. More importantly, whereas IPC reduces RV infarct size and improves haemodynamic recovery in sham-operated rats and in rats with moderate banding, the protective effects are abolished in rats undergoing severe banding. Interestingly, the infarct size reduction by IPC is also lost after severe banding in the LV. The analysis of signal transduction proteins classically involved in IPC's cardioprotection in the LV demonstrates no differences in the phosphorylation of **AKT** or glycogen synthase kinase 3 β (**GSK3β**) between RV tissues of sham-operated rats or rats undergoing moderate or severe banding. However, the phosphorylation of **ERK** is decreased both after moderate and severe banding, whereas the amount of cGMP and the activity of PKG are increased in rats after severe banding. Since these data are obtained under baseline conditions only, they may not explain the differences in the extent of myocardial damage after I/R without and with IPC between the analysed groups. To address the role of the cGMP/PKG pathway in RV infarct size and in the cardioprotection by IPC in more detail, pharmacological approaches to modulate the cGMP/PKG pathway are studied. Here, the use of **vardenafil** (to inhibit PDE-5 and thereby to decrease the breakdown of cGMP) protects the healthy, but not the hypertrophied or failing RV against I/R injury (Andersen et al., 2016). The PKG blocker KT 5825 has no influence on infarct size after I/R injury per se in the healthy heart, the hypertrophied or failing RV. Therefore, the inhibition of cGMP breakdown and the up-regulated PKG under baseline conditions are not sufficient to induce cardioprotection in the failing RV.

In patients with acute inferior myocardial infarction caused by right coronary artery occlusion, the absence of pre-infarction angina is an independent predictor of the occurrence of RV infarction (Shiraki et al., 1998). Therefore, the beneficial effects of pre-infarction angina, which is considered a clinical surrogate of IPC, are not specific for the LV where pre-infarction angina also improves ejection fraction and reduces infarct size (Reiter, Henry, & Traverse, 2013).

Clinical data on the effectiveness of remote IPC in patients with diseases affecting the RV are contradictory, showing either beneficial effects (Cheung et al., 2006) or no protection (Lee et al., 2012; Pavione, Carmona, de Castro, & Carlotti, 2012).

Data on the effects of I/R injury, IPC and remote IPC as well as pharmacological preconditioning on the RV and the LV are summarized in Table 1. Taken together, whereas differences exist in molecular pathways between the LV and the RV under physiological conditions and also in response to stress, the right heart can be principally protected by similar IPC protocols as the LV. More studies are needed to address the molecular mechanisms of cardioprotection in the RV and also those pathophysiological conditions in which the cardioprotection of the RV is abolished. Studies addressing the effectiveness of ischaemic postconditioning and remote IPC in the RV are needed, and the response of the diseased RV towards such cardioprotective manoeuvres should be investigated in more detail (Fig. 2).

3 | ACTIVATION OF SIGNALLING PROTEINS IN RIGHT HEART HYPERTROPHY AND FAILURE

Data on the activation of classical cardioprotective signalling pathways in the context of I/R injury and IPC in the RV are limited. Changes in the expression/activation of proteins involved in right heart hypertrophy and failure may contribute to the loss of IPC's cardioprotection in the diseased RV (Andersen et al., 2013). In the following, we discuss the expression and phosphorylation of some proteins belonging to different pathways classically activated by preconditioning, which are affected in the failing RV.

AKT is part of the RISK pathway, a pro-survival signalling cascade, which is induced by a preconditioning stimulus (Heusch, 2015). The inhibition of AKT phosphorylation results in an abrogation of infarct size reduction by IPC (Heusch, 2015). In both rats (Yang et al., 2014) and mice (Hu, Sharifi-Sanjani, & Tofovic, 2017), pulmonary artery banding (PAB) induces the phosphorylation of AKT, an effect prevented by nitrite treatment (Hu et al., 2017). In this line, an improvement of RV systolic performance by caffeic acid phenethyl ester is associated with the inhibition of AKT phosphorylation, which is induced by monocrotaline (Cheng et al., 2019). However, the studies by Mosele et al. (2012) and Andersen et al. (2013) demonstrate no effect of monocrotaline or pulmonary trunk banding on the phosphorylation of AKT. Since in preconditioning protocols of the LV, AKT phosphorylation is necessary for cardioprotection and since in the failing RV, AKT is phosphorylated—or at least not down-regulated—it is questionable whether AKT is involved in the loss of IPC's cardioprotection in the failing RV.

Downstream of AKT in the RISK pathway is GSK3β, a kinase contributing to cardioprotection by mechanisms involving mitochondrial function (Juhaszova et al., 2004), but also by mitochondria-

TABLE 1 Effects of ischaemia/reperfusion (I/R) injury and cardioprotection by ischaemic preconditioning (IPC), remote IPC and pharmacological preconditioning on the RV and the LV

Parameter	Model	Effect on LV or RV tissue	Reference
I/R injury	Physiological conditions or I/R in isolated perfused working hearts (30 min isch, 2 hr rep)	Physiological conditions: LV > RV: angiogenesis, autophagy, mitophagy; I/R: ↑ apoptosis in LV and RV; RV < LV: GATA4/Bc-xL	(Zungu-Edmondson & Suzuki, 2016)
	Ligation of porcine distal RCA, 90 min isch, 2 hr rep, 30 min after isch bolus of milrinone (50 $\mu g \cdot kg^{-1}$) followed by 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or levosimendan (24 $\mu g \cdot kg^{-1}$ bolus, then 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	↓ RV IS ↓ neutrophil infiltration	(Hein et al., 2009)
	Guinea pig heart, working heart perfusion, 0.1 μM levosimendan, 10 min before coronary artery ligation, 40 min isch, 30 min rep	↓ LV IS	(du Toit et al., 2008)
	Open-chest dogs, 90 min isch, 6 hr rep, milrinone 30 $\mu g \cdot kg^{-1}$, 30 min before isch	↓ LV IS	(Sanada et al., 2001)
	Isolated rat hearts, 33 min isch, 1 hr rep, levosimendan 0.1 and 0.3 μM, 10 min before isch	↓ IS	(Bunte et al., 2018)
	Patients with severe dominant RCA disease awaiting elective PCI with normal RV function, pressure volume recordings, GLP-1 1.2 $pmol \cdot kg^{-1} \cdot min^{-1}$ for 30 min after first balloon occlusion	No effect of GLP-1 on RV stunning and dysfunction	(Giblett et al., 2019)
	Patients with single-vessel left anterior descending coronary artery disease awaiting elective PCI with normal LV function, pressure volume recordings, GLP-1 1.2 $pmol \cdot kg^{-1} \cdot min^{-1}$ for 30 min after first balloon occlusion	↓ LV dysfunction and stunning by GLP-1	(McCormick et al., 2015; Read et al., 2011)
IPC	Isolated rat hearts, IPC 2× 5 min I/R, followed by 40 min isch and 2 hr rep	↓ RV IS; ↑ recovery of RV function	(Andersen et al., 2012)
	Isolated rat hearts, IPC 2× 5 min I/R, followed by 40 min isch and 2 hr rep	↑RV IS in hearts with compensated RV hypertrophy and hearts with RV failure compared to sham ↓ RV infarct size by IPC in sham and in hearts with compensated RV hypertrophy, but not in hearts with RV failure	(Andersen et al., 2013)
	Isolated rat hearts, IPC 2× 5 min I/R, followed by 40 min isch and 2 hr rep, vardenafil (66 nM) or KT 5825 (1 μM) 5 min before index isch and during rep	Healthy hearts: ↓ RV IS by IPC and vardenafil, KT 5825 no effect per se, but abolished protection by vardenafil; failing RV (pulmonary trunk banding): no IS reduction by IPC or vardenafil	(Andersen et al., 2016)
	Patients with acute inferior myocardial infarction, without and with preinfarction angina	Preinfarction angina is an independent predictor of the absence of RV infarction	(Shiraki et al., 1998)
	Patients with ST elevation myocardial infarction in the setting of primary percutaneous coronary intervention acute myocardial infarction, without and with preinfarction angina	Preinfarction angina improved LV function and reduced IS	(Reiter et al., 2013)
Remote IPC	Children undergoing repair of congenital heart defects without or with remote IPC by 4× 5 min lower limb isch and rep directly before surgery	Higher troponin I levels in control than in remote IPC group	(Cheung et al., 2006)

