Heart, Lung and Circulation (2014) **23,** 897–904
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2014.05.022

REVIEW

The Mitochondrion as a Key Regulator of Ischaemic Tolerance and Injury

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Received 11 March 2014; accepted 16 May 2014; online published-ahead-of-print 24 June 2014

Vascular pathologies pose a significant health problem because of their wide prevalence and high impact on the rate of mortality. Blockade of blood flow in major blood vessels leads to ischaemia associated with oxidative stress, where mitochondria act as a major source of reactive oxygen species (ROS). While low levels of ROS perform a necessary function in normal cellular signalling and metabolism, elevated levels under pathological conditions are detrimental both at the cell and organ level. While cellular oxygenation is necessary to maintain tissue viability, a key pathological occurrence when restoring blood flow to ischaemic tissues is the subsequent burst of ROS generation following reoxygenation, resulting in a cascade of ROS-induced ROS release. This oxygen 'paradox' is a constraint in clinical practice, that is, the need for rapid and maximal restoration of blood flow while at the same time minimising the harmful impact of reperfusion injury on damaged tissues. Mitochondria play a central role in many signalling pathways, including cardioprotection against ischaemic injury and ROS signalling, thus the main target of any anti-ischaemic protective or post-injury therapeutic strategy should include mitochondria. At present, one of the most effective strategies that provide mitochondrial tolerance to ischaemia is ischaemic preconditioning. In addition, pharmacological preconditioning which mimics intrinsic natural protective mechanisms has proven effective at priming biological mechanisms to confront ischaemic damage. This review will discuss the role of mitochondria in contributing to acute ischaemia-reperfusion (IR) injury, and mechanisms of cardioprotection in respect to mitochondrial signalling pathways.

Keywords Reperfusion • Preconditioning • Antioxidants • Kidney • Brain • Heart

Introduction

Pathologies associated with acute circulatory disorders in organs and their consequent complications occupy a leading position as a cause of worldwide mortality. It is estimated more than 17 million people died worldwide from cardiovascular diseases (CVD) in 2008, with three million of these deaths occurring before the age of 60, many of which could have been prevented. The percentage of premature deaths from CVD ranges from 4% in high-income countries to 42% in low-income countries, leading to growing inequalities in the occurrence and outcome of CVD between countries

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and populations (Fig. 1) [1]. Among the causes of death, stroke takes second place after cardiovascular pathologies, with the consequences of stroke being the leading cause of primary disability. Population studies have shown that less than 15% of patients who have undergone stroke returned back to work or full implementation of their previous domestic responsibilities, with the remaining 85% requiring life-long medical and social support due to their disabilities [2]. In addition, 40-50% of survivors suffer permanent deterioration of cognitive functions such as loss of memory and attention span [3]. Other common pathologies associated with ischaemia are prerenal and renal aetiologies of kidney dysfunction. The mortality rate from acute kidney failure is currently around 22-25% [4]. Despite the development of treatment methods, the number of patients with ischaemic acute renal failure has not reduced [5].

Previous work on ischaemia-reperfusion injury mechanisms indicates that the main damaging effects involve the pathological consequences following restoration of blood flow to the tissue, rather than ischaemia itself. Reperfusion following cessation of blood flow leads to the development of oxidative stress, which is a profound and largely irreversible destructive process leading to the death of reoxygenated cells and may eventually lead to organ failure [6].

Under physiological conditions reactive oxygen species (ROS) formation may vary widely depending on the type of tissue, their functions and conditions (See [7],[8]). In actively proliferating cells and in those which are most often subjected to attacks by pathogens (for example, lung or blood cells) endogenous levels of ROS are high and very much determined by the metabolism and the degree of pathogenic burden, while in poorly metabolising cells with small proliferative potential these levels are much lower. Thus, in actively metabolising tissues such as the brain, heart and kidneys, the problem of homeostasis of ROS is of paramount importance. While ROS play an essential function as intracellular signalling elements, transition to pathological

