

## Editorial

### **Special Issue "Implications of oxidative stress and redox biochemistry for heart disease and cardioprotection - The EU-CARDIOPROTECTION COST Action (CA16225)"**

Acute myocardial infarction (AMI) and the heart failure that complicates it are the leading causes of death and disability in Europe and worldwide [1]. The most effective treatment for limiting myocardial infarct (MI) size and preventing heart failure following AMI, is timely myocardial reperfusion using primary percutaneous coronary intervention (PPCI) [2]. However, despite timely treatment, mortality and morbidity following AMI remain significant. Accordingly, new treatments are required to reduce MI size, in order to preserve left ventricular (LV) systolic function and prevent the development of post-MI heart failure – a treatment strategy termed ‘cardioprotection’ [3, 4]. Besides these acute cardiac events, there are numerous chronic heart diseases such as congestive heart failure, heart valve insufficiency/damage and psychosocial stress-related disease such as Takotsubo syndrome that will be also addressed by this special issue. Importantly, oxidative stress, redox biochemistry and dysregulated inflammatory processes represent hallmarks of almost all of these heart diseases as envisaged by a wide range of redox biomarkers reported for clinical and preclinical studies [5, 6].

In this Special Issue, which is a collaboration with the EU-CARDIOPROTECTION COST Action (CA16225 <http://www.cardioprotection.eu/>), we aim to highlight the redox biochemistry and oxidative stress underlying heart disease and cardioprotection as well as the existing research gaps. We will also emphasize emerging mechanisms impacting cardiac health and disease such as the circadian clock, the microbiome, epigenetic and neuronal/central pathways. Also therapeutic approaches and their impact on the redox biochemistry and oxidative stress of heart disease will be discussed in detail, including ischemic pre- and post-conditioning or physical exercise as non-drug-based therapies as well as modern cardiovascular drugs with pleiotropic antioxidant/anti-inflammatory properties. Special emphasis, although not exclusively, will be made on the following points and how they are

related to oxidative stress and redox biochemistry of heart disease: (1) redox signalling in ischemia/reperfusion (I/R) injury and heart failure; (2) discovery of new therapeutic targets and innovative strategies for cardioprotection against I/R injury and heart failure; (3) testing the effects of combination therapy to target multiple signalling pathways both within and outside the cardiomyocyte; (4) investigating the effects of confounders (co-morbidities and co-medications) on cardioprotection.

### *Impact of redox regulation and oxidative stress on energy metabolism in heart diseases*

As heart failure is one of the leading causes of death and disability worldwide, new treatment targets and therapies are needed to prevent the onset and progression of heart failure in order to improve health outcomes in this patient group. In this regard, Weissman & Maack [7] review the role of cardiac energetic perturbations as a key mediator of oxidative stress and impaired excitation-contraction coupling, both of which contribute to the cardiac dysfunction characterizing heart failure. In their article, they provide an overview of reactive oxygen species (ROS) production in the setting of heart failure, and focus on the role of mitochondrial ROS as a viable therapeutic target for improving cardiac energetics, excitation-contraction coupling, and ultimately heart function.

A well-balanced intercellular communication between the different cells within the heart is vital for the maintenance of cardiac homeostasis and function. Dysregulation of these processes, e.g. by adverse redox signaling or oxidative damage, contributes significantly to the onset and progression of cardiometabolic disease. Martins-Marques and colleagues [8] provide detailed insights into the cellular crosstalk in cardioprotection including a critical discussion on the spatial and temporal involvement of ROS in these processes. They summarize the reports on the impact of oxidative stress on gap junctions, the concept of tunneling nanotubes, the role of extracellular vesicles and processes of intracellular communication (e.g. between mitochondrial voltage-dependent anion channels and ryanodine receptors), all of which determines cellular crosstalk in heart disease. Finally, redox therapeutic approaches are discussed that may improve cellular crosstalk for cardioprotection.

The heart intensively produces and consumes energy to maintain cardiac functionality and blood circulation. Thereby the heart is the most metabolically flexible organ with respect to the use of substrates available in different states of energy metabolism. Normally, fatty acids and glucose are the primary fuels in the healthy adult heart. However, extreme concentrations of both, hyperglycemia and dyslipidemia, likely contribute to cardiovascular disease and associated morbidity and mortality. Dambrova and colleagues [9] summarize the current knowledge of the importance of substrate availability (such as during hyperglycemia) and/or the intracellular accumulation of metabolites (such as long-chain acylcarnitines or succinate) for ROS production through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzymes (hyperglycemia) or the mitochondrial electron transport chain (succinate) especially under pathophysiological conditions such as myocardial I/R and how increased oxidative stress contributes to I/R injury under these conditions. They further highlight that therapies targeting energy metabolism pathways by regulating substrate concentrations may prevent ROS production and protect the heart against I/R injury thereby improving patients' morbidity and mortality.

Mitochondrial dysfunction including disturbances in mitochondrial metabolic and redox signaling pathways are known to contribute to a number of cardiac diseases including acute ischemia and reperfusion injury and the development and progression of heart failure, positioning mitochondrial metabolism and ROS as attractive therapeutic targets to combat cardiac dysfunction in these settings. In this regard, Vujic et al [10] provide an outline of the sources of ROS in the heart and the mitochondrial metabolic pathways in health and disease, and focus on the role of mitochondrial ROS as a therapeutic targets for preventing the onset and progression of cardiac disease.

#### *Impact of redox regulation and oxidative stress in the circulatory system, the periphery and cardiometabolic comorbidities*

Circulating blood cells including red blood cells and platelets are paramount for maintaining central physiological functions and to protect from disease and tissue injury. The review by Mahdi and coworkers [11] describes recent advances in the

understanding of redox biology and function of red blood cells and platelets, since both cell types undergo important changes in redox regulation shifting from antioxidant defense under physiological conditions to a pro-oxidative state under pathophysiological conditions (cardiovascular risk factors and in developed cardiovascular disease). Under disease conditions, red blood cells and platelets interact not only with each other but also with other circulating cells and resident cells of the vasculature and the heart thereby promoting the progression of cardiovascular disease. These findings highlight that cardiovascular disease not only occurs within the vascular wall but is also a consequence of the interaction of circulating cells (red blood cells, platelets) with the vasculature. Therefore, the authors emphasize that the functional alterations identified in circulating cells are important targets for therapeutic interventions; a key to target dysfunctional red blood cells in patients with comorbidities may be to boost nitric oxide signaling and/or reduce oxidative stress. Other intriguing perspectives include interventions that modify the interactions between red blood cells and platelets under pathophysiological conditions.

Metabolic diseases such as obesity, hyperlipidemia, diabetes mellitus (DM), non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) as well as hypertension are the most common comorbidities in patients with CVD. These comorbidities result in increased myocardial oxidative stress. Andreadou and coworkers [12] provide detailed insights in the ROS sources and adverse redox changes in these comorbidities. They also highlight how comorbidities contribute to the incidence and severity of MI and heart failure and thereby affect cardiovascular prognosis. Finally, they summarize and discuss the therapeutic interventions that may restore the redox imbalance in the diseased myocardium in the presence of these comorbidities.

Endothelium-dependent remote signaling largely influences cardiovascular risk by interfering with ischemia and reperfusion damage. Endothelial function plays a central role in cardioprotection by remote conditioning. Erkens et al. [13] highlight how endothelial function and remote signaling are affected by hyperglycemia, insulin resistance, hyperinsulinemia and DM and thereby influence cardiovascular risk. The authors provide a summary of how insulin signaling, the glycocalyx, endothelial progenitor cells and shear stress via alterations of protein kinase B (Akt) and calcium-

dependent pathways influence endothelial function, remote signals and thereby cardiovascular risk. Details are provided on the involved kinase signaling cascades, antioxidant stress response genes (e.g. nuclear factor-E2-related factor 2 (Nrf2)), apoptotic processes and mitochondrial dysfunction. Finally, therapeutic redox modulation of endothelial remote signals by different approaches (e.g. by ischemic conditioning) are discussed with regards to cardioprotection.

### *Therapeutic targets and strategies for redox modulation of metabolic and heart diseases*

There is no doubt that ROS formation and oxidative damage play a major role for I/R injury and onset of heart failure. However, yet now only few “real” redox therapies have been reported and almost no redox therapeutic approach for cardioprotection was advanced to the clinical stage. Daiber and colleagues [14] provide a detailed overview on adverse redox processes in heart diseases, namely MI and heart failure, and summarize the classical surgical interventions (e.g. percutaneous coronary interventions) and cardiovascular drugs (e.g. statins, angiotensin II converting enzyme inhibitors) that are established in the clinical routine. Besides these traditional therapies, they discuss in detail the rare examples of established redox drug therapy (e.g. activators of soluble guanylyl cyclase). In addition, experimental redox therapeutic approaches are presented and critically evaluated (e.g. ROS source inhibitors, hydrogen sulfide (H<sub>2</sub>S) donors).

Diabetic cardiomyopathy describes a ventricular dysfunction in diabetic patients in the absence of ischemic heart disease, hypertension, valvular heart disease, congenital heart disease, and other classical causes of cardiomyopathy. The disease is characterized by LV hypertrophy and impaired relaxation, reflecting a clinical phenotype of diastolic LV dysfunction, which precedes the development of LV systolic dysfunction thereby mimicking features of heart failure with preserved ejection fraction, a disease with poor prognosis and almost no therapeutic potential. In their review, Byrne and coworkers [15] present clear evidence supporting the role of oxidative stress for the development of diabetic cardiomyopathy. Defects in both ROS-producing and detoxification enzymes render the heart susceptible to oxidative damage leading to

cardiac dysfunction. Sources of increased ROS production include the electron transport chain, monoamine oxidases, calpains, NADPH oxidases, xanthine oxidase and uncoupled nitric oxide synthase. Interestingly, the authors point out that clinically used glucose-lowering drugs and renin-angiotensin-aldosterone system inhibitors may have antioxidant properties thereby improving LV function in diabetic patients. However, novel strategies for the treatment of diabetic cardiomyopathy are needed, but these strategies may include targeting redox stress.

Excessive mitochondrial ROS production plays a central role for the pathophysiology in the aging heart and other organs. Thereby, ROS have a major impact on several cardiac diseases that display a higher incidence in the elderly, such as MI and heart failure, the two worldwide leading causes of death and disability. Bou-Teen et al. [16] describe in detail how the aging process alters mitochondrial calcium cycling, ROS production and bioenergetics. They also highlight the acute damage caused by ROS formation during I/R in comparison with the adverse effects by chronic ROS formation during the aging process. An in-depth discussion of the pathophysiological consequences of these adverse redox modulations and oxidative stress for cardiac function is also provided. Finally, the opportunities to beneficially influence the aging-associated higher cardiovascular risk by established and emerging therapeutic approaches based on mitochondria-targeted antioxidants are summarized.

Cardiac hypertrophy is caused by an adaptation to increased workload the heart, which leads to structural remodeling and an increase in muscle mass in order to preserve normal function. Oxidative stress represents a critical inducer of both genetic and acquired forms of cardiac hypertrophy. Ramachandra and coworkers [17] discuss the opportunities by antioxidant therapies in patients with and preclinical models of cardiac hypertrophy. They provide a full picture of the pathophysiological processes that are involved in the onset and progression of cardiac hypertrophy. For each of these processes (e.g. hypertrophic stimuli, obesity, diabetes) the molecular targets for redox and antioxidant therapeutic approaches are identified (e.g. NOX-2/4, AMP-activated protein kinase (AMPK), mitochondrial superoxide dismutase (SOD2), forkhead box protein O3 (FOXO3a)) and potential drug-based therapies are suggested.

The broken heart (Takotsubo) syndrome is a special form of cardiomyopathy that develops after episodes of severe life stress (e.g. teariness) characterized by a

transient LV dysfunction recovering spontaneously within days or weeks. The exact pathophysiological mechanism is still elusive but the onset and contribution of severe oxidative stress is accepted. Münzel and colleagues [18] provide details on the ROS sources (NOX-2, NOX-4 and mitochondria) that contribute to the pathophysiology of Takotsubo syndrome and also highlight endothelial dysfunction as a clinical marker of this severe heart disease. The authors summarize data on oxidative stress markers from human and animal studies. They also discuss in detail the few examples of successful redox therapeutic approaches in the treatment of Takotsubo syndrome and present new concepts of nitro-oxidative and nitrosative stress.

Chemotherapeutic agents have resulted in huge improvements in overall survival and disease-free survival in patients with cancer. However, a substantial number of patients go onto to develop cardiac dysfunction due to the cardiotoxic effects of these anti-cancer agents. As such, new therapeutic targets and treatments are needed to prevent the development and progression of cardiotoxicity in this setting. In this regard, Attanasio et al. [19] review the dichotomous role that oxidative stress plays given that the production of ROS is a fundamental property underlying the beneficial effects of these anti-cancer therapies on the one hand, while the ROS are known to act as key mediators of cardiotoxicity induced by these anti-cancers agents on the other hand. The authors discuss potential therapeutic strategies for targeting oxidative stress to prevent cardiotoxicity induced by anti-cancer agents given these challenges.