(Continues)

TABLE 1 (Continued)

Parameter	Model	Effect on LV or RV tissue	Reference
	Infants with pulmonary hypertension undergoing ventricular septal defect repair without or with remote IPC by 4× 5 min lower limb isch and rep	Similar troponin I levels according to time or total amount between control and remote IPC	(Lee et al., 2012)
	Children undergoing repair of congenital heart defects without or with remote IPC by 4× 5 min lower limb isch and rep performed 24 hr before surgery	Remote IPC does not reduce troponin I release	(Pavione et al., 2012)

Abbreviations: ↑, increased; ↓, decreased; GATA4, GATA-binding protein 4; GLP-1, glucagon-like peptide 1; IS, infarct size; isch, ischaemia; LV, left ventricle; PCI, percutaneous coronary intervention; RCA, right coronary artery; rep, reperfusion; RV, right ventricle.

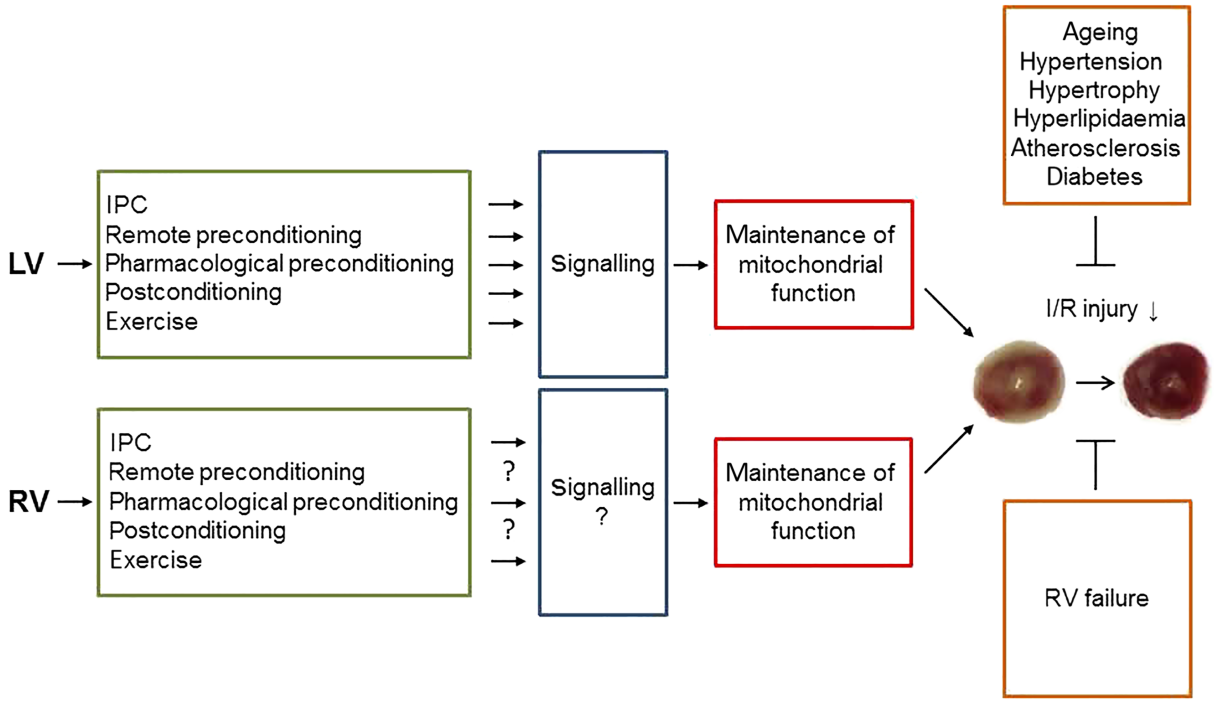

FIGURE 2 Cardioprotection in LV and RV myocardium. Schematic overview of the different cardioprotective strategies, which are analysed or not yet investigated in healthy or diseased LV and RV myocardium. ?, unknown; ↓, decreased; ⊤, inhibition

independent pathways (Nikolaou et al., 2019). The role of the protein in conditioning of the RV has not been studied yet, however the importance of the phosphorylation status of GSK3β for RV dysfunction has been analysed. Here, the phosphorylation of GSK3β—which induces an inactivation of the protein—is not affected in the RV after moderate or severe pulmonary trunk banding (Andersen et al., 2013). However, other studies suggested an involvement of GSK3β in RV dysfunction since the phosphorylation of GSK3β is enhanced in monocrotaline-induced hypertrophy (Colombo et al., 2013). Therefore, the roles of GSK3β in RV dysfunction and in RV I/R injury need to be elucidated in further detail.

In addition to GSK3β, endothelial NOS (eNOS) is phosphorylated by AKT and is upstream of cGMP/PKG in the signalling cascades induced by cardioprotective manoeuvres (Heusch, 2015). In the RV of monocrotaline-treated rats, the expression of eNOS is decreased (Campos-Carraro et al., 2018), but statin therapy might restore reduced myocardial eNOS expression as demonstrated in a post-cardiopulmonary bypass pig model (Kuhn et al., 2013).

