

Editorial

Exploring the Link between Metabolic Remodelling and Reactive Oxygen Species in the Aged and Diseased Heart

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The heart, one of the first functional organs to be formed in the embryo, begins developing at the start of the third week of gestation. By the end of the fourth week, it starts contracting to pump blood [1]. The metabolic energy required for the foetal heart to contract is primarily provided by anaerobic glycolysis and approximately 15% by β -oxidation of fatty acids due to the low availability of oxygen. In the immediate postnatal period, as oxygen and substrates essential for fatty acid oxidation (FAO) become readily available, the reliance on glucose and lactate as a source of energy is reduced, shifting predominantly to FAO. This metabolic substrate switch is essential to meet the increasing energy demands of cardiac cells, which are more efficiently supplied by β -oxidation of fatty acids [2]. Often referred to as ‘omnivores’, cardiac cells can utilise a variety of substrates such as fatty acids, glucose, lactate, ketones, and amino acids to produce adenosine triphosphate (ATP). In a healthy adult heart, FAO is the primary energy source during fasting. However, postprandial increases in glucose and insulin levels suppress FAO and favour using glucose as an energy substrate [3]. This metabolic flexibility is crucial for normal heart function. However, it is impaired in the ageing heart and under pathophysiological conditions such as myocardial ischemia and hypertrophy, which increases the risk of cardiovascular diseases (CVDs) [3]. This is likely due to the gradual impairment of several factors associated with the uptake and oxidation of substrates. This editorial will discuss the adverse effects of age-associated and pathophysiological changes mediated metabolic remodelling in the cardiovascular system.

1. Age- and Disease-Associated Metabolic Remodelling in Cardiomyocytes

Metabolic remodelling in the aged heart is a complex process and is impaired by several factors. One significant factor is the age-related reduction of carnitine palmitoyl-transferase I (CPT-1) in the heart [4]. CPT-1 is a key rate-limiting enzyme in FAO, which decreases the utilisation of free fatty acids (FFA) and increases reliance on glycolysis and glucose oxidation [4]. In contrast, phosphofructokinase (PFK), the rate-limiting enzyme of glycolysis, is not affected by age, thus maintaining a steady or compensatory

increase in glucose oxidation [5]. Additionally, increased lactate due to enhanced lactate dehydrogenase activity in the aged hearts competes with and inhibits FAO by suppressing FFA utilisation [5].

Pathophysiological conditions such as myocardial ischemia and hypertrophy can alter how cardiomyocytes utilise metabolic substrates. The risk and prevalence of these conditions are strongly correlated with age [5,6]. In the ischemic areas of the heart, the reduced oxygen supply essential for mitochondrial oxidative phosphorylation leads to cardiomyocytes relying on glycolysis for ATP production, creating an energy deficit. This process creates an excess of pyruvate, which is converted to lactic acid, lowering intercellular pH and impeding Ca^{2+} homeostasis, thus reducing contractile force [7]. In hypertrophied hearts, increased glycolysis coupled with unchanged or lower glucose oxidation indicates that glucose is converted to pyruvate but does not undergo oxidative phosphorylation. Instead, the pyruvate is converted to lactate by lactate dehydrogenase, which is also elevated in hypertrophied hearts, inhibiting FAO and providing an alternative energy source [8]. Downregulation of peroxisome proliferator-activated receptor alpha (*PPAR- α*) in the aged heart, reduces the expression of key enzymes of FAO, such as CPT-1 and medium chain acyl Co-A dehydrogenase and increases the expression of the lipid transporter CD36. This leads to accumulation of FFA in the myocardium, causing cardiac lipotoxicity, which increases the risk of cardiac fibrosis, cardiomyocyte apoptosis, and subsequent heart failure [9]. While most studies indicate metabolic remodelling in the diseased heart has a detrimental effect, some studies suggest it is beneficial. For instance, transgenic mice with cardiac-specific overexpression of Glucose transporter 1 (GLUT1) were more resistant to heart failure progression compared to wild-type mice. In another study, elderly patients with ischemic cardiomyopathy who were administered trimetazidine (a FAO inhibitor) showed improved left ventricular function. Thus, more studies are warranted to better understand the effects of metabolic remodelling in the diseased heart [8].

One of the most concerning adverse effects of impaired FAO is an increase in the production of reactive oxygen species (ROS), a by-product of oxidative phosphoryla-



tion. As discussed next, this increase plays a crucial role in the metabolic remodelling of the aged and diseased heart.

2. ROS Production Increases in the Aged and Diseased Heart

The process of FAO begins in the cytoplasm and concludes in the mitochondrial matrix, where nicotinamide adenine nucleotide (NAD) and flavin adenine nucleotide (FAD) are reduced to NADH and FADH₂, respectively. These molecules are oxidised by the electron transport chain (ETC) to produce ATP [10]. This oxidative phosphorylation, occurring in the mitochondrial matrix, is a significant source of ROS such as superoxide (O₂^{•−}), hydrogen peroxide (H₂O₂), and hydroxyl radical (•OH). ROS are a double-edged sword that is beneficial as signalling molecules and pathogen defenders at low to moderate levels, but at higher than normal levels, they can damage DNA and proteins, induce cell apoptosis, and contribute to CVDs and cancer [10]. Under normal physiological conditions, antioxidant mechanisms protect the cells against ROS, but under excessive stress, the production of ROS exceeds the endogenous antioxidant capacity to maintain redox balance. The production of ROS increases in the aged and diseased hearts due to several factors, such as lower activity of mitochondrial respiratory chain complexes, increased mitophagy, leakage of electrons due to reduced fluidity of mitochondrial membrane, and mitochondrial DNA mutations. In addition, metabolic remodelling in the aged heart triggers increased ROS production, which along with other factors, leads to cellular and organ dysfunction. This dysfunction results in cardiomyocyte hypertrophy, apoptosis, contractile dysfunction, and vascular remodelling [11].

For instance, H₂O₂-induced apoptosis is caused by activating pro-apoptotic kinases such as c-Jun N-terminal kinase (JNK), p38 kinase, and Akt [11]. Activator protein-1 (AP-1) regulates several pathways that cause cardiac remodelling and hypertrophic response, which are characterised as activated by hydroxyl radical and superoxide ions. ROS is also implicated in the hypertrophic response induced by angiotensin II, endothelin-I, and tumour necrosis factor- α (TNF- α) [11]. At high concentrations, superoxide and hydroxyl ions inhibit sarcoplasmic reticulum Ca²⁺-ATPase (SERCA), alter the opening of ryanodine receptors and decrease L-type calcium channel current, all of which eventually cause contractile dysfunction [11]. While the pathways mentioned represent only a fraction of pathways affected by ROS, it is evident that an increase in ROS due to ageing or other factors is a significant contributor to CVDs.

3. Conclusion

In conclusion, the heart's metabolic flexibility is crucial to meeting its high energy requirements. Age- and disease-associated metabolic remodelling and impairment

in ROS production can be a contributing factor in age-associated CVDs. More research is required to determine a link between metabolic remodelling and ROS production.

Author Contributions

LNV conceived and conceptualized the idea, wrote the first draft of the manuscript. RK, conceived and conceptualized the idea, made critical revision to the manuscript. Both the authors agreed with the final version of the manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

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