Loss of cardioprotection with ageing

Kerstin Boengler, Rainer Schulz, and Gerd Heusch*

Institut für Pathophysiologie, Universitätsklinikum Essen, Hufelandstraße 55, 45122 Essen, Germany

Received 19 December 2008; revised 21 January 2009; accepted 23 January 2009; online publish-ahead-of-print 28 January 2009

Time for primary review: 20 days

Not only the prevalence, but also the mortality due to ischaemic cardiovascular disease is higher in older than in young humans, and the demographic shift towards an ageing population will further increase the prevalence of age-related cardiovascular disease. In order to develop strategies aimed to limit reversible and irreversible myocardial damage in older patients, there is a need to better understand age-induced alterations in protein expression and cell signalling. Cardioprotective phenomena such as ischaemic and pharmacological pre and postconditioning attenuate ischaemia/reperfusion injury in young hearts. Whether or not pre and postconditioning are still effective in aged organs, animals, or patients, i.e. under conditions where such cardioprotection is most relevant, is still a matter of debate; most studies suggest a loss of protection in aged hearts.

The present review discusses changes in protein expression and cell signalling important to ischaemia/reperfusion injury with myocardial ageing. The efficacy of cardioprotective manoeuvres, e.g. ischaemic pre and postconditioning in aged organs and animals will be discussed, and the development of strategies aimed to antagonize the age-induced loss of protection will be addressed.

KEYWORDS
Cardioprotection; Ischaemic preconditioning; Ischaemic postconditioning; Myocardial infarction; Myocardial ischaemia; Reperfusion; Ageing

1. Introduction

The incidence and prevalence of myocardial infarction increase with age, and the developed countries are faced with an increasingly ageing population. Not only is there an increase in incidence and prevalence of myocardial infarction with ageing, but also possibly a loss of endogenous protection against infarction. Ischaemic pre and postconditioning are powerful cardioprotective phenomena, in which infarct size is reduced by one or several short episodes of myocardial ischaemia with reperfusion preceding or following, respectively, the infarct-inducing sustained ischaemia. Both phenomena have been identified in all species studied so far, including man; they are relevant in the context of interventional and surgical coronary revascularization, but also in preinfarction angina. In a number of experimental studies, the power of these cardioprotective interventions waned with ageing, and the present review will address evidence and potential mechanisms of attenuated cardioprotection with ageing, as well as the potential relevance to humans.

2. Ageing and cardiomyocytes

During ageing, cardiomyocytes undergo complex changes which finally result in loss of contractile function and loss of endogenous protection against irreversible injury. Ageing affects cardiomyocytes at several subcellular and molecular levels, including alterations at the level of the DNA (mutations and telomere shortening), increased oxidative stress [reactive oxygen species (ROS) formation], changes in the gene/protein expression and posttranslational modifications (e.g. advanced glycation endproducts and protein oxidation), and handling of cellular ‘waste’ material by autophagy.

The ends of eukaryotic chromosomes are protected from degradation by telomere complexes, and a decrease of telomere length was observed with increasing age in male mouse and rat myocardium. In humans older than 60 years, a shortening of the telomeres, which was assessed from the DNA of blood cells, was associated with increased mortality. Telomere shortening was enhanced in hearts from aged patients with heart failure.

Nuclear and mitochondrial gene expression profiles are altered during ageing, resulting in corresponding alterations in cardiomyocyte phenotype. The analysis of cardiomyocyte mRNA’s isolated from young (4 months) and old (20 months) C57BL/6 mice revealed differential levels for transcripts encoding transcription factors, mitochondrial proteins, and other proteins important for energy metabolism, proteins of the cytoskeleton, and proteins related to signal transduction, such as heat shock proteins. A shift from fatty acid towards carbohydrate metabolism, an induction of extracellular matrix components, increased collagen deposition and cell adhesion, as well as a decrease in protein synthesis with ageing (5 and 30 months old mice) were noted.

* Corresponding author. Tel: +49 201 723 4480; fax: +49 201 723 4481. E-mail address: gerd.heusch@uk-essen.de

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2009.
For permissions please email: journals.permissions@oxfordjournals.org.
3. Ageing and mitochondrial function

According to the free radical theory of ageing, ROS are causal for the process of ageing. Ageing cardiomyocytes are subjected to enhanced oxidative stress, which damages mitochondria and—possibly by reducing mitochondrial fission—contributes to their enlargement. With increasing age, larger mitochondria are not removed by autophagy with the same effectiveness than smaller mitochondria and therefore accumulate within cells. These giant mitochondria often contain mutated DNA and accordingly mutated proteins of the respiratory chain and therefore contribute to excessive ROS formation and further oxidative protein damage. Indeed, an age-dependent (from 2 to 12 months) increase in ROS formation was detected in mouse mitochondria, which was the predominant cellular source of ROS. The amount of ROS is critical for cell survival, since low amounts of ROS function as signalling molecules and are central for cardioprotective signalling cascades, whereas high amounts of ROS are detrimental by opening the mitochondrial permeability transition pore (MPTP), which induces mitochondrial swelling, depolarization, and ultimately cell death.

Several mechanisms contribute to enhanced mitochondrial ROS formation in aged myocardium. The amount of hydrogen peroxide, which is produced by the reduction of superoxide anions, is increased in mitochondria isolated from aged hearts. 