In the LV, the phosphorylation of STAT3, an essential protein of the SAFE pathway, which is involved in preconditioning's cardioprotection, is induced by IPC (Xuan, Guo, Han, Zhu, & Bolli, 2001). In addition, STAT3 is involved in the cardioprotection by ischaemic postconditioning (Boengler et al., 2008). Pulmonary arterial hypertension enhances the phosphorylation of STAT3 and an improvement in RV function is associated with a decreased phosphorylation of the protein (Alzoubi et al., 2013; Paulin et al., 2011). A role of mitochondrial STAT3, which may contribute to myocardial I/R injury (Szczepanek et al., 2011), in the context of RV dysfunction has not been studied yet. Therefore, whereas in pulmonary arterial hypertension, an amelioration of RV function involves decreased STAT3

activation, STAT3 is essential for the cardioprotection in the LV. If STAT3 plays a similar role in conditioning of the RV than in the LV is unknown at present.

STAT5, another member of the STAT protein family, is implicated in the protection achieved by remote conditioning in LV tissue of rabbits and humans (Andreadou et al., 2015; Heusch et al., 2012). In hypoxic pulmonary arterial hypertension, vascular remodelling is induced by activation of the RhoA-ROCK pathway, and this activation is associated with reduced phosphorylation of STAT5 and enhanced phosphorylation of STAT3 in peripheral blood and spleen in hypoxic rats (Li et al., 2018).

Connexin 43 (Cx43), the major gap junction protein in ventricular myocytes, contributes to the cardioprotection by IPC (Leybaert et al., 2017). In addition, Cx43 is localized at the inner mitochondrial membrane and influences mitochondrial function in terms of respiration, potassium uptake, and ROS formation (Boengler et al., 2012; Boengler, Ungefug, Heusch, Leybaert, & Schulz, 2013; Soetkamp et al., 2014). The amounts of the Cx43 mRNA and protein decrease in the RV after monocrotaline injection (Tanaka, Takase, Yao, & Ishihara, 2013), and the administration of the PDE III inhibitor cilostazol to treat monocrotaline-induced pulmonary hypertension increases the expression of Cx43 in the RV (Chang et al., 2008). If such putative involvement of Cx43 in RV failure encompasses the function of Cx43 as a protein involved in arrhythmias, calcium handling or mitochondrial function remains to be determined. Also, if Cx43 (gap junctional and/or mitochondrial) plays a role in the cardioprotection of the RV remains unknown at present.

A summary of the proteins involved in LV cardioprotection and in RV hypertrophy and failure is presented in Table 2.

Taken together, signalling proteins known to be involved in the cardioprotection against I/R injury of the LV are also affected in the failing RV. However, the roles of the proteins may differ between the LV and the RV, and more research is needed to clarify the role of the signalling proteins in RV injury and protection from it.

4 | ROLE OF MITOCHONDRIA IN RIGHT VENTRICULAR ISCHAEMIA AND FAILURE

Downstream targets of the NO/PKG, the RISK and the SAFE pathways are mitochondria, organelles central for LV I/R injury and the protection from it by cardioprotective strategies. Mitochondria are affected by I/R in several aspects, among them oxygen consumption, formation of ROS and opening of the mitochondrial permeability transition pore (MPTP) and mitochondrial ATP-dependent potassium channels (mitoK$_{ATP}$ channels) as well as mitophagy and mitochondrial dynamics. Whereas mitochondria from LV origin are intensively studied in the context of I/R injury and cardioprotection (Boengler et al., 2018; Lesnefsky, Chen, Tandler, & Hoppel, 2017), data on RV mitochondria are less substantial.

Using proteomic approaches, the baseline protein composition of the LV and the RV shows no major difference between the ventricles. Whereas this includes proteins involved in oxidative phosphorylation (Phillips et al., 2011), another study demonstrates alterations in the amounts of proteins involved in energy metabolism between the LV and the RV (Cadete, Lin, Sawicka, Wozniak, & Sawicki, 2012). Also, a higher expression of proteins contributing to contractile function, stress response and the respiratory chain is detected in the LV than in the RV, which is presumably due to the higher LV workload (Birner et al., 2012). In addition to the differences in the protein amounts between the LV and the RV, also a baso-apical heterogeneity in the ventricular protein distribution has to be considered (Eckhardt et al., 2018). With ischaemia, the amounts of some RV proteins—involved in energy metabolism, proteins with antioxidative function and heat shock proteins—are changed (Cadete et al., 2012). The antioxidative capacity also differs under stress conditions between the RV and the LV (Schreckenberg et al., 2015).

Due to the lower workload in the RV, the mitochondrial oxygen consumption at rest is lower than in the LV (Rumsey et al., 1999). This finding is supported by a lower mitochondrial membrane potential, which is used as a surrogate marker for mitochondrial function, in the RV than in the LV (Nagendran et al., 2008). However, mitochondrial oxygen consumption is affected under chronic hypoxic conditions. In a rat model of chronic normobaric hypoxia, mitochondrial respiration is enhanced in the LV but not in mitochondria from the hypertrophied RV, which indicates an LV-specific compensation for the decreased oxygen availability (Ferri et al., 2018). However, another study shows that the oxidative capacity, which is higher in the LV than in the RV under control conditions, declines with chronic hypoxia in LV mitochondria only (Rumsey et al., 1999). It is suggested that the decrease in oxidative capacity with chronic hypoxia in the LV precedes that occurring in the RV, suggesting adaptation processes in the RV with the onset of hypertrophy (Nouette-Gaulain et al., 2005). In two models of RV dysfunction (**SU5416**/hypoxia and pulmonary artery banding), the yield of mitochondria isolated from the RV is decreased. However, ADP-stimulated respiration on glutamate is impaired in mitochondria isolated from RV tissue after SU5416/hypoxia treatment only. In this model, mitochondrial ultrastructure is highly abnormal (Gomez-Arroyo et al., 2013). Reduced oxygen consumption occurring in the SU5416/hypoxia model is partially restored by **oestrogen** treatment (Liu et al., 2017).

In the rat monocrotaline model, mitochondrial respiration decreases in RV hypertrophy and failure (Daicho et al., 2009; Wust et al., 2016). Interestingly, such decrease in mitochondrial oxygen consumption during the transition towards RV failure is not associated with reduced mitochondrial oxygenation, which argues against hypoxia as an important contributor for RV failure (Balestra et al., 2015). Decreased respiration may be based on alterations of the mitochondrial transcriptomic pathway with 413 dysregulated genes in RV failure (Potus, Hindmarch, Dunham-Snary, Stafford, & Archer, 2018). The reduction of the mitochondrial oxygen consumption in the RV after monocrotaline treatment is prevented by **dichloroacetate** therapy and it is hypothesized that RV dysfunction is caused at least in part by a pyruvate dehydrogenase kinase-mediated glycolytic shift (Piao et al., 2010a; Piao, Marsboom, & Archer, 2010b). However, succinate dehydrogenase and cytochrome c oxidase activities are

TABLE 2 Signalling proteins involved in LV cardioprotection and RV hypertrophy and failure