A specific redox target for cardioprotection is the AMPK, which represents a central regulator of energy metabolism. Marino and colleagues [20] highlight the protective mechanisms of AMPK to prevent heart failure onset and progression by beneficial modulation of angiogenesis, ATP production, cardiac fibrosis, endothelial dysfunction and cardiac hypertrophy, all of which decreases the risk of MI. The authors discuss the molecular biological details of different AMPK isoforms, their expression and specific features. The therapeutic opportunities to activate AMPK are also summarized. Finally, the molecular protective pathways mediated by AMPK are discussed in full detail, including vascular endothelial growth factor (VEGF)/endothelial nitric oxide synthase (eNOS)/nitric oxide (NO) pathway, Akt and glycogen synthase kinase-3 (GSK-3 $\beta$ ) axis, mammalian target of rapamycin (mTOR) kinase signaling, mitochondrial permeability transition pore (mPTP), PTEN-induced kinase 1 (PINK-1)

and sirtuin signaling, regulation of down-stream antioxidant proteins, and the role of these processes in autophagy and apoptosis.

Barteková et al. [21] reviewed the therapeutic potential of widely used and studied natural antioxidants (for example resveratrol, quercetin, curcumin, vitamins A, C, and E, coenzyme Q10, etc.), synthetic antioxidants (including N-acetylcysteine, SOD mimetics, mitoTEMPO, SkQ1, etc.), and promoters of antioxidant enzymes in cardiometabolic diseases such as obesity, diabetes, atherosclerosis and rare genetic metabolic diseases. Since clinical trials brought showed controversial results on the cardioprotective potential of antioxidants in the treatment of cardiac dysfunction in cardiometabolic diseases, the authors discuss the significant translational gaps in the use of antioxidants and provide reasons and explanations for this failure.

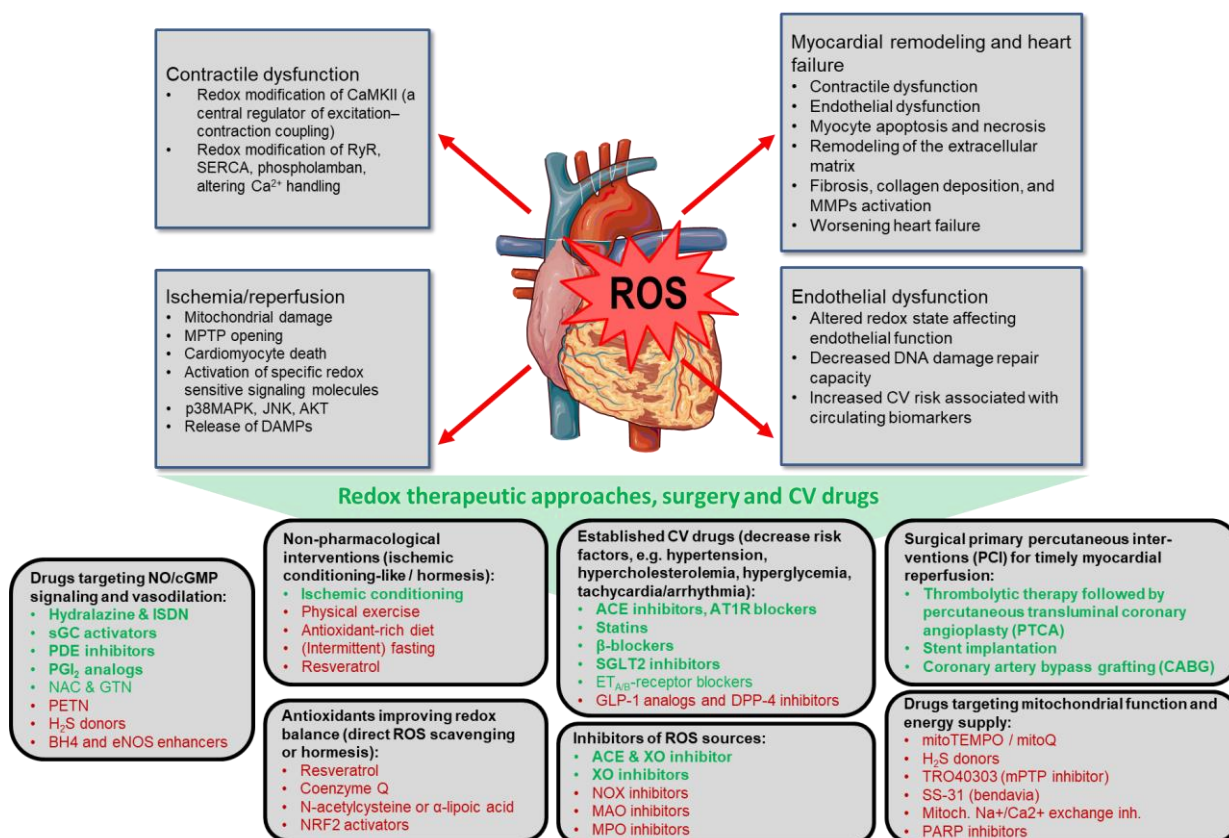
A specific example of a natural antioxidant is oleuropein, an olive oil constituent, which confers cardioprotective effects. Tsoumani and coworkers [22] report with their in vivo studies that oleuropein can additively increase the myocardial protection by postconditioning. In two animal species (rabbits and mice) with experimental MI, induced by defined I/R episodes in the heart, oleuropein in combination with postconditioning showed an additive decrease in infarct area. The protective effects of oleuropein were neither suppressed by inhibition of PI3K/Akt (wortmannin), eNOS (L-NAME) nor JAK2 (AG490), all well-known inhibitors of ischemic conditioning protective pathways. Oleuropein did also not affect mPTP activity or cyclic guanosine monophosphate (cGMP) generation and had no additional anti-inflammatory effects over postconditioning alone. Oleuropein seemed to mainly act via induction of antioxidant genes such as Nrf2, heme oxygenase-1 and SOD2 as well as suppression of NOX-2 expression.