### Table 1 Age-related changes in the expression/activity of proteins involved in cardioprotection

<table>
<thead>
<tr>
<th>Protein</th>
<th>Species</th>
<th>Age</th>
<th>Tissue/cell</th>
<th>Expression/activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinin receptor</td>
<td>Rat</td>
<td>24 m</td>
<td>Total heart</td>
<td>↑ B1 receptor</td>
<td>Kintsurashvili et al. 88</td>
</tr>
<tr>
<td>IGF, IGFR</td>
<td>Rat</td>
<td>26 m</td>
<td>LV cardiomyocytes</td>
<td>↓ IGF-1</td>
<td>Leri et al. 86</td>
</tr>
<tr>
<td>IL-6</td>
<td>Mouse</td>
<td>24–26 m</td>
<td>Total heart</td>
<td>↓</td>
<td>Hacham et al. 87</td>
</tr>
<tr>
<td>TNFα</td>
<td>Mouse</td>
<td>28–31 m</td>
<td>Total heart</td>
<td>↑</td>
<td>Batkai et al. 110</td>
</tr>
<tr>
<td>PKCe</td>
<td>Mouse</td>
<td>&gt;13 m</td>
<td>RV</td>
<td>No change</td>
<td>Boengler et al. 110</td>
</tr>
<tr>
<td>ERK1/2</td>
<td>Rat</td>
<td>24 m</td>
<td>Total heart, soluble fraction</td>
<td>↓</td>
<td>Korzick et al. 92</td>
</tr>
<tr>
<td>Akt</td>
<td>Rat</td>
<td>18 m</td>
<td>LV</td>
<td>↓ Phospho↑, total ↓</td>
<td>Aoyagi and Izumo 165</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>23 m</td>
<td>LV</td>
<td>↓</td>
<td>Hunter et al. 166</td>
</tr>
<tr>
<td>GS3Kβ</td>
<td>Rat</td>
<td>23 m</td>
<td>LV</td>
<td>↓</td>
<td>Hunter et al. 166</td>
</tr>
<tr>
<td>MKP-1</td>
<td>Mouse</td>
<td>20–24 m</td>
<td>Total heart</td>
<td>↑</td>
<td>Przyklenk et al. 102</td>
</tr>
<tr>
<td>PTP1B</td>
<td>Mouse</td>
<td>26–28 m</td>
<td>LV</td>
<td>↑</td>
<td>Fang et al. 167</td>
</tr>
<tr>
<td>PP2A</td>
<td>Rat</td>
<td>21–22 m</td>
<td>LV, RV</td>
<td>↑</td>
<td>Fenton et al. 103</td>
</tr>
<tr>
<td>Cx43</td>
<td>Mouse</td>
<td>&gt;13 m</td>
<td>LV, RV myocardium, and LV mitochondria</td>
<td>↓</td>
<td>Boengler et al. 10</td>
</tr>
<tr>
<td>MnSOD</td>
<td>Rat</td>
<td>24 m</td>
<td>Total heart</td>
<td>↓ No change in protein level, ↓ SOD activity</td>
<td>Ferrara et al. 108</td>
</tr>
<tr>
<td>Catalase</td>
<td>Rat</td>
<td>24 m</td>
<td>Total heart</td>
<td>↓</td>
<td>Ferrara et al. 108</td>
</tr>
<tr>
<td>STAT3</td>
<td>Mouse</td>
<td>&gt;13 m</td>
<td>RV</td>
<td>↓</td>
<td>Boengler et al. 141</td>
</tr>
<tr>
<td>iNOS</td>
<td>Mouse</td>
<td>16 m</td>
<td>Total heart</td>
<td>↑</td>
<td>Yang and Larson 109</td>
</tr>
<tr>
<td>Mouse</td>
<td>28–31 m</td>
<td>Total heart</td>
<td>↑</td>
<td>Batkai et al. 110</td>
<td></td>
</tr>
<tr>
<td>Sirt1</td>
<td>Rat</td>
<td>24 m</td>
<td>Total heart</td>
<td>↓</td>
<td>Ferrara et al. 108</td>
</tr>
</tbody>
</table>

**Abbreviations:** Akt, protein kinase B; Cx43, connexin 43; ERK1/2, extracellular signal-regulated kinase 1/2; GS3Kβ, glycogen synthase kinase 3 β; IGF, insulin-like growth factor; IGFR, insulin-like growth factor receptor; IL-6, interleukin 6; IOK, inducible nitric oxide synthase; LV, left ventricle; m, months; MKP-1, mitogen-activated kinase phosphatase 1; MnSOD, manganese superoxide dismutase; PKCe, protein kinase C ε; PP2A, protein phosphatase 2A; PTP1B, protein tyrosine phosphatase 1B; RV, right ventricle; Sirt1, sirtuin 1; STAT3, signal transducer and activator of transcription 3; TNFα, tumor necrosis factor α; ↑, increased expression/activity with aging; ↓, decreased expression/activity with aging. The factors/proteins are listed according to their sequence in the scheme of Figure 1.
from 14 and 18 months old rat hearts and in subsarcolemmal mitochondria from 24 months old rat hearts over that of young hearts (3 or 6 months, respectively). Also, monoamine oxidases (MAO) in the outer mitochondrial membrane produce ROS by transferring electrons from amine compounds to oxygen. The age-induced increase in hydrogen peroxide in heart homogenates is accordingly abolished by inhibition of MAO-A. The protein p66Shc, which can be translocated into the mitochondria, oxidizes cytochrome c and thereby catalyzes the reduction of oxygen to hydrogen peroxide (for review see 22). p66Shc knockout mice have a reduced production of ROS and an increased life span.

Apart from mitochondria, ROS are generated by NAPDH oxidases, and the expression of the cytosolic subunit p47phox, which determines the activity of the enzyme, is increased in aged (24–26 months) mouse myocardium. Not only enhanced ROS formation, but also a progressive decrease in the antioxidant capacity from young (3–4 or 6 months) to middle-aged (13–15 months) and aged (>24 months) myocardium contributes to the elevated cellular ROS level in rat hearts.

ROS damage macromolecules such as DNA or proteins and thereby contribute to cellular dysfunction and ultimately to cell death. The proximity of mitochondrial DNA to the production site of ROS, the lack of protection of mitochondrial DNA by histones, and the limited capacity of repair mechanisms render the mitochondrial DNA highly susceptible to oxidative stress. During ageing, mutations accumulate in the nuclear as well as in the mitochondrial DNA. Mutations in mitochondrial DNA may contribute to the process of ageing, as demonstrated in transgenic mice with a proof-reading-deficient mitochondrial DNA-polymerase, which acquire point mutations and deletions in mitochondrial DNA and develop symptoms of ageing already within 25–40 weeks of age and have a reduced lifespan. The oxidative stress-induced damage of mitochondrial DNA leads to transcription and translation of defective proteins, predominantly subunits of respiratory chain complex I, and accordingly induces dysfunction of the respiratory chain. Protein oxidation in mouse hearts is increased with age (young: 2 months, aged: 24–26 months), and the enhanced oxidative protein modifications of respiratory complexes with ageing (young: 3–5 months, middle-aged: 12–14 months, aged: 20–22 months) further decrease the activity of the respiratory chain. The age-induced decrease of respiratory complex IV activity and oxidative phosphorylation in inter fibrillar mitochondria of 24 months old rat hearts are reversed by acetylcarnitine, which acts presumably via increased transcription and translation of mitochondrially encoded proteins.

Whether or not the increased level of ROS in the aged heart contributes to a decline in mitochondrial oxygen consumption is still under debate (for review see 32). A decline in ADP-stimulated respiration in cardiac mitochondria isolated from rats older than 20 months has been described more than 30 years ago and been confirmed later in 24 months old rats. However, other studies failed to demonstrate an influence of age on mitochondrial oxygen consumption. These divergent results are possibly reconciled in that cardiomyocytes contain two subpopulations of mitochondria, subsarcolemmal, and inter fibrillar mitochondria, which differ in their respiratory capacity. When the two subpopulations were analysed separately, ADP-stimulated respiration declined specifically in rat interfibrillar mitochondria with age (young: 6 months, aged: 24 months).

Thus, oxidative stress induces mitochondrial dysfunction in a DNA-dependent and independent manner. According to di Lisa and Bernardi, mitochondria are involved in the amplification, accumulation, and spreading of oxidative stress within and among neighbouring cells.

4. Ischaemia/reperfusion injury in the aged myocardium

With ageing, baseline cardiac function declines. When the aged heart is exposed to various forms of stress, an amplification of damage, i.e. a further deterioration of cardiomyocyte function is observed. Whereas the ischaemic threshold and the area at risk are not affected by age, the tolerance to ischaemic injury is reduced, suggesting that ageing decreases the intrinsic tolerance to ischaemia. The loss of intrinsic myocardial tolerance to ischaemia in mouse myocardium begins during middle-age (12 months) and becomes more manifest with ageing (18 months and 24–28 months).

Apart from mitochondria, ROS are generated by NAPDH oxidases. The age-induced decrease of respiratory complex IV activity and oxidative phosphorylation in inter fibrillar mitochondria of 24 months old rat hearts are reversed by acetylcarnitine, which acts presumably via increased transcription and translation of mitochondrially encoded proteins.

ROS damage macromolecules such as DNA or proteins and thereby contribute to cellular dysfunction and ultimately to cell death. The proximity of mitochondrial DNA to the production site of ROS, the lack of protection of mitochondrial DNA by histones, and the limited capacity of repair mechanisms render the mitochondrial DNA highly susceptible to oxidative stress. During ageing, mutations accumulate in the nuclear as well as in the mitochondrial DNA. Mutations in mitochondrial DNA may contribute to the process of ageing, as demonstrated in transgenic mice with a proof-reading-deficient mitochondrial DNA-polymerase, which acquire point mutations and deletions in mitochondrial DNA and develop symptoms of ageing already within 25–40 weeks of age and have a reduced lifespan.

The oxidative stress-induced damage of mitochondrial DNA leads to transcription and translation of defective proteins, predominantly subunits of respiratory chain complex I, and accordingly induces dysfunction of the respiratory chain. Protein oxidation in mouse hearts is increased with age (young: 2 months, aged: 24–26 months), and the enhanced oxidative protein modifications of respiratory complexes with ageing (young: 3–5 months, middle-aged: 12–14 months, aged: 20–22 months) further decrease the activity of the respiratory chain. The age-induced decrease of respiratory complex IV activity and oxidative phosphorylation in inter fibrillar mitochondria of 24 months old rat hearts are reversed by acetylcarnitine, which acts presumably via increased transcription and translation of mitochondrially encoded proteins.

Whether or not the increased level of ROS in the aged heart contributes to a decline in mitochondrial oxygen consumption is still under debate (for review see 32). A decline in ADP-stimulated respiration in cardiac mitochondria isolated from rats older than 20 months has been described more than 30 years ago and been confirmed later in 24 months old rats. However, other studies failed to demonstrate an influence of age on mitochondrial oxygen consumption. These divergent results are possibly reconciled in that cardiomyocytes contain two subpopulations of mitochondria, subsarcolemmal, and inter fibrillar mitochondria, which differ in their respiratory capacity. When the two subpopulations were analysed separately, ADP-stimulated respiration declined specifically in rat interfibrillar mitochondria with age (young: 6 months, aged: 24 months).

Thus, oxidative stress induces mitochondrial dysfunction in a DNA-dependent and independent manner. According to di Lisa and Bernardi, mitochondria are involved in the amplification, accumulation, and spreading of oxidative stress within and among neighbouring cells.
Aged rat hearts (24 months) treated with acetylcarnitine, which may impact on mitochondrial DNA transcription and translation (see above), had better contractile recovery during reperfusion and less tissue damage after ischaemia/reperfusion, as evaluated by lactate dehydrogenase release, than untreated hearts.31

Taken together, ageing decreases the tolerance of the heart to ischaemia/reperfusion; this increased susceptibility to ischaemia/reperfusion is likely a consequence of enhanced oxidative stress, and antioxidative strategies may be protective.

5. Ischaemic and pharmacological preconditioning in aged myocardium

5.1 Ischaemic and pharmacological preconditioning in aged mammalian myocardium

Myocardial damage by ischaemia/reperfusion can be limited by the activation of endogenous cardioprotective mechanisms. One of these mechanisms is ischaemic preconditioning (IP), i.e. the ischaemic or non-thermal episodes of ischaemia/reperfusion preceding a period of sustained ischaemia/reperfusion.53 The cardioprotection by IP occurs in several stages, an acute phase or first window, in which an ischaemic size reduction is achieved during the first 1–3 h of reperfusion following the preconditioning ischaemic episodes, and a late phase or second window, in which IP’s protection is manifest after 24–72 h.54 In pig myocardium with coronary microembolization, there is also a third window of IP after 6 h.55 Since its first description in 1986, many studies have attempted to unravel the molecular mechanisms of IP.5 The complex signal transduction cascade of IP involves activation of receptors in the plasma membrane, which transduce their signals via activation of multiple protein kinases.56–58 Mitochondria are central elements in the cardioprotective signalling pathway.59,60 Small amounts of mitochondrial ROS function as trigger molecules of IP’s cardioprotection. The formation of small amounts of ROS depends on the opening of mitochondrial ATP-dependent potassium channels (mitoKATP) in the inner mitochondrial membrane.17,61,62,63 which, in turn, are regulated by protein kinases C (PKC) and/or G (PKG).62,63 The ROS production induced by dazoxize, which is cardioprotective presumably by opening mitoKATP channels,64 is dependent on the amount of mitochondrial Cx43.65 Uncoupling of mitochondria—i.e. proton influx into the mitochondrial matrix without phosphorylation of ADP—also contributes to ROS formation.66 ROS are involved in cardioprotection potentially by activating protein kinases such as protein kinase C67 or p38 MAP kinase and nuclear translocation of NFκB.68 Apart from their function in the trigger phase, mitochondria have been suggested to act as end-effectors of cardioprotection by IP.59 The MPTP, a voltage-dependent, high conductance mitochondrial membrane channel, opens when exposed to high concentrations of ROS (radical burst) and calcium at a normal intracellular pH. Inhibition of MPTP opening is important for cardiomyocyte survival and the cardioprotection by IP.70,71 The signalling cascade of IP, especially that of late preconditioning, comprises changes in the transcription of genes, which encode proteins involved in cardioprotection. One of the factors regulating transcription is STAT3 (signal transducer and activator of transcription 3). STAT3 is central for IP’s cardioprotection, since STAT3-deficient mouse hearts and isolated cardiomyocytes cannot be preconditioned (for review see 72). The details of the signal transduction cascade of IP are reviewed elsewhere.5,73,74 A schematic representation of the signal transduction pathways of cardioprotection, including age-related changes in the expression and/or activity of the involved proteins, is shown in Figure 1.

The cardioprotection by IP can be mimicked pharmacologically by various agents such as diazoxide, or anaesthetics such as isoflurane, as well as by exogenous administration of endogenous mediators such as adenosine, bradykinin, or opioids.75

The majority of studies designed to identify the signal transduction cascades of ischaemic and pharmacological preconditioning with protection from infarction as endpoint have been performed in young and healthy animals and/or hearts.75 The relevance of age for the prevention of ischaemia/reperfusion injury by IP has been extensively studied (Table 2). Loss of infarct size reduction by IP was observed already in middle-aged rat hearts (12–13 months), demonstrating that the loss of cardioprotection manifests earlier than only in senescence.76 An increase of the preconditioning stimulus strength preserved cardioprotection by IP in middle-aged rat hearts (12 months).77 However, cardioprotection by IP was lost in aged rat hearts (18–20 months), independent of the strength of the preconditioning stimulus and the endpoint analysed.

 Whereas the results of the in vitro studies indicate loss of cardioprotection by IP in the aged heart, the data obtained in in vivo experiments are not as consistent. In 2- and 4-year-old rabbit hearts in vivo, IP reduced infarct size.78 Also, IP reduced infarct size equally in 0.5–1-year-old and in 6–8-year-old sheep.79 However, when looking at the maximal life span of these species (13 years for rabbits and 20 years for sheep, Figure 2), it was questioned whether 4-year-old rabbits represent a suitable model of ageing.80 The same argument applies to the use of 6–8-year-old sheep. In contrast to the aforementioned studies, a loss of the cardioprotective effect of IP was observed in middle-aged (13 months) mouse hearts in vivo.40

Anaesthetic preconditioning was effective in middle-aged (10–12 months), but not in aged (20–24 months) rat hearts,81,82 indicating that the loss of cardioprotection with advancing age was not specific for IP. Pharmacological preconditioning with adenosine or delta opioid receptor stimulation activates signalling cascades similar to those involved in IP (for review see 5,58,83). Cardioprotection by adrenaline receptor stimulation was lost in aged rat hearts (18–20 months).77 Also, activation of PKC or opening of mitoKATP channels, both downstream in the adenosine-mediated signalling cascade, did not elicit cardioprotection in aged rat hearts (18–20 months).77 In contrast, morphine given directly before ischaemia was not protective, whereas morphine given for 5 days before ischaemia induced cardioprotection in aged mouse hearts,84 suggesting persistence of late pharmacological preconditioning in aged hearts.

The effectiveness of anaesthetic and pharmacological preconditioning in aged hearts is summarized in Table 3.
5.2 Impact of age on the signalling cascades mediating ischaemic or pharmacological preconditioning

To investigate the mechanisms responsible for the loss of cardioprotection in aged hearts, genes and/or proteins known to be important for the cardioprotection by IP were analysed in young and aged myocardium (Table 1). Apart from and in addition to decreased protein expression in the aged heart, also blunted responses in terms of activation or inhibition of a signalling molecule by a cardioprotective stimulus may contribute to loss of cardioprotection in aged hearts. For example, the stress-induced increase in heat shock protein 70 content was abrogated in aged myocardium (for review see 85).

An impaired response to a cardioprotective stimulus in aged hearts may originate from a decreased level of the extracellular ligand, and indeed reduced levels of insulin-like growth factor 1 and IL-6 were found in aged hearts (24–26 months old mice or 26 months old rats). Studies analysing the expression of the bradykinin receptors 1 and 2 in aged (24 months) rat hearts found a decreased level of the bradykinin receptor 2, which mediates cardioprotection. However, loss of adenosine-induced cardioprotection in aged hearts was not associated with a decreased expression of adenosine receptors, but rather with impaired downstream signalling elements (for review see 89). PKC, which is present in multiple cellular compartments, is central for the cardioprotection by IP and by adenosine, presumably by its activation of mitoKATP-channels. IP is associated with a translocation of PKCe from the cytosol to the particulate fraction. However, the importance of PKC translocation has been questioned in aged (4 years old) rabbit hearts, in which IP was still effective in reducing infarct size despite a lack of PKC translocation.

Cx43 is located not only at the gap junctions but also in mitochondria, and can be phosphorylated by PKC isoforms. Since the cardioprotection by IP is dependent on a normal protein level of Cx43, the age-associated decrease of Cx43 (13 months), especially in mitochondria, is proposed to contribute to the loss of cardioprotection in aged mouse hearts (13 months). Cx43-deficiency impairs ROS formation in response to diazoxide and thereby limits

Figure 1 Protein kinase activation in cardioprotection. (A) GPCR/NPR-AKT-eNOS-PKG pathway. (B) RISK pathway. (C) gp130-JAK-STAT pathway. Abbreviations: AMPK, AMP-activated kinase; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CB-R, cannabinoid receptor; Cx43, connexin 43; eNOS, endothelial NO synthase; ERK, extracellular regulated kinase; FGF-2, fibroblast growth factor 2; gp130, glycoprotein 130; GPCR, G-protein-coupled receptor; GSK3β, glycogen synthase kinase 3 β; H11K, H11 kinase; IGF, insulin-like growth factor 1; IL-6, interleukin 6; iNOS, inducible NO synthase; JAK, Janus kinase; KATP, ATP-dependent potassium channel; MnSOD, manganese superoxide dismutase; MPTP, mitochondrial permeability transition pore; NO, nitric oxide; NPR, natriuretic peptide receptor; p38, p38 mitogen activated protein kinase; p70S6K, p70 ribosomal S6 protein kinase; pGK, particulate guanylyl cyclase; P70S6K, phosphoinositide 3-kinase; PKC, protein kinase C; PKG, protein kinase G; ROS, reactive oxygen species; sGC, soluble guanylyl cyclase; SIRT1, sirtuin 1; STAT3, signal transducer and activator of transcription 3; TNF-α, tumour necrosis factor receptor; UCN, urocortins; factors/proteins affected with aging are shown in yellow. Modified from Ref. 5.
<table>
<thead>
<tr>
<th>Species</th>
<th>Model</th>
<th>Age Young / mature</th>
<th>middle-aged</th>
<th>old</th>
<th>IP stimulus</th>
<th>Duration of index isch./ rep.</th>
<th>Endpoint</th>
<th>IP protective in aged hearts</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Isolated cardiomyocytes</td>
<td>3 m</td>
<td>24 m</td>
<td></td>
<td>1 × 5 min isch. / 10 min rep.</td>
<td>30 min isch./30 min rep.</td>
<td>Cell viability (trypan blue exclusion)</td>
<td>No</td>
<td>O’Brien et al. [45]</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>12 w</td>
<td>50 w</td>
<td></td>
<td>3 × 5 min isch./5 min rep.</td>
<td>20 min isch. young, 15 min isch. MA/30 min rep.</td>
<td>LVDP, LVEDP, ATP, CK release</td>
<td>No</td>
<td>Tani et al. [170]</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>6 m</td>
<td>24 m</td>
<td></td>
<td>1 × 2 min isch./10 min rep.; 4 × 5 min isch./5 min rep.</td>
<td>20 min isch./40 min rep.</td>
<td>LVDP, LVEDP</td>
<td>No</td>
<td>Abete et al. [171]</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>3–4 m; 7–8 m</td>
<td>12–13 m</td>
<td></td>
<td>2 × 5 min isch./5 min rep.</td>
<td>35 min isch./120 min rep.</td>
<td>Infarct size (TTC staining)</td>
<td>No</td>
<td>Ebrahim et al. [76]</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>3 m</td>
<td>22 m</td>
<td></td>
<td>2 × 5 min isch./5 min rep.</td>
<td>45 min isch./2–3 h rep.</td>
<td>Infarct size (TTC staining)</td>
<td>No</td>
<td>Fenton et al. [172]</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>3 m</td>
<td>12 m</td>
<td>18–20 m</td>
<td>1 × 5 min isch./5 min rep.; 3 × 5 min isch.; 5 min rep.</td>
<td>35 min isch./120 min rep.</td>
<td>Infarct size (TTC staining)</td>
<td>Yes; 3 × 5 min isch./ rep. in MA, no: in old</td>
<td>Schulman et al. [77]</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Isolated heart</td>
<td>&gt;135 w</td>
<td></td>
<td></td>
<td>1 × 5 min isch./5 min rep.</td>
<td>30 min isch./120 min rep.</td>
<td>LVEDP, infarct size (TTC staining)</td>
<td>Yes</td>
<td>McCully et al. [173]</td>
</tr>
<tr>
<td>Mouse</td>
<td>LAD occlusion and rep.</td>
<td>&lt;3 m</td>
<td>&gt;13 m</td>
<td></td>
<td>1 × 10 min isch./10 min rep.</td>
<td>30 min isch./120 min rep.</td>
<td>Infarct size (TTC staining)</td>
<td>No</td>
<td>Boengler et al. [40]</td>
</tr>
<tr>
<td>Rabbit</td>
<td>LCx occlusion and rep.</td>
<td>4–6 m</td>
<td>2 year; 4 year</td>
<td></td>
<td>1 × 5 min isch./10 min rep.</td>
<td>30 min isch./3 h rep.</td>
<td>Infarct size (TTC staining)</td>
<td>Yes</td>
<td>Przyklenk and Whittaker [78]</td>
</tr>
<tr>
<td>Sheep</td>
<td>LAD occlusion and rep.</td>
<td>0.5–1 year</td>
<td>5.7–8 year</td>
<td></td>
<td>3 × 5 min isch./10 min rep.</td>
<td>60 min isch./150 min rep.</td>
<td>Infarct size (TTC staining)</td>
<td>Yes</td>
<td>Burns et al. [79]</td>
</tr>
</tbody>
</table>

Abbreviations: CK, creatine kinase; Cx, circumflex artery; isch., ischaemia; LAD, left anterior descending coronary artery; LVDP, left ventricular developed pressure; LVEDP, left ventricular end-diastolic pressure; m, months; MA, middle-aged; rep., reperfusion; TTC, 2,3,5-triphenyl-tetrazolium-chloride; w, weeks.
loss of cardioprotection with ageing

preconditioning is dependent on iNOS.\textsuperscript{111,112} the enhanced iNOS levels may contribute to the preservation of late cardioprotection in aged (78 weeks rat or 24–26 months mouse) hearts.

The function of mitochondria from young hearts is better preserved by IP.\textsuperscript{59,113} The ADP-stimulated (state 3) respiration is improved by IP.\textsuperscript{513,114} Whether or not the impairment of respiration in mitochondria from aged hearts can also be reversed by IP, has not been studied up to now. Clearly, several cardioprotective signal transduction cascades converge on the MPTP and prevent their opening, however, evidence that MPTP opening is affected by age is lacking.

5.3 Ischaemic preconditioning in aged patients

Since the most rigorous endpoint of IP, infarct size, is not easily available in controlled, prospective studies in humans for obvious ethical reasons, the existence and significance of IP in humans is less clear than in animal studies.\textsuperscript{2,115} In clinical studies, surrogate endpoints such as ST-segment shifts in the surface or intracoronary ECG, metabolic markers such as ATP or lactate, or release of creatine kinase or troponin are used. Apart from potentially unreliable endpoints, clinical studies inducing IP by percutaneous transluminal coronary angioplasty are confounded by the potential of collateral recruitment, which may attenuate ischaemia and its consequences independently of any preconditioning.

In patients, IP—as reflected by preinfarction angina within 24 h prior to infarction—was protective when the clinical endpoints mortality, heart failure, arrhythmias (mean age: preinfarction angina 59 ± 9 years; control 58 ± 11 years;\textsuperscript{116} preinfarction angina 59 ± 1 years; control 59 ± 1 years;\textsuperscript{117} preinfarction angina 59 ± 11 years; control 61 ± 8 years) or the laboratory endpoints creatine kinase release and left ventricular dilation (mean age 59 ± 12 years)\textsuperscript{119} were evaluated. Cardiac enzymes and the in-hospital outcomes death, recurrent ischaemia, heart failure, and atrioventricular block were similar in patients with preinfarction angina 48 h prior to acute myocardial infarction (56 ± 12 years) compared with patients without preinfarction angina (57 ± 10 years).\textsuperscript{120} In contrast, Abete et al.\textsuperscript{121} demonstrated a protective effect of preinfarction angina 48 h prior myocardial infarction against in-hospital death and heart failure or shock in patients younger than 65 years. The retrospective analysis of patients without or with angina before myocardial infarction does not allow to distinguish between the cardioprotection by early and late IP.

IP performed during cardiac surgery was associated with reduced ventricular arrhythmias, inotrope requirements, and intensive care unit stay,\textsuperscript{122} with an improvement in cardiac index (mean age without IP: 65 ± 2 years, mean age with IP: 62 ± 2 years),\textsuperscript{123} reduced release of troponin T (mean age without IP: 62 ± 2 years, mean age with IP: 57 ± 2 years),\textsuperscript{124} and preservation of the myocardial ATP levels (age of patients not specified).\textsuperscript{125} However, the use of cardiopulmonary bypass per se has been suggested to confer cardioprotection.\textsuperscript{126}

The impact of age on IP induced during surgery or in isolated human tissue in vitro remains controversial, since both loss and preservation of cardioprotection have been
<table>
<thead>
<tr>
<th>Species</th>
<th>Model</th>
<th>Age</th>
<th>Preconditioning stimulus</th>
<th>Duration of index isch./rep.</th>
<th>Endpoint</th>
<th>PC protective in aged hearts</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute preconditioning</td>
<td>Mouse</td>
<td>Isolated heart</td>
<td>2 m</td>
<td>25 μM adenosine</td>
<td>20 min isch./ 60 min rep.</td>
<td>LVEDP</td>
<td>No</td>
</tr>
<tr>
<td>Mouse</td>
<td>Isolated heart</td>
<td>10–14 w</td>
<td>1 mM [D-pen2,5] enkephalin (delta opioid agonist)</td>
<td>20 min isch./ 45 min rep.</td>
<td>LVEDP, − dP/dt</td>
<td>No</td>
<td>Peart et al. 101</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>2–4 m</td>
<td>2.5% sevoflurane for 10 min, 5 min washout</td>
<td>25 min isch./ 60 min rep.</td>
<td>LVEDP, CK release, infarct size (TTC staining)</td>
<td>Yes, in MA; no, in old</td>
<td>Sniecinski and Liu 82</td>
</tr>
<tr>
<td>Rat</td>
<td>LAD occlusion and rep.</td>
<td>3–5 m</td>
<td>30 min 1 minimum alveolar anaesthetic concentration isoflurane</td>
<td>30 min isch./ 120 min rep.</td>
<td>Infarct size (TTC staining)</td>
<td>No</td>
<td>Nguyen et al. 81</td>
</tr>
<tr>
<td>Rat</td>
<td>LAD occlusion and rep.</td>
<td>2–3 m</td>
<td>3 × 5 min 70% helium, 5 min washout</td>
<td>25 min isch./ 20 min rep.</td>
<td>Infarct size (TTC staining)</td>
<td>No</td>
<td>Heinen et al. 174</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>3 m</td>
<td>30 μM diazoxide for 10 min, 5 min washout</td>
<td>35 min isch./ 120 min rep.</td>
<td>Infarct size (TTC staining)</td>
<td>No</td>
<td>Schulman et al. 77</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>3 m</td>
<td>200 nM CCPA (adenosine A1 receptor agonist) for 10 min, 5 min washout</td>
<td>35 min isch./ 120 min rep.</td>
<td>Infarct size (TTC staining)</td>
<td>No</td>
<td>Schulman et al. 77</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>3 m</td>
<td>30 μM DOG (PKC analog) for 10 min, 5 min washout</td>
<td>35 min isch./ 120 min rep.</td>
<td>Infarct size (TTC staining)</td>
<td>No</td>
<td>Schulman et al. 77</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Isolated heart</td>
<td>&gt;135 w</td>
<td>1 mM adenosine</td>
<td>30 min isch./ 120 min rep.</td>
<td>LVEDP, infarct size (TTC staining)</td>
<td>Yes</td>
<td>McCully et al. 173</td>
</tr>
<tr>
<td>Late preconditioning</td>
<td>Mouse</td>
<td>Isolated heart</td>
<td>10–14 w</td>
<td>30 μM morphine acute, 75 mg morphine pellet 5 d prior to isch./rep.</td>
<td>25 min isch./ 45 min rep.</td>
<td>LVEDP, LDH release</td>
<td>Yes, in 5 d morphine; no, in acute morphine</td>
</tr>
<tr>
<td>Rat</td>
<td>Isolated heart</td>
<td>12 w</td>
<td>BW337U86 (delta opioid receptor agonist), 24 h prior to ischaemia</td>
<td>20 min isch./ 20 min rep.</td>
<td>LVEDP, CK release, lactate dehydrogenase activity</td>
<td>Yes</td>
<td>Shinmura et al. 175</td>
</tr>
</tbody>
</table>

Abbreviations: CCPA, 2-chloro-N6-cyclopentyladenosine; CK, creatine kinase; DOG, 1,2-dioctanoyl-sn-glycerol; isch., ischaemia; LAD, left anterior descending coronary artery; LVEDP, left ventricular developed pressure; LVEDP, left ventricular end-diastolic pressure; m, months; MA, middle-aged; PKC, protein kinase C; rep., reperfusion; TTC, 2,3,5-triphenyl-tetrazolium-chloride; w, weeks.
Table 4  Cardioprotection by ischaemic preconditioning in young and aged human atrial tissue and in patients