Protein	Cardioprotection in the LV	RV hypertrophy and failure
AKT	Stimulated by cardioprotection (Rossello & Yellon, 2018) ↓ AKT phosphorylation abrogates IS reduction by IPC (Hausenloy, Tsang, Mocanu & Yellon, 2005)	PAB in mice: ↑ AKT phosphorylation, which is prevented by nitrite (Hu et al., 2017) PAB in rats: ↑ AKT phosphorylation (Yang et al., 2014) Rat MCT model: no effect on RV AKT phosphorylation (Mosele et al., 2012) Rats subjected to moderate or severe pulmonary trunk banding: no effect on AKT phosphorylation (Andersen et al., 2013) Hypoxic hPASMC: ↑ AKT phosphorylation, which is prevented by CAPE, CAPE improves systolic performance in MCT-treated rats (Cheng et al., 2019)
GSK3β	Inhibition of GSK3β reduces MPTP opening (Juhaszova et al., 2004) Inhibition of GSK3β reduces IS (Nikolaou et al., 2019)	Rats subjected to moderate or severe pulmonary trunk banding: no effect on GSK3β phosphorylation (Andersen et al., 2013) GSK3β phosphorylation ↑in MCT-treated rats (Colombo et al., 2013) GSK3β inhibition by SB216763 ↓ LPS-induced RV hypertrophy (Baarsma et al., 2013)
eNOS	eNOS is phosphorylated by AKT and upstream of cGMP/PKG signalling, is central for cardioprotection; for a review, see Heusch (2015)	eNOS expression ↓ in MCT-treated rats (Campos-Carraro et al., 2018) Statin recapture therapy post-cardiopulmonary bypass: ↑ eNOS expression and ↑ NO-dependent relaxation of right coronary arteries (Kuhn et al., 2013)
STAT3	IPC induces nuclear translocation of STAT3 (Xuan et al., 2001) Cardioprotection by IPC is abrogated in STAT3-deficient mice (Smith et al., 2004) Cardioprotection by ischaemic postconditioning is abrogated in STAT3-deficient mice (Boengler et al., 2008) STAT3 is an essential component of the cardioprotective SAFE pathway (Lecour, 2009) Mitochondrial STAT3 protects against ischaemic mitochondrial damage (Szczepanek et al., 2011)	RV STAT3 phosphorylation ↑ in pulmonary arterial hypertension induced by Sugen 5416/hypoxia/normoxia in rats (Alzoubi et al., 2013) STAT3 phosphorylation and nuclear translocation ↑ in PASMCs from patients with pulmonary arterial hypertension (Paulin et al., 2011) STAT3 phosphorylation ↑ in MCT-treated rats, dehydroepiandrosterone: STAT3 phosphorylation ↓ in MCT-treated rats and reduced RV hypertrophy (Paulin et al., 2011)
STAT5	STAT5 phosphorylation ↑ in remote preconditioning in rabbits (Andreadou et al., 2015)	Activation of the RhoA-ROCK pathway decreases STAT5 phosphorylation in rats with pulmonary arterial hypertension induced by hypoxia (Li et al., 2018)

(Continues)

TABLE 2 (Continued)

Protein	Cardioprotection in the LV	RV hypertrophy and failure
	STAT5 phosphorylation ↑ in remote preconditioning in humans (Heusch et al., 2012)	
Cx43	Infarct size reduction by IPC is abrogated in Cx43-deficient mice (for a review, see Schulz et al., 2015)	RV Cx43 mRNA and protein ↓ in MCT-treated rats (Tanaka et al., 2013) RV Cx43 protein ↓ in MCT-treated rats, decrease prevented by cilostazol (Chang et al., 2008)

Abbreviations: ↓, decreased; ↑, increased; CAPE, caffeic acid phenethyl ester; IPC, ischaemic preconditioning; IS, infarct size; LV, left ventricle; MCT, monocrotaline; PAB, pulmonary artery banding; PASMC, pulmonary arterial smooth muscle cell; RV, right ventricle.

unchanged after monocrotaline treatment, but activities increase after a combination treatment with the PDE 5 inhibitor sildenafil and the endothelin receptor blocker **bosentan** (Mouchaers et al., 2009). The β-adrenoceptor antagonist **metoprolol** decreases RV hypertrophy, resulting in a less hypoxic myocardium, which is associated with better functional coupling between mitochondria and the creatine kinase system (Fowler et al., 2019). However, in another study (Power, Norman, Jones, Hickey, & Ward, 2019) metoprolol does not regress RV hypertrophy, which may be due to the differences in the age of experimental animals and in the duration of metoprolol treatment. A reduction in mitochondrial respiration is not specific for the hypertrophied or failing myocardium but is also common in organelles isolated following I/R (for a review, see Boengler et al., 2018; Lesnefsky et al., 2017). In RV samples from children and young adults undergoing cardiac surgery for congenital heart disease and which are classified based on compensated or decompensated RV function, the activities of citrate synthase and succinate dehydrogenase are unaffected during hypertrophy but reduced in the failing state (Karamanlidis, Bautista-Hernandez, Fynn-Thompson, Del Nido, & Tian, 2011). Since a depletion of the mitochondrial DNA occurs prior to the reduction of enzyme activities, it is suggested that impaired mitochondrial DNA replication is important for the transition from RV hypertrophy to failure.

In the LV, IPC often preserves the I/R-induced decrease of mitochondrial oxygen consumption (Crestanello et al., 2002). The already reduced mitochondrial respiration in the failing RV may contribute to the inability to protect such tissue from I/R damage.

ROS originate from different sources, such as **NADPH oxidase** (NOX), xanthine oxidase, uncoupled NOS, MAO and p66shc, as well as from the mitochondrial electron transport chain. In addition, scavenging enzymes such as catalase or SOD contribute to the ROS balance. Under physiological conditions, ROS formation is higher in RV than in LV mitochondria (Schluter, Kutsche, Hirschhauser, Schreckenberg, & Schulz, 2018). The transition from RV hypertrophy to failure is characterized by increased ROS formation and concomitant reduction of the antioxidative defence (for a review, see Schluter et al., 2018). Accordingly, up-regulation of ROS-forming proteins is detected in various models of RV hypertrophy and failure. In a pharmacological model of hypertension induced by chronic administration of **L-NAME**, uncoupling of NOS induces the formation of ROS in the RV (Schreckenberg et al., 2015). Also, the expression of iNOS (NOS2) increases in mice undergoing pulmonary artery banding operation and the induction of iNOS is associated with increased ROS formation. Such increases in ROS are prevented in iNOS-deficient mice (Boehm et al., 2019). The amount of ROS and the **MMP**-2, -9, and -13 are enhanced after pulmonary artery banding in mice and the administration of folic acid, which is known to ameliorate oxidative stress, reduces ROS formation, the expression of the aforementioned MMPs and improves RV function (Qipshidze, Tyagi, Metreveli, Lominadze, & Tyagi, 2012). In the rat monocrotaline model, the increase in ROS in the failing RV is associated with an up-regulation of complex II of the electron transport chain, of $gp91^{phox}$ (Redout et al., 2007) and of **NOX4** (He et al., 2017). In the same model, the administration of trapidil reduces the NOX activity and improves RV remodelling (Turck et al., 2018). Also, whereas the activity of xanthine oxidase is unchanged in RV hypertrophy, it increases in the failing RV and is not affected in the LV (de Jong et al., 2000). In patients with ischaemic heart disease, the activity of MAO increases in the RV and correlates with enhanced oxidative stress (Manni et al., 2016).