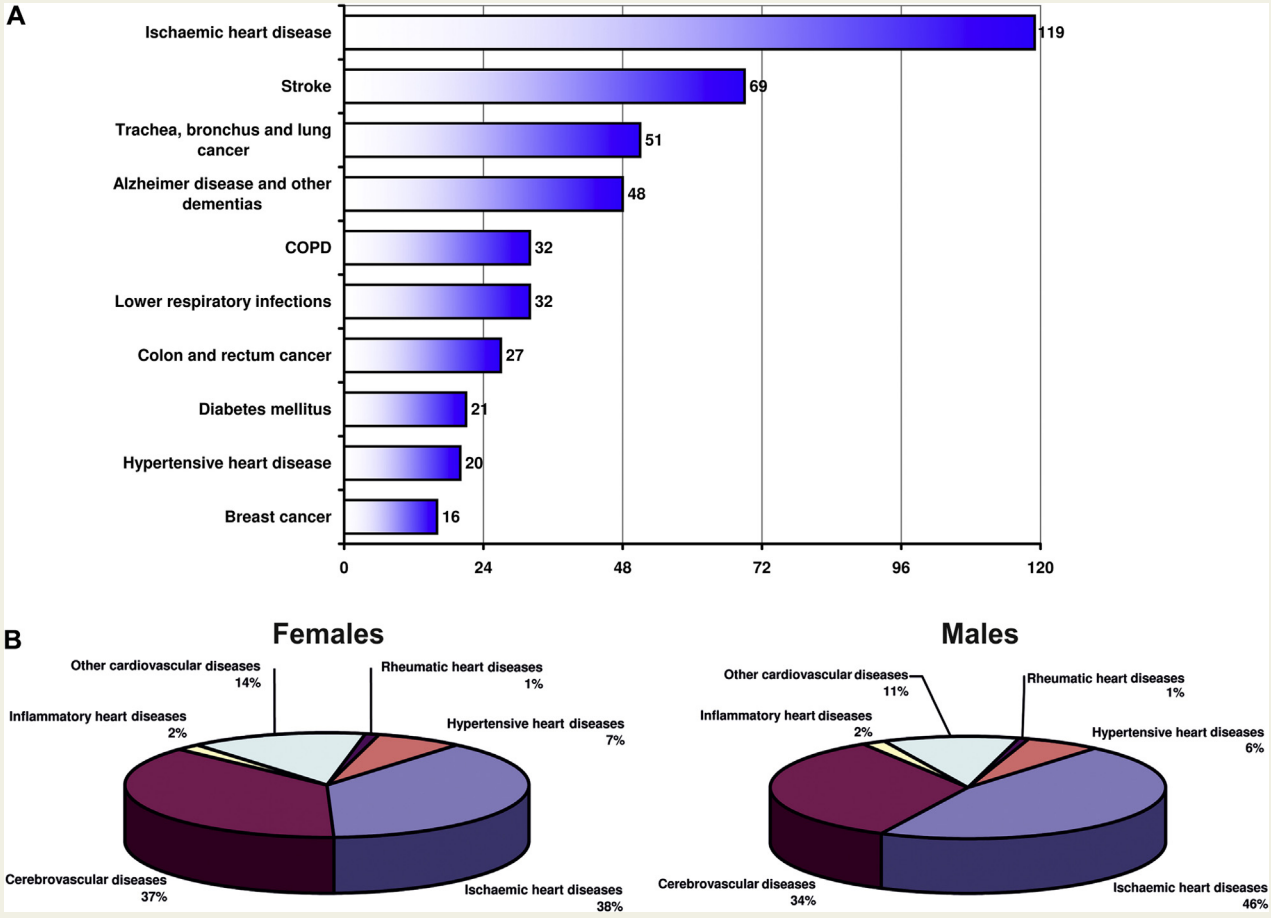

Figure 1 The epidemiology of cardiovascular diseases. (A) The 10 leading causes of death in high income countries (2011), adapted from the public domain article by the World Health Organization (http://www.who.int/mediacentre/factsheets/fs310/en/index1.html). (B) Distribution of deaths from cardiovascular diseases including heart attacks, strokes and other types of cardiovascular diseases. Reproduced with publisher's permission, from the World Health Report: Global Atlas On Cardiovascular Disease Prevention And Control. Geneva, World Health Organization, 2011. (http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf).