Energy metabolism in the aging heart

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Abstract

Aging is a well-recognized risk factor in the development of cardiovascular disease, which is the primary cause of death and disability in the aging population. Although the mechanisms responsible for age-related cardiovascular disorders are likely multifactorial, derangements in myocardial energy substrate metabolism may play an important role in the progressive decline of cardiac function commonly observed with advancing age. Indeed, a decrease in the overall capacity for mitochondrial oxidative metabolism with reductions in both fatty acid and glucose oxidation in the aged heart has been associated with impaired cardiac performance. However, the mechanisms by which these pathophysiological changes occur have not been completely described nor is it known if changes in cardiac energy metabolism are sufficient on their own to impair cardiac performance in the aged heart. Therefore, a better understanding of the metabolic changes that occur in the heart during the normal process of aging could shed light on the pathogenesis of age-related cardiomyopathy and may ultimately lead to improved therapeutic strategies for the treatment of contractile dysfunction in the elderly.

Keywords: aging; myocardial metabolism; contractile dysfunction; mitochondria

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Basic Article

Introduction

Age is a significant risk factor for the development of a number of cardiovascular diseases (CVDs), such as ischemic heart disease and heart failure [1, 2]. The prevalence of CVD increases dramatically with advanced age [3], and given the rapidly growing size of the aging population, this will undoubtedly increase the burden of age-related diseases on the healthcare system. Progressive alterations in cardiovascular structure and deterioration of cardiac function may be intrinsically associated with the normal process of aging even in the absence of atherosclerosis and hypertension [2, 4], which are major contributing factors to aging-related cardiac dysfunction [5, 6]. As such, these specific age-related changes in the heart may then predispose the elderly to developing age-mediated cardiomyopathy or negatively impact cardiac disease outcomes. Indeed, advanced age is associated with several cardiovascular abnormalities, including endothelial dysfunction, arterial stiffening, cardiac interstitial fibrosis, blunted β-adrenergic response and cardiomyocyte apoptosis [1, 7, 8]. These cardiac changes are considered part of the normal aging process that is then influenced by environmental factors such as diet and physical activity. Although the mechanisms responsible for age-related cardiac dysfunction are likely multifactorial, derangements in the pattern of myocardial energy metabolism is thought to play an important role in the progressive decline of cardiac function with age [9–11].

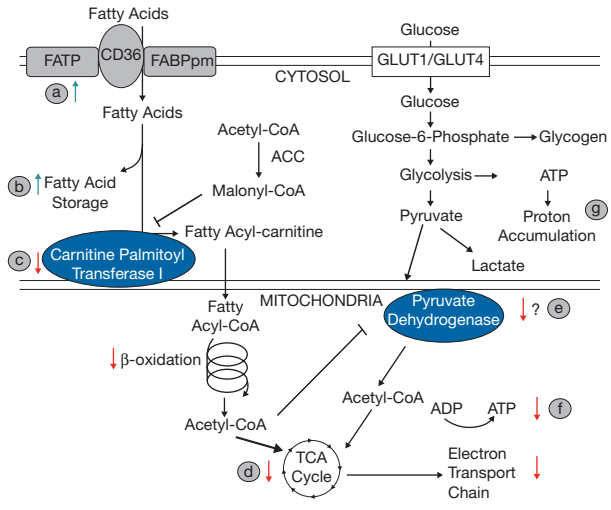

Fig. 1 *Energy metabolism in the aging heart. Increased levels of cluster of differentiation 36 (CD36) in the aged heart promotes the uptake of fatty acids across the plasma membrane (**a**) and together with reduced fatty acid oxidation rates may result in excessive accumulation of potentially toxic lipid intermediates (e.g. ceramides, diacylglycerol) and cardiac contractile dysfunction (**b**), in a phenomenon commonly known as "lipotoxic cardiomyopathy." The age-related decline in cardiac fatty acid oxidation may be the result of reduced activity of carnitine palmitoyl transferase-1 resulting in reduced uptake of fatty acids into the mitochondria for subsequent oxidation (**c**). Mitochondrial oxidative capacity has also been shown to decline in the aged heart due to decreased activity of several tricarboxylic acid (TCA) cycle enzymes and complexes of the electron transport chain (**d**). Although the alterations in glucose metabolism that occur in the aged heart have not been clearly defined, decreased levels of glucose handling proteins (e.g., glucose transporter type 4 [GLUT4], pyruvate dehydrogenase), as well as rates of glucose oxidation (**e**) may contribute to an overall deficit in adenosine-5'-triphosphate (ATP) production and produce an energetically compromised heart (**f**). Under ischemic conditions, the heart relies more heavily upon glycolysis for ATP production, however, the hydrolysis of glycolytically-derived ATP in the presence of diminished glucose oxidation results in proton and lactate accumulation that may impair cardiac function during reperfusion following ischemia (**g**). Due to potential alterations in glucose metabolism that occur in the aged heart, the degree of ischemia-reperfusion injury may be worsened in the elderly.* FATP *fatty acid transport protein,* FABPpm *plasma membrane isoform of fatty acid binding protein,* CoA *coenzyme A,* ADP *adenosine diphosphate,* ACC *acetyl CoA carboxylase*

