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Research Article

Post-Myocardial Infarction and Exercise Training on Myosin Heavy Chain and Cardiac Function

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ABSTRACT

Myosin heavy chain (MyHC) acts as the chemical-mechanical transducer of motion in muscle fibers by converting energy from ATP into the sliding myofilaments. The isoform α-MyHC has about three-fold higher ATPase activity than the isoform β-MyHC. In the failing heart, however, α-MyHC expression is profoundly downregulated and β-MyHC is reciprocally upregulated. The shift of MyHC isoforms contributes to the development of myocardial systolic dysfunction and cardiomyopathy. Although this can be attributed to a multitude of factors, well-documented findings illustrate the shift as an adaptive response to chronic overload conditions resulting from the MI itself. Endurance training has been well documented as a leading technique to attenuate unfavorable post-MI cardiac dysfunction. Endurance training studies consisting of aerobic-style exercises prompts beneficial effects on cardiac function by attenuating myocardial MyHC remodeling following MI and congestive heart failure. However, endurance training promotes eccentric cardiac hypertrophy characterized by the addition of sarcomeres in series, elongation of the myocyte cell, and a consequential increase in cell size and chamber diameter, which may worsen the MI-induced cardiac dilation. In contrast, resistance training stimulates pressure-overload hemodynamic characteristics. Concentric cardiac hypertrophy is a unique resistance training adaptation characterized by cardiac wall thickening without cardiac chamber expansion. Whether resistance training also beneficially reverses MI-induced detrimental α- to β-MyHC shift and improves post-MI systolic function remains to be elucidated.

Introduction

Located within the A-band of the sarcomere, myosin heavy chain (MyHC) proteins comprise much of the thick filament in striated muscle fibers in addition to other regulatory proteins like myosin-binding protein C (MyBP-C) and myosin regulatory light chain (MRLC) [1, 2]. MyHC serves as the key chemical-mechanical transducer of energy into motion within each myocyte and is the principal protein responsible for force generation during muscular contraction [3]. The globular head of each MyHC protein is the primary location of myosin-actin cross-bridge cycling and the binding site for adenosine triphosphate (ATP) in cardiac and skeletal muscle [4]. Myosin adenosine triphosphatase (ATPase) catalytic reactions occur near each globular myosin head, providing energy for actomyosin contraction [5]. Differentiations in these ATPase reactions are often used to distinguish gene-coded MyHC variants [6]. Multiple MyHC gene specific isoforms have been identified and characterized, yet two specific heterologous phenotypes are expressed within the human myocardium: α-MyHC [coding primarily for V1 isoform] and β-MyHC (coding primarily for V3 isoform) [3, 7, 8]. Representations of α- and β-MyHC isoforms are regulated developmentally and governed through various types of pathologic and physiologic stimuli, giving rise to similar proteins with different hydrolytic and mechanical characteristics.

Both α- and β-MyHC exhibit 93% similar amino acid profiles, however each isoform has been shown highly correlated with differing mechanical properties of the heart [8, 9]. The capacity of each isoform to hydrolyze ATP at different rates is believed to determine independent

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shortening velocities associated with each MyHC isoform [10, 11]. Stark differences in isoform performance characteristics exist; for example, α-MyHC has been shown to produce two to three times higher shortening velocities than β-MyHC [11-15]. Furthermore, a study published by Locher et al. (2009) using rat skinned trabeculae expressing either 100% α- or 100% β-MyHC showed a 2-fold higher ATP utilization and force production in α-MyHC compared to β-MyHC, further confirming this comparison [16].

Post-Myocardial Infarction (MI) MyHC Isoform Shift

The expression of MyHC isoform phenotypes vary developmentally and pathophysiologically. For example, in the healthy human heart α-MyHC accounts for approximately 7% (±3%) of the thick filament myosin distribution within a predominantly slow-oxidative β-MyHC background array [17]. This ratio shifts significantly toward β-MyHC in models of diabetes and hypertension and has been reported similarly with age [18-20]. Of further similarity, models of human heart failure have indicated a significant loss in α-MyHC expression (to nearly undetectable) from pathologic conditions associated with chronic heart failure [16, 17]. Although a relatively small percentage of expressed α-MyHC protein may not appear significant, even small amounts of α-MyHC expression are shown to increase power output of cardiac myocytes in rats [21]. Because α-MyHC proteins provide most of the high velocity contractile forces in the heart, the decrease or absence of such could prove detrimental to ejection fraction and hemodynamic output, specifically following any increases in systemic circulation (i.e. oxygen consumption; VO_2). In fact, the shift from α- to β-MyHC reported after MI has been correlated with LV dysfunction and consequentially poor clinical prognoses [22-24]. Although this can be attributed to a multitude of factors, well-documented findings illustrate the shift as an adaptive response to chronic overload conditions resulting from the MI itself [25-27].

LV remodeling following MI originates as an adaptive response to pathologic signaling from decreased cardiac function and increased myocardial stress [28-30]. Although initial survival responses of the sympathoneural (SNS) and renin-angiotensin-aldosterone-systems (RAAS) are necessary to regain adequate plasma volume and blood pressure following MI, overtime this SNS/RAAS activation causes a sodium-induced plasma volume expansion and fluid retention [31-34]. Eventually, chronic volume-overload conditions give rise to a host of pathologic maladies such as eccentric LV dilation, infarct expansion, cardiac wall thinning, pathologic cardiac hypertrophy, and myocardial fibrosis [35-37]. Furthermore, the MyHC isoform shift corresponds with deleterious post-MI hormonal activation [38, 39]. Angiotensin II (AngII), the primary mediator of RAAS, has been suggested as a critical component for activation of the β-MyHC gene in a rodent model of pathologic hypertrophy and cultured myocardial cells [40, 41]. This relationship may cause increasing pathologic stimulus and further elevation of β-MyHC, but importantly, the influence is overridden by thyroid hormone (TH) [41]. TH is well-known to have a profound effect on MyHC isoform regulation in the myocardium, beneficially stimulating expression of α-MyHC, with the ability to alter MyHC ratios in a reversible manner in healthy adult hearts [42-44]. Hormonal manipulation may very well be a predominant mechanism of the post-MI MyHC shift, however, conclusive evidence for direct relationships remains unclear.

Timing of the shift has also become an important topic to consider. Hypertrophic models of heart failure have indicated an extremely rapid response of myosin isoforms to changing pathologic conditions (e.g. β-MyHC increased from 5% to 31% after 7 days of aortic constriction) as well as in post-MI models (e.g. remodeling began 1 week following left coronary artery ligation) [45-46]. If attenuated effects are to be attempted on pathologic myosin redistribution, exercise interventions should be implemented no later than 1-week post-MI.

Post-MI Endurance Exercise Training

Endurance training has been well documented as a leading technique to attenuate unfavorable post-MI cardiac dysfunction [37, 47-50]. Cardiac rehabilitation consisting of exercise-based therapies has become an effective complementary intervention when treating heart failure, shown to lower the risk of mortality and reinfarction in cardiac patients [51, 52]. Endurance training studies consisting of aerobic-style exercises (i.e., treadmill running, bicycling, swimming, etc.) have been widely published for decades, prompting beneficial effects on cardiac function by attenuating myocardial MyHC remodeling following MI and congestive heart failure [34, 53-58]. Currently, endurance training comprises the standard for exercise-based therapy to prevent MyHC shifting in cardiac patients, however, the effects of post-MI resistant exercise on MyHC remain to be expounded [59]. Although success is found with endurance training in a post-infarct environment, mechanisms and physiologic determinants that initiate beneficial adaptations remain to be completely elucidated. Of what is currently published, correlations to cardiac contractility exist: (1) α-MyHC has been associated with increased levels of myosin ATPase activation and enhanced LV contractility as a result of endurance training; (2) endurance training induces resting bradycardia by way of increased vagal effects, decreased sympathetic cardiac activation, a reduction in intrinsic heart rate, and a longer atrioventricular conduction time; and (3) endurance training promotes eccentric cardiac hypertrophy characterized by the addition of sarcomeres in series, elongation of the myocyte cell, and a consequential increase in cell size and chamber diameter [24, 60-64].