<table>
<thead>
<tr>
<th>Model</th>
<th>Age</th>
<th>IP stimulus</th>
<th>Duration of index isch./rep.</th>
<th>Endpoints</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial appendages from patients undergoing elective coronary artery surgery or aortic valve replacement</td>
<td>30–49 y</td>
<td>1 × 5 min isch./5 min rep.</td>
<td>30 min isch./10 min rep.</td>
<td>CK release, MTT reduction</td>
<td>Loubani et al. 125</td>
</tr>
<tr>
<td>Right atrial appendages from patients undergoing elective coronary artery surgery or aortic valve replacement</td>
<td>65 y (65–78)</td>
<td>2 × 3 min isch./5 min rep.</td>
<td>Angina within 48 h prior to infarction</td>
<td>In hospital death, heart failure, or shock</td>
<td>Abe et al. 126</td>
</tr>
<tr>
<td>Right atrial appendages from patients undergoing elective coronary artery surgery or aortic valve replacement</td>
<td>60–69 y (20–70 years)</td>
<td>2 × 2 min isch./5 min rep.</td>
<td>ST segment shift, chest pain</td>
<td>No, 2 min isch./5 min rep.</td>
<td>Wu et al. 127</td>
</tr>
<tr>
<td>Patients with heart failure</td>
<td>&lt; 69 y</td>
<td>&gt; 65 y (≤ 70)</td>
<td>Lactate extraction</td>
<td>No</td>
<td>Bartling et al. 128</td>
</tr>
</tbody>
</table>

Abbreviations: CK, creatine kinase; isch., ischaemia; rep., reperfusion; y, years.

Loss of cardioprotection with ageing

The loss of cardioprotection with ageing cannot be attributed to a differential expression of genes important for cardioprotection, since the expression of cardioprotective genes, such as heat shock protein 70 (HSP70), Bcl-2/-xl, or IAP (inhibitor of apoptosis protein), in right atrial appendages from patients older than 70 years was preserved. Similar to IP in aged rat hearts, patients older than 65 years undergoing coronary angioplasty benefited from a stronger preconditioning stimulus.

Apart from age and concomitant cardiovascular diseases, the analysis of the effectiveness of IP in patients is further complicated by confounding factors such as medical treatment e.g. inhibition of angiotensin-converting enzyme, which has been demonstrated to confer cardioprotection via inhibition of bradykinin breakdown or sulfonylureas which may inhibit mitoKATP channels.

In summary, the aged mammalian and human heart is characterized by loss of cardioprotection by ischaemic or pharmacological preconditioning. The defects in the signalling cascades occur at several levels, ranging from changes in the expression and/or activity of extracellular ligands, sarcoclemmal receptors, protein kinases to mitochondrial proteins, and mitochondrial function.

6. Ischaemic postconditioning in aged myocardium

6.1 Ischaemic postconditioning in aged myocardium of laboratory mammals

Ischaemic postconditioning is the infarct size reduction by brief cycles (5–60 s) of ischaemia/reperfusion following a sustained ischaemic insult. The phenomenon of ischaemic postconditioning was first described in dogs, subsequently in other species, and can also be recruited clinically in humans to reduce infarct size.

The signal transduction pathways of ischaemic pre and postconditioning share some, but not all signalling elements. Activation of the so-called RISK (reperfusion injury salvage kinase) pathway, which includes the phosphorylation of Akt, ERK1/2, p70 S6 ribosomal protein S6 kinase (p70S6K), and GSK3β was suggested to be causal for the cardioprotection by ischaemic postconditioning. However, the importance of RISK phosphorylation has been recently questioned, notably its relevance in larger mammals. The infarct size reduction by ischaemic postconditioning depends both on number and duration of the reocclusions (for review see 140). The dependence of cardioprotection on the postconditioning algorithm is seen not only in young but also in aged hearts. In young C57/B16 mice (<3 months), ischaemic postconditioning by either five cycles of 5 s ischaemia and 5 s reoxygenation (5 × 5) or by three cycles of 10 s ischaemia and 10 s reoxygenation (3 × 10)
reduced infarct size, whereas in middle-aged mice (>13 months) the cardioprotection by the 5 × 5 postconditioning algorithm was maintained but that of the 3 × 10 protocol was abolished,141 supporting the idea that the stimulus strength is important. The loss of infarct size reduction by 3 × 10 ischaemic postconditioning was associated with reduced expression and phosphorylation of STAT3 in aged (>13 months) mouse hearts.141,142 Also, in hearts isolated from 20 to 24 months old C57/Bl6 mice ischaemic postconditioning by either three cycles of 10 s ischaemia/10 s reperfusion or six cycles of 10 s ischaemia/10 s reperfusion failed to reduce infarct size.102 In this study, the loss of cardioprotection by ischaemic postconditioning was associated with increased levels of the phosphatase MKP-1 in aged (20–24 months) mouse hearts. The infusion of sodium orthovanadate, which inhibits protein tyrosine phosphatases and adenosine triphosphatases, reduced the increased levels of MKP-1 and restored the cardioprotection by ischaemic postconditioning in aged hearts. The phosphorylation of ERK1/2, which is a target protein of MKP-1, was enhanced by the postconditioning manoeuvre in young, but once more not in aged hearts. However, in aged hearts treated with sodium orthovanadate ischaemic postconditioning once again restored ERK1/2 phosphorylation.102 Therefore, impaired ERK1/2 phosphorylation by ischaemic postconditioning in aged hearts may interfere with downstream signalling proteins such as STAT3 and thereby limit the resistance of the aged heart against ischaemia/reperfusion injury.

Taken together, the aged heart is not only characterized by an impaired response to a pre, but also to a postconditioning stimulus. The loss of cardioprotection by ischaemic postconditioning is associated with a loss of activity of parts of the signal transduction pathways.

6.2 Ischaemic postconditioning in human myocardium

After the initial description of the phenomenon of ischaemic postconditioning in dog myocardium, the effectiveness of ischaemic postconditioning’s cardioprotection was also shown in humans. In patients with acute myocardial infarction undergoing primary percutaneous coronary intervention (mean age control: 56 ± 3 years; mean age postconditioning: 58 ± 4 years), repeated inflation and deflation of the angioplasty balloon after stenting conferred cardioprotection in terms of creatine kinase release.134 The beneficial effects of postconditioning persisted for at least 1 year.4 The involvement of inhibition of MPTP opening at reperfusion, which is cardioprotective in animal studies, was confirmed in patients with myocardial infarction, who received a bolus of the MPTP inhibitor cyclosporine A before the percutaneous coronary intervention (mean age control: 57 ± 2 years, mean age cyclosporine A: 58 ± 2 years).143 Here, creatine kinase release and the area of hyperenhancement on MRI imaging, which reflects infarcted tissue, were attenuated compared to the control group receiving saline.