Cardiac energy substrate metabolism

The heart possesses a high energy demand and must produce considerable amounts of adenosine-5'-triphosphate (ATP) in order to support proper contractile function and ionic homeostasis [12]. Normally, the heart displays a high degree of metabolic flexibility and can utilize multiple substrates to generate ATP including fatty acids, glucose, lactate, and ketone bodies [11, 13]. Under normal physiological conditions, >95 % of total ATP is derived from mitochondrial oxidative phosphorylation, with the remainder coming from glycolysis [12]. The healthy adult heart has a preference for fatty acids as a fuel substrate and obtains 50–70% of its ATP from the oxidation of fatty acids, with the remainder largely accounted for by carbohydrate (glucose and lactate) oxidation [14, 15].

Glucose utilization

Glucose is taken up from the circulation by facilitative glucose transporters and can be stored in the form of glycogen or undergo glycolysis [15, 16]. Under aerobic conditions, the process of glycolysis converts glucose into pyruvate where the majority of pyruvate enters the mitochondria, is converted to acetyl coenzyme A (CoA) by pyruvate dehydrogenase (PDH) and then enters the tricarboxylic acid (TCA) cycle to eventually produce significant amounts of ATP [15]. During anaerobic conditions, mitochondrial oxidative metabolism is inhibited, and glycolysis becomes the major source of ATP [12]. How glucose utilization is altered in the aged heart and the relation that this has to age-mediated cardiac dysfunction has yet to be fully explained.

Fatty acid utilization

Long-chain fatty acids can enter the cardiac myocyte either by passive diffusion via a flip-flop mechanism of fatty acids across the lipid bilayer or by protein facilitated transport [17]. The three major fatty acid transport proteins identified to date, include fatty acid translocase (FAT)/cluster of differentiation 36 (CD36), the plasma membrane isoform of fatty acid binding protein (FABPpm), and fatty acid transport protein (FATP) 1–6 [17]. Of these, CD36 has been shown to mediate >50% of myocardial fatty acid uptake [18] and significantly impacts subsequent fatty acid oxidation in the mitochondria [19]. Another major site of regulation of fatty acid oxidation is the import of the intracellular fatty acids into the mitochondria [14]. The rate-limiting enzyme involved in this process is carnitine palmitoyl transferase (CPT)-1, and alterations in the activity of this enzyme indirectly governs mitochondrial β-oxidation and subsequent ATP production [12]. Importantly, many of these pathways involved in regulating myocardial fatty acid utilization have been shown

to be altered in the aged heart and have been suggested to contribute to cardiac dysfunction in the elderly [20, 21].

Energy metabolism in the aging heart

Alterations in cardiac energy substrate metabolism occur in several cardiac pathologies, such as myocardial ischemia, ventricular hypertrophy, and heart failure [12]. Interestingly, only a few studies have investigated the effect of advanced age on myocardial energy metabolism. Although earlier studies have reported that fatty acid oxidation is reduced in hearts from both aged rodents [22] and humans [20], detailed examination of these studies reveal that overall oxidative metabolism may be depressed as opposed to just fatty acid oxidation. Given the close relationship between metabolism and cardiac contractile function, impaired oxidative metabolism may contribute to the age-related decline in mechanical function and increases in CVD commonly observed in older patients [8, 23]. Consistent with this, we have shown using the *ex vivo* isolated working mouse heart model that both glucose and fatty acid oxidation are reduced by 2.5- and 4-fold, respectively, in hearts from aged mice as compared to young mice under both normal and high workloads [21]. This reduction in glucose and fatty acid oxidation rates translated into a 60% decrease in total acetyl CoA-derived ATP production in the aged heart [21] (Fig. 1f). However, whether this is due to a specific decrease in fatty acid oxidation or to an overall reduction in oxidative metabolism has not been fully explored. Consistent with the latter concept, Hyyti et al. [24] have recently shown that fatty acid and ketone oxidation is impaired in the aged murine heart, supporting that overall oxidative metabolism may be reduced.