Although beneficial in athletes and healthy subjects, endurance training may present possible contraindications in post-MI cardiac patients. The endurance training-induced modifications to cardiomyocytes and increased LV chamber diameter resulting from eccentric cardiac hypertrophy may further contribute to LV remodeling caused by MI. Furthermore, endurance training elicits similar pathologic mechanisms to LV geometry as chronic post-MI RAAS-induced plasma volume expansion. Endurance training has been shown to elevate plasma albumin levels in healthy individuals to support elevated free fatty acid transportation into working skeletal muscles for aerobic respiration [65, 66]. Indeed, endurance training-mediated improvements in peak oxygen uptake is a well-known beneficial adaptation to aerobic-style exercise; however, the associated albumin uptick increases cellular water binding capacity, promoting water retention [64, 67, 68]. Elevated plasma-albumin concentrations in cardiac patients may lead to even greater intravascular volume than MI alone. This albumin-induced plasma volume expansion could increase volumetric load to an already compromised myocardium, further contributing to overload related conditions such as LV dilation [69].

The Effect of Resistance Training on Cardiac Geometry and Function

In comparison, both the mechanical and physiologic response of the myocardium during resistant training initiates a compensational LV morphology similar to that of exercise training, yet without affect to albumin-induced chamber dilation. Resistance training stimulates pressure-overload hemodynamic characteristics and recruits glucose transport mechanisms in place of free fatty acid carriers, negating the need for plasma-albumin expansion [70]. Concentric cardiac hypertrophy is a unique resistance training adaptation characterized by LV wall thickening without cardiac chamber expansion. Concentric hypertrophy elicits adaptive responses such as lateral cardiac myocyte expansion and parallel addition of sarcomeres in effort to offset large intravascular pressure increases during resistance training [71-73]. It is well known that myocardial contractility is positively correlated to the expression of α- and β-MyHC in the heart, however the MyHC response to resistance training may differ from that of endurance training [11, 13-15]. For example, Barauna *et al*. (2008) found no changes in pathologic cardiac hypertrophy molecular markers or the α- to β-MyHC-ratio with resistance training in healthy male Wistar rats [74]. Still, resistance training induces concentric cardiac hypertrophy, which significantly increases contraction force [61, 75, 76].

In response to increased pressure overloads, the myocardium adapts by adding new sarcomeres in parallel to existing sarcomeres, also known as concentric remodeling; this response results in: a) greater contractile force, b) thickening of the LV wall, c) no change with respect to LV dimension or blood volume [61, 77, 78]. Surely, these adaptations would be favorable to the failing infarcted heart, as increases in contractile force and concentric LV wall thickening could theoretically result in restored systolic function. The increased pressure load may promote the favorable transformation of β-MyHC to α-MyHC. Thus, resistance training could eventually prove as a viable treatment option for cardiac patients with already compromised myocardia and weakening cardiac output.

Summary

Currently, Post-MI endurance exercise is the main stream exercise mode in cardiac rehabilitation. Studies have shown that such endurance exercise training reversed MI-induced MyHC isoform switch and improved cardiac function. The influence of various forms of exercise (endurance vs. resistance training) on post-MI MyHC isoform distribution may provide future direction for research. The endurance-trained heart undergoes eccentric hypertrophy when cardiac sarcomeres (contractile units in myocardium) are added in-series to existing sarcomeres (muscle fiber elongation), due to albumin-induced blood volume expansion [61, 77]. Eccentric hypertrophy results in enlargement of the interior dimension of LV. The enlargement of LV is necessary for the heart to accommodate and pump out more blood to meet the demand of aerobic metabolism during exercise. In contrast, in resistance-trained hearts, the myocardium adapts by adding new sarcomeres in parallel to existing sarcomeres, known as concentric hypertrophy. These result in increase of LV wall thickness and contractile force, but not changing the interior dimension of the heart [61, 77, 78]. Whether resistance training exercise also beneficially attenuate the detrimental α- to β-MyHC shift and preserve post-MI systolic function remains to be elucidated.

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