In general, postconditioning is beneficial in human myocardium, however, data on a possible age-dependency of postconditioning are still lacking.

7. Strategies to prevent the loss of cardioprotection in aged hearts

7.1 Caloric restriction

Caloric restriction is an established intervention to attenuate cellular ageing by inducing transcriptional reprogramming11 and to promote longevity.144 Since caloric restriction also increases the tolerance to ischaemia,145 the potential impact of caloric restriction to restore or maintain the ability of the aged heart to respond to a preconditioning stimulus has been investigated. Most studies on caloric restriction and IP in aged hearts have focussed on ventricular function and not on infarct size. Whereas the recovery of left ventricular function after reperfusion per se was improved and the release of creatine kinase and lactate dehydrogenase per se was reduced by short-term caloric restriction (90% caloric intake for 2 weeks, then 65% caloric intake for 2 weeks) both in young (6 months) and in aged (24 months) rat hearts, the protection by IP was not restored by caloric restriction in aged hearts.146 In isolated rat hearts (10 months), IP had no effect on postischaemic cardiac output, whereas in caloric restricted rats (40% food reduction for 6 months) IP significantly improved postischaemic cardiac output.147 IP improved the recovery of developed pressure and this protection was lost with ageing, but partially preserved in 24 months old caloric restricted isolated rat hearts.148,149

The analysis of the mechanisms involved in the potential preservation of IP by caloric restriction in aged hearts has focussed on the adipokine adiponectin. Adiponectin-knockout mice have larger infarcts and enhanced apoptosis after ischaemia/reperfusion. On the signal level, higher concentrations of superoxide and peroxynitrite were detected in adiponectin-deficient mice than in controls, suggesting that adiponectin is cardioprotective by reducing oxidative/nitrative stress.150 Evidence for the involvement of adiponectin and AMPK (AMP-activated kinase) in the cardioprotective signalling induced by caloric restriction has been provided in adiponectin-antisense transgenic mice.151 Whereas short-term caloric restriction improved the recovery of left ventricular function after ischaemia/reperfusion, reduced infarct size, and enhanced AMPK phosphorylation, the protective effects of caloric restriction were abolished in the adiponectin-antisense transgenic mice. Recombinant adiponectin restored the protective effect of caloric restriction in adiponectin-deficient mice, and inhibition of AMPK phosphorylation in wild-type mice abrogated the cardioprotection induced by caloric restriction. The concentration of serum adiponectin induced by caloric restriction was higher in young (6 months) than in aged (24–26 months) rats, and loss of adiponectin inducibility by caloric restriction in aged rats was only partially compensated by a higher degree of caloric restriction.152 Caloric restriction restored the protective effect of IP in 12 months old rat hearts, and the cardioprotection was associated with a nitric oxide-dependent increase of the histone deacetylase Sirt1 (sirtuin 1).153 A moderate Sirt1 overexpression protected the heart from oxidative stress and retarded ageing.154 Therefore, the enhanced nuclear translocation of Sirt1 by caloric restriction may be involved in the restoration of IP in aged hearts and underlying mechanisms may relate to reduced oxidative stress and apoptosis. Along this line,
long-term caloric restriction decreases mitochondrial hydrogen peroxide formation at complex I, lowers oxidative damage to mitochondrial DNA in aged (24 months) rat hearts, and possibly thereby contributes to attenuated ageing.155

7.2 Exercise

Exercise confers cardioprotection against ischaemia/reperfusion injury (for review see 156). The improved tolerance to ischaemia is sex-dependent and greater in male than in female hearts.157 Studies aimed at identifying the mechanisms mediating the protection by exercise revealed a reduction of mitochondrial ROS formation,158 an increased antioxidant capacity, and a differential gene/protein expression, such as an enhanced expression of heat shock proteins (for review see 159) or cardiac telomere-stabilizing proteins and IGF-1.6 Exercise improves the recovery of function and reduces apoptosis both in young (4 months) and in aged (21 or 24 months, respectively) rat hearts subjected to ischaemia/reperfusion was attributed to limited proteolysis capacity, and a differential gene/protein expression, such as an enhanced expression of heat shock proteins (for review see 159) or cardiac telomere-stabilizing proteins and IGF-1.6 Exercise improves the recovery of function and reduces apoptosis both in young (4 months) and in aged (21 or 24 months, respectively) rat hearts subjected to ischaemia/reperfusion.160,161 In aged rat hearts (24 months), the lost cardioprotection by IP was partially restored by exercise alone and more completely restored by the combination of exercise and caloric restriction.149 Whereas the improved postischaemic recovery of developed pressure by IP was lost in aged (24 months) compared to that in adult (6 months) rat hearts, 6 weeks of swim training preserved the cardioprotective effect of IP in aged hearts.162 Exercise enhanced the oxidative defence, since the levels of Sirt1, manganese superoxide dismutase, and catalase, which were decreased in aged rat hearts (24 months), were restored by training.168 The protective effect of 12 week treadmill training in aged rat hearts (24 months) subjected to ischaemia/reperfusion was attributed to limited protein oxidation and enhanced myocardial protein levels of Hsp70 and eNOS.163

The beneficial effect of exercise on the cardioprotection by IP in aged hearts was confirmed in patients older than 65 years (mean age about 72 years).164 Here, the protection by preinfarction angina against in hospital mortality was present only in elderly patients with higher levels of physical activity.

In summary, the loss of cardioprotection with ageing is not irreversible. Caloric restriction, exercise, or both contribute to the preservation of cardioprotection in aged hearts.

8. Conclusion

Structural and functional changes during ageing render the heart more susceptible to cell death from ischaemia/reperfusion. Cardioprotective manoeuvres such as ischaemic pre and postconditioning loose their effectiveness with ageing. The mechanisms responsible for the loss of protection in the aged heart include alterations in gene/protein expression, signal transduction cascades, and mitochondrial function (e.g. ROS formation, respiration). As human life expectancy increases due to effective treatment of cardiovascular and other diseases, there is a need for the development of strategies designed to preserve the efficiency of cardioprotective mechanisms in the aged heart. Caloric restriction and physical exercise may contribute to the prevention of the age-induced loss of cardioprotection.

Conflict of interest. None declared.

References


Loss of cardioprotection with ageing


121. Abete P, Ferrara N, Caciatorre F, Madrid A, Bianco S, Calabrese C et al. Angina-induced protection against myocardial infarction in adult and...