Increased oxidative stress is not only caused by increased expression/activity of ROS-generating enzymes but also caused by defects in the ROS defence in the failing RV. For example, in dogs treated with dehydromonocrotaline, the amounts of the ROS scavenging proteins periredoxin 5 and the cytosolic form of the SOD are reduced compared to sham-operated animals (Aziz et al., 2015). Additionally, an inability to induce antioxidant proteins such as GSH peroxidase is seen in the rat monocrotaline model (Ecarnot-Laubriet, Rochette, Vergely, Sicard, & Teyssier, 2003). **Melatonin**, which exerts antioxidative effects, is known to reduce LV I/R injury via the SAFE pathway (Lamont, Somers, Lacerda, Opie, & Lecour, 2011). Melatonin reduces plasma oxidative stress when administered as a curative treatment after or as a preventive treatment before the injection of monocrotaline, furthermore it decreases RV hypertrophy and improves RV function (Maarman et al., 2015). A reduction of oxidative stress using the mitochondria-targeted antioxidant MitoQ inhibits pulmonary artery banding-induced RV dilatation (Pak et al., 2018) and

the use of ROS scavengers such as N-acetylcysteine protects against the development of pulmonary hypertension in the rat monocrotaline model (Guo et al., 2016).

Uncoupling protein 2 (UCP2) is located in the inner mitochondrial membrane and plays a role in the dissipation of the proton electrochemical gradient across the inner mitochondrial membrane, as well as calcium movements and is necessary for the protection by IPC (McLeod, Aziz, Hoyt, McCoy, & Sack, 2005; Motloch et al., 2016). The deletion of UCP2 in mice, which is expressed at higher levels in the RV than in the LV, demonstrated that these mice are protected against pressure overload induced by pulmonary artery banding, an effect presumably involving UCP2-dependent regulation of fibrosis (Esfandiary et al., 2019).

The role of ROS in I/R injury and protection from it demonstrates that the highest amount of ROS is produced at the onset of reperfusion (Murphy & Steenbergen, 2008) and that in IPC, this ROS release is reduced (Quarrie et al., 2012). However, also a role of ROS as signalling molecules triggering the protection by IPC has been described (Heusch, 2015). Whereas the role of ROS in the cardioprotection of the RV has not been analysed yet, high amounts of ROS in the failing RV may enhance I/R-induced tissue damage.

Opening of the mitochondrial permeability transition pore (MPTP) is important for LV injury following I/R, and the prevention of mitochondrial permeability transition pore opening at the onset of reperfusion is demonstrated to confer cardioprotection in different species and also in some but not all human studies (Cung et al., 2015; Ong, Dongworth, Cabrera-Fuentes, & Hausenloy, 2015). The analysis of the proteins forming the mitochondrial permeability transition pore indicates that the ATP synthase is involved (Alavian et al., 2014; Giorgio et al., 2013). Opening of the mitochondrial permeability transition pore is favoured, for example, by high amounts of ROS, mitochondrial calcium-ion overload, high pH and low mitochondrial membrane potential. Data on the role of the mitochondrial permeability transition pore in the RV are sparse. In the study by Lee and Jung (2018), rats were treated with the MPTP inhibitor **cyclosporin A** (CsA) in combination with monocrotaline or with monocrotaline alone. Monocrotaline induces mitochondrial swelling and rupture of mitochondrial membranes and CsA prevents this mitochondrial damage. However, CsA has no beneficial effect on the development of RV hypertrophy. Whereas CsA protects the RV against I/R damage remains to be determined.

Based on pharmacological approaches, opening of mitoK$_{ATP}$ channels is important for the cardioprotection of IPC (for a review, see Smith, Nehrke, & Brookes, 2017). Treatment with 5-hydroxydecanoate (5-HD) abolishes the infarct size reduction induced by IPC in mouse (Vigneron et al., 2011), rat and rabbit (Munch-Ellingsen et al., 2000) LV myocardium. One study (Andersen et al., 2012) addresses the role of mitoK$_{ATP}$ channels in IPC on the RV. Here, administration of 5-hydroxydecanoate prevents both the infarct size reduction and the haemodynamic recovery of IPC and thereby demonstrates similar effects of 5-hydroxydecanoate in IPC's cardioprotection in right and left ventricular tissues.

Mitochondria are dynamic organelles undergoing fission and fusion, and mitochondrial dynamics contribute to I/R injury in the LV. Mitochondrial fragmentation is induced by I/R injury and is associated with a translocation of the fission protein dynamin-related protein 1 (Drp1) to mitochondria. Accordingly, an inhibition of Drp1 reduces cell death following ischaemia (Sharp et al., 2014). First data also show an involvement of mitochondrial dynamics in ischaemic injury of the RV. Ischaemia-induced diastolic dysfunction is associated with a translocation of Drp1 to the mitochondria. In this model, the inhibition of Drp1 (by Mdivi-1 or P110) preserves diastolic function after I/R and inhibits Drp1-mediated mitochondrial fission (Tian et al., 2017). Mitochondrial dynamics are involved not only in RV ischaemia but also in pulmonary arterial hypertension (for a review, see Ryan, Dasgupta, Huston, Chen, & Archer, 2015). In monocrotaline-treated rats, the mitochondrial amount of Drp1 increases, mitochondria are depolarized, and cristae are disrupted (Tian et al., 2017). Accordingly, the administration of Mdivi-1 improves RV function (Marsboom et al., 2012). Interestingly, the expression of mitochondrial fusion protein mitofusin 2 and the fission protein Drp1 is unaltered in the RV tissue of mice undergoing pulmonary artery banding or sham operation (Figure 3). However, mitofusin 1 is down-regulated in rats with pulmonary arterial hypertension (Joshi et al., 2016). Whether or not the expression/activity of proteins involved in mitochondrial fission and fusion is altered in the diseased RV and impacts on infarct size after I/R without and with IPC is unclear at present and needs further investigation.

During the process of mitophagy, damaged mitochondria are removed from the cellular pool of the organelles, and thereby cellular structure and mitochondrial function are ensured. The expression of microtubule-associated protein 1 light chain 3A/B (LC3A/B) is increased in the failing RV (Qipshidze et al., 2012). However, in the RV of mice 3 weeks after pulmonary artery banding operation, the ratio of LC3A/B-II over LC3A/B-I remains unchanged (Figure 3). While these data suggest unaltered mitophagy in the pulmonary artery banding model, mitobiogenesis seems to be reduced as shown by a decreased mitochondrial transcription factor A expression (Figure 3).

Table 3 summarizes the involvement of mitochondria in RV I/R and RV hypertrophy and failure.