In addition to reduced oxidative metabolism observed in the aged heart, accumulation of lipids within the cardiac myocyte has also been observed [21, 25]. This is relevant since increased lipid accumulation in the heart has been strongly implicated in lipotoxicity and cardiac dysfunction in the setting of obesity and diabetes [26]. As such, myocardial lipid accumulation observed in the aged heart may be deleterious to cardiac function and may result from not only reduced fatty acid oxidation but also from excessive fatty acid uptake into the heart. Indeed, upregulation of myocardial CD36 expression has been shown to occur in the aged heart [21] (Fig. 1a), thus rendering the aged heart more susceptible to lipid accumulation during increased dietary fat intake [27] (Fig. 1b). Thus, it is possible that excessive myocardial lipid accumulation in the aged heart contributes to the impairment in contractile function that is often observed in the elderly.

Although the mechanisms responsible for the potential age-related decline in fatty acid oxidation is not fully understood, reductions in activity of CPT-1 and carnitine-acylcarnitine translocase have been observed in the aged heart [22, 28, 29], which suggests impaired fatty acid entry into the mitochondria for subsequent ATP production (Fig. 1c). Consistent with this, peroxisome proliferator-activated receptor (PPAR)-α, a key transcriptional regulator of target genes controlling lipid metabolism, is markedly reduced in the aged murine myocardium [24, 30], which may also decrease fatty acid utilization.

Mitochondrial function has also been shown to decline with age [31, 32] and may be a key contributor to impaired fatty acid and glucose oxidation. Several studies have demonstrated an age-dependent reduction in mitochondrial oxidative capacity in the heart due primarily to decreased activity of complexes I, III and IV of the electron transport chain, [32–39] as well as decreased activities of TCA cycle enzymes [33] (Fig. 1d). While the exact cause of this mitochondrial dysfunction is not clear, a popular theory proposes that enhanced mitochondrial reactive oxygen species (ROS) production can lead to mitochondrial DNA damage, lipid peroxidation, and mitochondrial dysfunction, creating a vicious cycle of oxidative damage and reduced mitochondrial function [40] that may occur during aging.

Similar to fatty acid oxidation the effect of age on myocardial glucose utilization is also poorly defined, and there is a notable paucity of studies that examine glucose uptake, glycolysis, and glucose oxidation rates together in the aged heart. As mentioned above, data from our lab show that absolute glucose oxidation rates are markedly diminished in the aged heart [21] (Fig. 1e). The limited number of reports to date, suggest that myocardial glucose uptake and glycolysis are increased in the aged heart [20, 41], therefore, recapitulating the shift towards a more fetal metabolic phenotype that is commonly observed in the hypertrophied heart [9]. Indeed, a switch to increased

glucose utilization as characterized by accelerated glycolysis in the absence of a coordinated increase in glucose oxidation may contribute to the high prevalence of left ventricular hypertrophy in the aging population [2]. However, studies examining expression of glucose-handling proteins have yielded conflicting results with some reports showing increases in glucose transporter type (GLUT)-4, phosphofructokinase-1, and PDH [42, 43], while others have found age-associated declines in these enzymes and myocardial insulin resistance [44, 45]. Therefore, further study is needed to clearly elucidate the age-related alterations in myocardial glucose metabolism and their clinical implications. In particular, an acceleration of glycolysis and decrease in glucose oxidation in the aged heart may have the potential to result in uncoupling between glycolysis and glucose oxidation leading to acidosis and reduced cardiac efficiency (Fig. 1g). Of potential clinical significance, such metabolic alterations may exacerbate myocardial injury during ischemia/reperfusion [12]. Interestingly, hearts from mice with a cardiac-specific over expression of GLUT-1 are protected from age-related diastolic dysfunction and have improved recovery from ischemia/reperfusion injury [46]. Hearts from these mice have reduced fatty acid oxidation and importantly elevated glucose oxidation rates, suggesting that therapies promoting glucose oxidation, potentially by inhibiting fatty acid oxidation, may be of significant benefit to prevent ischemia/reperfusion injury in the aging population.

Conclusion

A growing body of evidence suggests that alterations in myocardial energy substrate metabolism occur with advancing age. A decline in overall mitochondrial oxidation may potentially contribute to impaired cardiac mechanical function, as well as predispose the aged heart to the development of cardiac dysfunction and susceptibility to ischemic injury. Indeed, it is clear that further studies are necessary to delineate the precise metabolic changes that occur and molecular mechanisms responsible for and, more importantly, the clinical implications of these changes. Together, this may lead to more targeted metabolic therapies for the treatment and/or prevention of the progressive decline in cardiac function that can occur with age. •

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