Background

Cardiovascular diseases (CVD) are the leading cause of death worldwide and it is estimated that by 2030 approximately 24 million people will die from CVD (2). Although the advances in the prevention, diagnosis and management of CVD have progressed in the past three decades, heart failure (HF). Its increasing incidence represents a serious danger especially in the elder population challenged with further comorbidities, the prognosis being more unfavourable in females. Pathophysiological mechanisms of HF are complex and involving processes such as hemodynamic overload, ischemia, fibrosis, inflammation, ventricular remodelling, neurohumoral disbalance, altered gene expression and Ca²⁺ cycling, oxidative stress, acceleration of apoptosis and mitochondrial dysfunction that subsequently leads to progressive decline of heart function and increased morbidity and mortality. Currently, neither effective prevention of AMI nor ultimate reduction of ischemia/ reperfusion (I/R) injury is available, therefore, there is an urgent need to search for alternative approaches based on the experimental findings. Ischemic preconditioning (PC) is a most robust form of innate cardioprotection based on the adaptation of the heart to I/R, which translation to clinical practice has been relatively successful albeit limited by technical requirements and short-term duration. Nevertheless, novel forms of adaptive interventions such as „remote” PC (RPC) appear as promising beneficial approaches. Although molecular mechanisms of RPC are not yet completely elucidated, some forms of RPC, in particular its non-invasive modifications, have been already used in clinical conditions in patients with AMI, PPCI, congenital defects and bypass surgery, albeit with different effectiveness. We assume that in contrast to a traditional approach to pharmacological treatment of HF often focused on only one pathophysiological mechanism, a complex targeting of several pathophysiological mechanisms upon activation of intrinsic adaptive pathways represents a platform for the development of novel strategies to fight HF.

Heart Failure and Its Origin

Syndrome of HF is so called „end point” for several diseases, of which ischemic heart disease (HHD) and its most serious manifestation, acute myocardial infarction (AMI) are on the first place. Although the number of patients that successfully survive AMI is increasing, due to the modern treatment including pharmacotherapy, interventional cardiology and cardiac surgery, the alteration of the heart muscle will manifest later on (even years after the heart attack) by chronic failing of pumping function of the heart [3,4]. Patients after AMI live longer, however, their already impaired heart is more susceptible to failing.

We and others have shown that risk factors associated with modern lifestyle such as hypertension, chronic stress, hyperglycemia, and dyslipidemia not only have an adverse impact on myocardial response to ischemia [5,6], but also suppress the intrinsic cardioprotective properties of the myocardium and accelerate thus the progression of HF.

To a large extent, different forms of cardiomyopathies, such as due to metabolic diseases [7-
Impact of Gender and Aging on the Development of Heart Failure

Incidence of cardiac ailments differs with gender and age [16-18]. It has been shown that the risk for developing heart failure is twice as high in males compared to females in the age group between 55 and 64, and several epidemiological studies have confirmed that pre-menopausal women have a reduced risk of CVD [17,18]. On the other hand, over the age of 65, both genders have the same risk for developing heart failure [19] and in females, the risk of HF is increasing even more than in males. This is attributed to the cardioprotective properties of ovarian hormones [20] and to the fact that their insufficiency also contributes to the development of hypertension, diabetes and hyperlipidemia [18]. However, this remains underestimated and often leads to improper management of AMI in females including late hospital attendance and the onset of revascularization interventions, as well as other adverse consequences leading to development of HF [19]. Despite that, much research effort (clinical and experimental) to date has been focused on the investigation of cardioprotection mostly in healthy male subjects of adult age although gender differences play an important role in the heart response to ischemia and subsequent preservation/deterioration of heart function, in particular, in elder population [20]. Our recent studies demonstrated gender-related rat heart response to ischemia associated with age [21,22] that has been manifested already during maturation, while gender differences with respect to ischemic tolerance were present even in the juvenile animals.

Management of Heart Failure

Pathophysiological mechanisms of HF are complex and heterogeneous involving processes such as hemodynamic overload, ischemia, fibrosis, inflammation, ventricular remodelling, neurohumoral disbalance, altered gene expression and Ca2+ cycling, oxidative stress, acceleration of apoptosis and mitochondrial dysfunction that subsequently lead to progressive decline of heart function and increased morbidity and mortality [23,24].

One of the important strategies to combat heart failure is to treat the initial disease that caused heart failure in the first instance, followed by supporting cardiac activity and cardioprotection. The treatment can be either pharmacological, instrumental (cardiac device), surgical or as a last option – heart transplantation. As the most common reason of heart failure is IHD and AMI, early restoration of blood flow in the ischemic myocardium is a prerequisite for its salvage. On the other hand, delayed revascularization may lead to ischemia/reperfusion (I/R) injury [25]. Despite improved pharmacological and cardiac device therapies, neither effective prevention of AMI nor reduction of I/R injury is currently available. Thus, there is a substantial unmet need for novel approaches, ideally those, that specifically address repair and regeneration of damaged and/or lost myocardium (given limited endogenous repair of cardiomyocytes in adults).

Current trends of alternative approaches to management of patients suffering from multiple ailments leading to heart failure differ from traditional pharmacological treatment often focused on targeting only one pathophysiological mechanism. We assume that in contrast to that, a complex targeting of several pathophysiological mechanisms represents a platform for the development of novel strategies to fight HF.

Short-term Cardiac Adaptation – Ischemic Preconditioning

It has been revealed in numerous experimental and clinical studies that some stressful stimuli (e.g., transient episodes of ischemia/hypoxia, reactive oxygen species) exert not only deleterious effects but also trigger short-term or longer lasting adaptive processes in the heart, which ensue in greater resistance against IR injury. The concept of heart’s own protection is based on the principle that short-term cardiac adaptation to certain forms of moderate stress increases resistance of the heart against subsequent sustained ischemia – phenomenon of preconditioning (PC). Ischemic PC has been observed in all animal species including humans [26,27]. It is manifested by a delay of necrotic and apoptotic processes in the cardiomyocytes [3], reduction of lethal arrhythmias [28] and by an improved post-I/R functional recovery [16,29].

Unfortunately, in clinical situations, application of classical ischemic PC has certain limitations, due to its short-term duration, whereby the occurrence of AMI is unpredictable, or due to requirement of chest opening (to get access to coronary arteries) that can be possible to perform only by trained personnel in the specialized hospitals.

Clinically Applicable Forms of Preconditioning

On the other hand, novel forms of PC appear to be perspective from the clinical point of view. One of these novel forms is so called remote ischemic preconditioning (RPC), in which induction of ischemia in any organ confers protection to other, distant organs/tissues [25,30,23,24].

It is important to note that animal (and some clinical) studies documented a beneficial effect of brief episodes of limb ischemia leading to cardiac protection against I/R [31-33]. This non-invasive modification of RPC does not require invasive surgery (such as chest opening), and thus, can be applied even in the ambulance or during the transportation of a patient to the hospital. These interventions include inflation (200 mmHg) and deflation of a pressure cuff placed on an upper or lower limb and realized in three 5-min cycles. Moreover, in relation to ischemia, RPC may be applied in settings of pre-, per- or post-conditioning (after the end of ischemia during surgical interventions). Its similar effectiveness in these settings offers relatively great time window for its realization, in contrast to classical ischemic PC, that makes RPC more attractive from the clinical point of view. In particular, non-invasive and easy application of RPC (limb ischemia, 33) has been started to be implemented in clinical conditions, e.g., in treatment of patients with AMI [34,35]. Beneficial effects of RPC have been also demonstrated during surgical interventions in children with congenital heart defects [36].

Further important breakthrough was a finding that with respect to the effect of RPC on the HF progression, this intervention could be applied not only in the acute setting of several bouts of limb ischemia, but it could be also administered as repeated cycles of limb I/R in the long-term that increases the efficiency of RPC: reduces the extent of ventricular remodelling and mortality over 28 days after AMI in a rat.
in vivo model [37]. Similarly, repeated RPC increased endothelium-dependent vasodilatation in healthy humans and in patients with chronic HF [38]. Thus, we may assume that this approach will enhance positive effect of RPC with respect to suppression of HF development.

**Potential Mechanisms of RPC**

Mechanisms of RPC have not been investigated in details so far, however, it is suggested that RPC triggers complex hormonal and neuronal signaling leading not only to an increased resistance to I/R in a distant organ, but also acts via activation of a systemic response as well (anti-inflammatory, anti-oxidative effects, changes in gene transcription and attenuation of endothelial dysfunction) [39], which is supported, e.g., by up-regulation of IL-10 in mice exposed to RPC 24 hrs prior to myocardial I/R [40]. It is proposed that humoral signaling is dependent on the activation of „survival“ RISK (reperfusion injury salvage kinase) – PI3K/Akt-GSK3β- mPTP [41] and SAFE (survival activating factor enhancement) - TNFα- IL-10- STAT3- mitoKATP [42] pathways. (MitoKATP – mitochondrial ATP-dependent K+ channels; mPTP – mitochondrial permeability transition pore).

**Micro-RNAs**

Several pathophysiological mechanisms of HF as well the mechanisms of protection against I/R are regulated by small non-coding RNA (micro-RNA or miRNA) [43]. It has been demonstrated that out of the great number of those miRNAs, in particular, miRNA-144 participates in cardioprotective effect of RPC, and it is also associated with enhanced RISK signaling [3,44].

**Nuclear Receptors PPAR**

Furthermore, the nuclear receptors PPAR-alpha have been also suggested to play a role in the mechanisms of RPC [45]. Their main role is regulation of genes involved in processes of metabolism and energy production in the heart [46], during different pathological conditions in CVS including I/R, diabetes and HF. Moreover, it has been shown that the ligands of these transcription factors (hypolipidemics) may induce preconditioning-like lipid-independent genomic and non-genomic effects including antiapoptotic, anti-oxidative and antiinflammatory effects (so called pharmacologically induced PC) with subsequent myocardial protection against acute I/R [47,48]. In addition, it is proposed that the activation of PPAR downstream pro-survival targets (PI3K/Akt-eNOS) and MMP-2 inhibition. However, the role of PPAR in chronic processes leading to the development of HF and in the mechanisms of protection conferred by RPC is still not completely understood.

**Mitochondria as a Key Effector of Cardioprotection**

With respect to energy metabolism as a part of cardioprotective mechanisms induced by RPC, maintenance of mitochondrial membrane function and respiratory properties has been shown as an important mechanism [49]. Mitochondria are important cell organelles involved in cardioprotection [50]. Experimental studies proposed that brief episodes of stress activate cell signaling mechanisms from membrane receptors through postreceptor enzyme systems of protein kinases up to the end-effector systems in the mitochondria (mitoKATP; mPTP) attenuating processes leading to cell death [51]. Opening of mitoKATP induces moderate increase in free oxygen radicals production, which in turn, activates protective signaling suppressing mPTP opening during reperfusion that is otherwise stimulated altogether with declined levels of ATP in the cell, also by increased concentration of intracellular Ca2+ and oxidative stress. That is followed by disruption of mitochondrial membranes integrity and release of proapoptotic molecules (e.g., cytochrome C) activating mechanisms of cell death [3,24]. Thus, with respect to cardioprotection, it appears as a promising approach – to simulate the effect of RPC by pharmacological modulators of mPTP opening by drug cyclosporin A [52], which, in addition, has been already successfully applied in patients with AMI prior to angioplastic intervention [53]. Pilot experiments with RPC from our laboratory demonstrated that this form of PC participates in the preservation of function (energy production) and biophysical properties of cardiac mitochondrial membranes that might represent a promising therapeutic approach under conditions of chronic heart ailment. Based on these results we assume that basic understanding of mitochondrial biology will be critical for the development and optimization of mitochondria-targeted therapies of chronically failing myocardium.

**Conclusion**

Our results confirm that cardiac resistance to acute I/R injury including lethal changes (size of infarction, severe arrhythmias) and myocardial dysfunction is to a major extent affected by the presence of further comorbidities (hypertension, hyperlipidemia), is related to the age of the subjects and their gender. Under these conditions, not only myocardial response to ischemia per se but also the efficiency of the heart’s own endogenous protective mechanisms are altered, which even more accelerates the progression of HF.

The translation of RPC to clinical practice (to patients with acute MI) has been relatively successful, however, negative outcomes have been reported as well, and pharmacological recruitment of cardioprotective signaling has been largely disappointing so far. Thus, further investigation of molecular mechanisms of RPC is urgently needed.

Activation of innate adaptive mechanisms of the heart might represent a promising therapeutic strategy under conditions of chronic heart ailments. Moreover, multifactorial approach to solving these problems is a way to prevent the development of HF. These approaches may increase the arsenal of non-invasive interventions that might be potentially implemented in human medicine, and lead to optimization of HF management preventing the rise in its incidence, especially in elder generation.

**Acknowledgement**


**References**