Taken together, whereas the exact contribution of mitochondria towards RV function after I/R needs to be studied in more detail, the available data suggest that a preservation of mitochondrial function is beneficial for the preservation of RV function after I/R.

5 | EXERCISE-DEPENDENT PRECONDITIONING OF THE RV

Whereas IPC has been considered as clinical less relevant than preconditioning or postconditioning, recent studies indicated that exercise exerts a preconditioning-like effect (Lennon et al., 2004). In

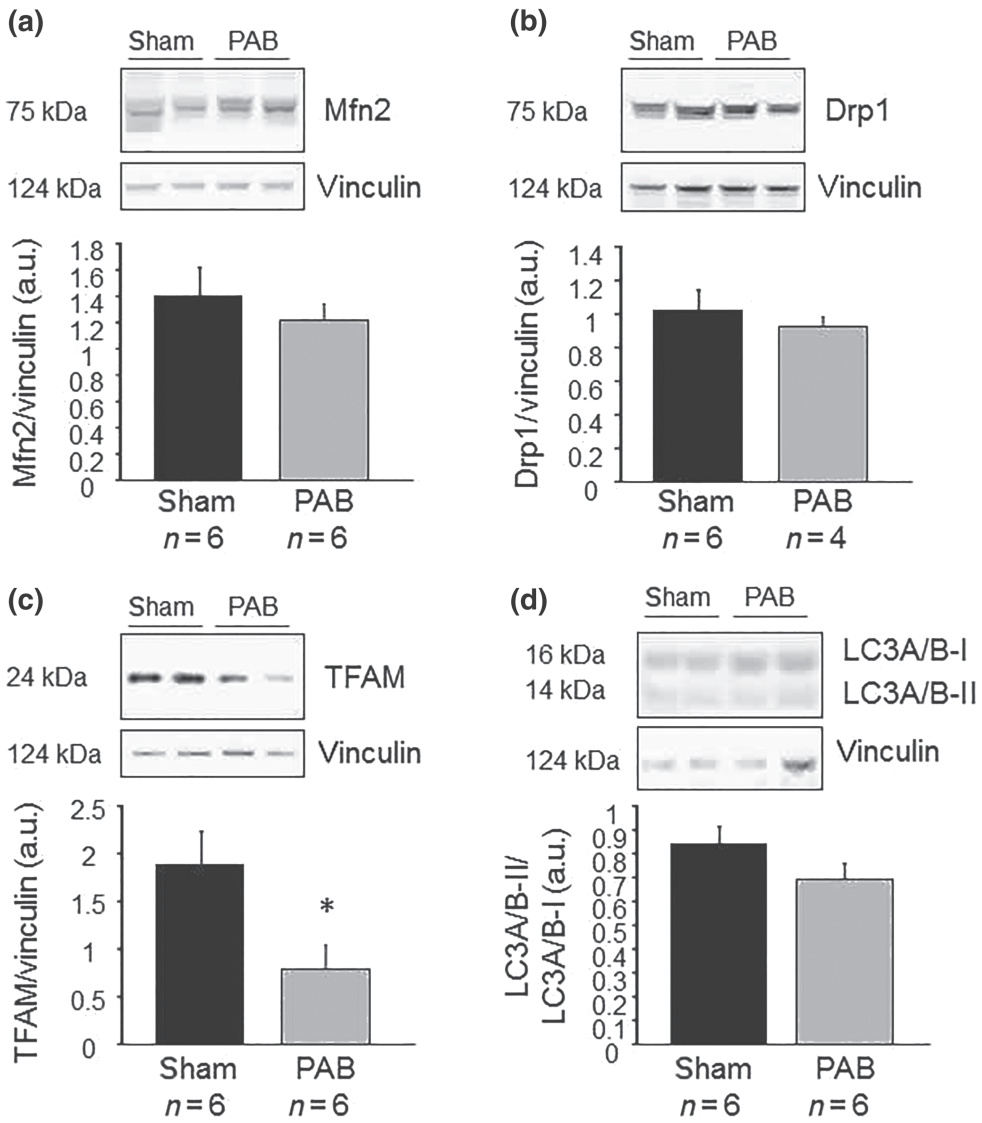

FIGURE 3 Mitochondrial dynamics, biogenesis, and autophagy in the failing RV. Western blot analysis was performed for (a) mitofusin 2 (Mfn2), (b) Drp1, (c) mitochondrial transcription factor A (TFAM), and (d) LC3A/B as well as vinculin as a housekeeping protein on RV total protein extracts from mice 3 weeks after pulmonary artery banding (PAB) or sham operation. Bar graphs demonstrate the ratios of the respective proteins normalized to vinculin. Data are presented as mean ± SEM and are compared by unpaired Student's *t* test. * indicates a *P* value <.05. The study was approved by the "Regierungspräsidium Giessen" (GI20/10 69/2013)

this context, rapid pacing-induced preconditioning may act in a similar way (Pipicz et al., 2015). Indeed, the protective effect of exercise is lost shortly after cessation of exercise, a phenomenon known for other exercise-dependent protective effects as well (Lennon et al., 2004). Thus, short-term effects of increased haemodynamics may act as a trigger for exercise-dependent cardioprotection. Briefly, exercise activates the following pathways that are also linked to cardiac protection: insulin growth factor 1 receptor/phosphoinositide 3-kinase/AKT pathway, SOD2, **heat shock protein** 70, **δ opioid receptors**, **K_{ATP} channels**, PKC-δ, cGMP/PKG, eNOS, PPARγ co-activator 1α, and AMP-activated protein kinase (**AMPK**; Andersen et al., 2016; Cheng et al., 2013; Hao, Pan, Shen, & Ge, 2014; Jew & Moore, 2002; Lawler, Kwak, Kim, & Suk, 2009; Miller et al., 2015; Powers et al., 1998; Solskov et al., 2012; Taylor & Starnes, 2012; Vettor et al., 2014). Exercise modifies post-infarct inflammation and sympathetic overdrive (Barboza et al., 2016). Among these molecules, the catalytic AMPK isoform **AMPKα2** has been given specific attention in the context of exercise-dependent increase in ischaemic tolerance. Exercise increases the expression and phosphorylation of AMPK (Musi et al., 2005). Activation of AMPK pathways (by **metformin**) was sufficient to attenuate RV failure in two pulmonary hypertension models indicating existence of this protective pathway in left and right ventricular tissues (Zhai et al., 2018). Furthermore, AMPK improves ischaemic substrate metabolism and reduces infarct size (Pons et al., 2013). Potential targets include mainly improvements in mitochondrial structure and function (Pons et al., 2013). However, AMPK activity does not directly relate to ischaemic tolerance (Budiono et al., 2016). In summary, AMPK is a likely candidate that is modified by exercise causing cardioprotection, although the exact molecular mechanism including reproducibility in different models is far from being clear.