### *Concluding note*

Despite timely treatment, mortality and morbidity following AMI remain high. Therefore, novel strategies are being introduced in patients or are currently tested in animal models comprising the limitation of infarct size and progression of heart failure by prevention of oxidative damage and adverse redox signalling during I/R episodes (summarized in **Figure 1**). As I/R damage or heart failure represent multi-factorial



cardiovascular disorders, a combination therapy comprising a fine-tuned mixture of the above mentioned treatments may be most promising. Any redox therapeutic approach should not interfere with the protective effects of ROS in processes such as eustress, hormesis and ischemic preconditioning as well as their involvement in essential redox signalling processes regulating cell differentiation, proliferation and migration.



**Figure 1. Upper part: Involvement of ROS in pathophysiological processes of myocardial infarction (MI) and heart failure and classical imaging techniques.** I/R induced ROS formation contributes to adverse processes such as contractile dysfunction, remodeling, mitochondrial damage and endothelial dysfunction. **Lower part: Summary of established and experimental therapies of I/R damage and heart failure including redox-based therapies.** Clinically established therapies (green bold letters) represent treatments that were applied to larger human cohorts and proved beneficial in either I/R damage or heart failure. Green standard letters indicate therapies that were tested in larger cohorts but do not represent the recommended standard therapy of I/R damage and heart failure, or were tested in related cardiovascular diseases. Experimental therapies (red letters) represent treatment that are still at the preclinical stage, were only tested in small cohort studies or showed no clear benefit in patients. Abbreviations: NO, nitric oxide; cGMP, cyclic guanosine monophosphate; ISDN, isosorbide dinitrate; sGC, soluble guanylyl cyclase; PDE, phosphodiesterase; PGI<sub>2</sub>, prostacyclin; NAC, N-acetylcysteine; GTN, nitroglycerin; PETN, pentaerythritol tetranitrate; H<sub>2</sub>S, hydrogen sulphide; BH4, tetrahydrobiopterin; eNOS, endothelial nitric oxide synthase; NRF2, nuclear factor-E2-related factor 2; CV, cardiovascular; ACE, angiotensin-converting enzyme; AT1R, angiotensin-receptor (type 1); SGLT2, sodium-glucose co-transporter 2; ET<sub>A/B</sub>, type A or B of endothelin receptor; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; mitoTEMPO, mitochondria-targeted 2,2,6,6-tetramethyl-1-piperidinyloxy; mitoQ, mitochondria-targeted coenzyme Q10; mPTP, mitochondrial permeability transition pore; PARP, poly(ADP-ribose) polymerase; XO, xanthine oxidase; NOX, NADPH oxidase; MAO, monoamine oxidase; MPO, myeloperoxidase. Heart cartoons taken from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported License. Scheme was summarized from [14] with permission.

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## **Conflict of interest**

None.

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