Furthermore, exercise protects against hypoxia-dependent endoplasmic reticulum stress and infarct size (Bourdier et al., 2016). In rat hearts, 2-day moderate exercise protected against I/R injury due to short-term effects on the transcriptional level (Taylor & Starnes, 2012). Exercise-induced protection against I/R injury in rats

TABLE 3 Mitochondria in RV ischaemia and failure

Parameter	Model	Effect on LV or RV mitochondria	Reference
mRNA/protein	Rabbit and porcine myocardial protein composition under baseline conditions	Amounts of electron transport chain complexes similar between the LV and the RV	(Phillips et al., 2011)
	Isolated rat hearts, 25 min isch and 30 min rep or aerobic conditions, proteomic analysis at end of rep	Different amounts of proteins involved in energy metabolism, between the LV and the RV under aerobic conditions; I/R: amounts of proteins involved, for example, in energy metabolism, antioxidative capacity, and heat shock proteins changed	(Cadete et al., 2012)
	Rabbit myocardial protein composition under baseline conditions	LV tissue: ↑ expression of contractile, stress response, and respiratory chain proteins	(Birner et al., 2012)
	Rat LV and RV separated in basal, middle, and apical parts	Proteins with higher amounts in apical than in basal parts differ between the LV and the RV	(Eckhardt et al., 2018)
	Rat MCT model, 4 weeks	Mitochondrial transcriptomic pathway affected with RV failure	(Potus et al., 2018)
	Dogs, dehydromonocrotaline, 8–10 weeks	ROS scavenging proteins ↓	(Aziz et al., 2015)
Mitochondrial respiration	Isolated adult rat cardiomyocytes, analysis of mitochondrial membrane potential	Mitochondrial membrane potential is higher in LV than RV cardiomyocytes	(Nagendran et al., 2008)
	Rat myocardium, 4 weeks of normobaric hypoxia	Mitochondrial respiration enhanced in the LV	(Ferri et al., 2018)
	Homogenates from rat myocardium, animals kept under normoxic conditions or under chronic hypoxia	Normoxia: mitochondrial respiration LV > RV; chronic hypoxia: mitochondrial respiration ↓ only in LV	(Rumsey et al., 1999)
	Rats kept for 2 and 3 weeks under hypobaric hypoxia or control conditions	Chronic hypoxia alters mitochondrial function (↓) and morphometry in the LV and the RV, but effects are delayed in the RV	(Nouette-Gaulain et al., 2005)
	Rat Sugen 5416/hypoxia model, 4 weeks Rat PAB model, 6 weeks	Yield of RV mitochondria ↓ in both models Respiration ↓ in Sugen 5416/hypoxia model only	(Gomez-Arroyo et al., 2013)
	Rat Sugen 5416/hypoxia model, 4 weeks	Oestrogen protects the RV by maintaining mitochondrial content and oxidative capacity	(Liu et al., 2017)
	Rat MCT model, 6 weeks	Oxygen consumption of RV mitochondria ↓ in MCT-treated rats	(Daicho et al., 2009)
	Rat MCT model to induce hypertrophy or failure, 23 days	Oxygen consumption of RV mitochondria: Complex 1: ↓ in hypertrophic and failing RV Complex 2: ↓ in failing RV	(Wust et al., 2016)
	Rat MCT model to induce hypertrophy or failure, 4 weeks	Higher mitochondrial oxygenation in vivo: ↓ mitochondrial metabolism in vivo as a possible trigger for RV failure	(Balestra et al., 2015)
	Rat PAB model, 7 weeks	Oxygen consumption ↓; impaired oxygen consumption prevented by dichloroacetate	(Piao, Marsboom, & Archer, 2010b)
	Rat MCT model, 25 days	Activities of succinate dehydrogenase and cytochrome c oxidase not affected by MCT alone but increased after combination of sildenafil and bosentan	(Mouchaers et al., 2009)
	Rat MCT model, 23 days	Metoprolol ↑ coupling between mitochondria and the creatine kinase system, ↓ hypertrophy	(Fowler et al., 2019)
	Rat MCT model, 4–5 weeks	Oxygen consumption ↓; impaired oxygen consumption after MCT not affected by	(Power et al., 2019)

(Continues)

TABLE 3 (Continued)

Parameter	Model	Effect on LV or RV mitochondria	Reference
		metoprolol; no effect of metoprolol on RV hypertrophy	
	Patients with compensated RV hypertrophy or failure	Hypertrophy: mitochondrial enzyme activities maintained, mitochondrial DNA content ↓; failure: mitochondrial enzyme activities ↓; mitochondrial DNA content ↓	(Karamanlidis et al., 2011)
ROS	Rat, physiological conditions	ROS: RV > LV	(Schluter et al., 2018)
	Rat, L-NAME, 4 weeks	ROS in RV ↑	(Schreckenberg et al., 2015)
	Wild-type and NOS2-deficient mice, PAB, 3 weeks	Wild type: ↑ NOS expression, ↑ ROS; NOS2 deficient: ↓ ROS, ↓ collagen	(Boehm et al., 2019)
	Mice, PAB, 4 weeks	ROS and MMPs in RV ↑; folic acid: ROS and MMPs ↓; fibrosis and RV pressure ↓	(Qipshidze et al., 2012)
	Rat MCT model, 25 days	ROS and complex 2 activity, $gp91^{phox}$ in RV ↑	(Redout et al., 2007)
	Patients with pulmonary hypertension Rat MCT model	NOX4 ↑	(He et al., 2017)
	Rat MCT model, 2 weeks	NOX activity ↓ by trapidil	(Turck et al., 2018)
	Rat MCT model, 4 weeks	Xanthine oxidase activity in failing RV ↑	(de Jong et al., 2000)
	Patients with ischaemic heart disease	Monoamino oxidase in RV ↑ Oxidative stress markers in RV ↑	(Manni et al., 2016)
	Rat MCT model	Scavenging enzymes in RV ↓	(Ecarnot-Laubriet et al., 2003)
	Rat MCT model, 4 weeks	Melatonin: oxidative stress in plasma ↓; fibrosis ↓; RV function ↑	(Maarman et al., 2015)
	Mice, PAB	MitoQ: ↓ oxidative stress, ↓ RV dilatation, hypertrophy, dysfunction	(Pak et al., 2018)
	Rat MCT model, 4 weeks	N-acetylcysteine: ↓ development pulmonary hypertension	(Guo et al., 2016)
	Mice, PAB, 3 weeks	$UCP2^{-/-}$ mice: ↑ RV function	(Esfandiary et al., 2019)
MPTP opening	Rat MCT model, 4 weeks	Cyclosporine A: ↓ mitochondrial disruption in RV, no beneficial effect on RV hypertrophy	(Lee & Jung, 2018)
Mitochondrial K_{ATP} channel	Isolated rat heart, 40 min isch, 2 hr rep, IPC: 2× 5 min isch, 5 min rep	5-HD: ↓ RV IS reduction and functional recovery by IPC	(Andersen et al., 2012)
Mitochondrial dynamics	Rat MCT model, 4 weeks; isolated hearts 15 min isch, 15 min rep	MCT: ↑ mitochondrial amount of Drp1, mitochondrial depolarization, cristae disruption; Mdivi-1: ↓ Drp1-mediated mitochondrial fission; ↓ I/R-induced RV diastolic dysfunction	(Tian et al., 2017)
	Rat MCT model, 4 weeks; rat chronic hypoxia, 4 weeks	Mdivi-1: ↑ RV function	(Marsboom et al., 2012)
	Rat Sugen 5416/hypoxia/normoxia model; 8 and 13 weeks	Mitofusin 1 protein 8 weeks: ↓ in RV	(Joshi et al., 2016)
	Mice, PAB, 4 weeks	LC3A/B: ↑ in RV	(Qipshidze et al., 2012)

Abbreviations: ↓, decreased; ↑, increased; IPC, ischaemic preconditioning; IS, infarct size; isch, ischaemia; LV, left ventricle; MCT, monocrotaline; PAB, pulmonary artery banding; PASMC, pulmonary arterial smooth muscle cell; rep, reperfusion; RV, right ventricle.

seems to be δ opioid receptor dependent (Miller et al., 2015). However, in the context of RV protection, the situation is more complex. In principle, preconditioning of RV tissue can be performed by the anaesthetics xenon or **isoflurane** (Hein et al., 2008). This preconditioning effect is lost with ageing and failure, see above. Exercise, on the other side induces effects on RV remodelling and myocyte function that differ from those on the LV. This may impact a potential conditioning-like effect on the RV. Physical activity is associated with severe structural alterations of the RV but without functional effects on it (Aaron et al., 2011; Oxborough et al., 2012). This difference to LV tissue is due to a stronger induction of fibrosis, triggered by collagen III, lack of effect on cardiomyocytes and

TABLE 4 Differences in the extent of exercise-induced changes between the LV and the RV

Variable	Model	LV	RV	Reference
TGF-β1	Rat, treadmill running; 5 days a week, for 16 weeks	±	↑	(Gay-Jordi et al., 2013)
Fibronectin	Rat, treadmill running; 5 days a week, for 16 weeks	±	↑	(Gay-Jordi et al., 2013)
Collagen-1	Rat, treadmill running; 5 days a week, for 16 weeks	±	↑	(Gay-Jordi et al., 2013)
Collagen-3	Rat, treadmill running; 5 days a week, for 16 weeks	±	↑	(Gay-Jordi et al., 2013)
Collagen-4	Rat, treadmill running; 5 days a week, for 10 days	±	↑	(Perhonen et al., 1997)
c-kit	Mouse, swimming protocol, 1, 2, and 3 weeks	↑	↑ (delayed)	(Xiao et al., 2014)
Coronary perfusion	Dog, treadmill running; 4 exercise intensities, 3 min each	↑	±	(Hart et al., 2001)
Cell volume	Rat, treadmill running; 5 days a week, for 8 weeks	↑	±	(Carneiro-Junior et al., 2013)
Cell shortening	Rat, treadmill running; 5 days a week, for 8 weeks	↑	±	(Carneiro-Junior et al., 2013)
Calcium transients	Rat, treadmill running; 5 days a week, for 8 weeks	↑	±	(Carneiro-Junior et al., 2013)
SERCA2a	Rat, treadmill running; 5 days a week, for 8 weeks	↑	±	(Carneiro-Junior et al., 2013)
PLB-Ser^{16}	Rat, treadmill running; 5 days a week, for 8 weeks	↑	±	(Carneiro-Junior et al., 2013)
PLB-Thr^{17}	Rat, treadmill running, for 120 min	↑	±	(Ljones et al., 2017)
ETC max. capacity	Rat, treadmill running, for 120 min	±	↓	(Ljones et al., 2017)

Abbreviations: ↓, decreased; ↑, increased; ±, unchanged; ETC, electron transport chain; LV, left ventricle; PLB, phospholamban; RV, right ventricle; SERCA, SR-Ca-ATPase.

reduced induction of c-kit positive cells and induction of GATA-binding protein 4 (Gay-Jordi et al., 2013; Perhonen, Wang, Han, Ruskoaho, & Takala, 1997; Xiao et al., 2014). At least in part, exercise-dependent adaptation of the RV seemed to be restricted to young and healthy rats (Anitha & Asha Devi, 1996; Lawler et al., 2009; Thomas, Cotter, Li, McCormick, & Gosselin, 2001). Mechanistically, differences have been described for the adaptation of the LV and the RV to exercise. For example, unlike in the LV, in the RV coronary perfusion is not increased unless the pO_2 is below 20 mmHg but shows a better oxygen extrusion (Hart et al., 2001). In this context, it is also relevant that exercise does not modify RV cardiomyocytes in the same way than LV cardiomyocytes and that RV cardiomyocytes cannot be protected by exercise-dependent preconditioning (Canan et al., 2016; Carneiro-Junior et al., 2013). Intensive exercise reduced RV cardiomyocyte function because phospholamban cannot be phosphorylated to the same extent than in the LV (Ljones, Ness, Solvang-Garten, Gaustad, & Hoydal, 2017). Differences in exercise-induced changes between the LV and the RV are summarized in Table 4.

In contrast to the lack of preconditioning effects evoked by exercise against I/R injury of the RV, exercise can protect the RV against pulmonary hypertension, **doxorubicin**-induced heart failure and pathological cardiac hypertrophy under certain conditions (Brown et al., 2017; Colombo et al., 2013; Hydock, Lien, Jensen, Schneider, & Hayward, 2011; Moreira-Goncalves et al., 2015; Yang et al., 2018). However, whether this is associated to a haemodynamic relevant improvement is less clear (Enache et al., 2017; Zimmer et al., 2017). At least during the progression of RV hypertrophy to failure, exercise does not improve the outcome (Handoko et al., 2009). However, post-infarct exercise can improve post ischaemic remodelling (Wisloff, Loennechen, Currie, Smith, & Ellingsen, 2002). Collectively, although pharmacological preconditioning of the RV in young and healthy pigs was shown, exercise-dependent preconditioning-like effects seem limited to the RV and even more important not feasible in non-healthy or elderly persons. The difference in exercise-dependent induced preconditioning between the LV and the RV may be related to the different response of both ventricles towards exercise.

6 | CONCLUSION

Despite differences between the LV and the RV under physiological conditions as well as in response to stress, a protection against I/R injury of the RV, which is more resistant to ischaemia than the left one, is principally feasible. However, it is not established yet whether the molecular mechanisms of IPC in the RV are comparable to those in the LV. The maintenance of mitochondrial function, however, seems to be crucial in both ventricles. An abrogation of cardioprotection in the LV is observed in aged or diseased myocardium, and the effectiveness of the cardioprotection by exercise or IPC is also impaired in the failing RV. Taken together, more research is needed to elucidate molecular targets induced by cardioprotective strategies in the RV and to identify conditions, in which protection of the RV tissue is abolished.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

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CONFLICT OF INTEREST

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