OPEN ACCESS
Global Journal of Research in Medical Sciences
ISSN: 2583-3960 (Online)
Volume 05 | Issue 06 | Nov.-Dec. | 2025
Journal homepage: https://gjrpublication.com/gjrms/
Research Article

Transformation of Cardiac Muscle Isoforms

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DOI: 10.5281/zenodo.17602553 **Submission Date:** 28 Sept. 2025 | **Published Date:** 13 Nov. 2025

Abstract

There are two types of cardiac muscle fiber isoforms, β-MHC (myosin heavy chain), also known as Type 1, and α-MHC, also known as Type 2. Although 91% identical in motor domain sequence, these two myosin isoforms have distinct mechanical and biochemical properties. With normal aging, and in certain cardiac pathologic conditions, much of the α-MHC is replaced by β-MHC. This review examines their transformation, and its effects on cardiac structure and function.

Keywords: *Transformation, cardiac, isoforms.*

Introduction:

Cardiac and skeletal muscles have similarities, but there are important differences. Cardiac fibers are shorter, branch, and are connected in a tight series. Skeletal fibers are longer, and do not branch. Heart muscle fibers are all interconnected via intercalated discs, and they contract as a unit (functional syncytium). Cardiac contraction is involuntary, while skeletal contraction is voluntary [1].

However, Type 1 slow twitch skeletal fibers share some similar properties with β-MHC cardiac fiber slow isoforms. Both have slower contraction velocities (lower Vmax) than Type 2. Both are more energy efficient, requiring less ATP per unit of work performed despite a lower ATPase activity, than Type 2. They have a larger capacity for aerobic metabolism, and a higher resistance to fatigue than Type 2 and α-MHC. They have a high mitochondrial volume and a higher concentration of myoglobin with more capillary density than Type 2 and α-MHC (fast isoform) [2].

In contrast, Type 2 skeletal, and cardiac α-MHC (fast isoform), are fast twitch fibers with a high ATPase activity (3-4 times that of β-MHC), a high Vmax (speed of shortening), a large anaerobic but limited aerobic metabolism, and are less resistant to fatigue. The rapid strong contractions of α-MHC are useful during atrial systole: this may partly explain why atria contract and relax faster than the ventricles. A subtype of skeletal fibers called Type 2x has the highest ATPase activity, and the highest Vmax, as well as high glycolytic metabolism.

Interestingly, skeletal muscle is a highly plastic tissue, and fiber contribution can be modified by factors such as exercise. Endurance exercise (distance running) is associated with a greater percentage of slow Type 1 fibers, in contrast to power athletes (sprinters, weight lifters), which is associated with a greater percentage shift to Type 2 (including Type 2x) fibers, compared to sedentary individuals. Cardiac muscle is far less plastic. However, fast twitch α-MHC fibers can be transformed to slow twitch β-MHC fibers due to a variety of conditions discussed in the next section [3].

Methods and Results:

A literature search was conducted. The normal fetal heart contains mostly β-MHC. In the atria, the α-MHC is predominant in youth. In middle age, there are approximately equal proportions of α-MHC and β-MHC. In old age, β-MHC predominates. In the ventricles, the β-MHC is very dominant in youth, and becomes even more so with aging. After age 75, the α-MHC is nearly undetectable in the ventricles [4].

In atrial fibrillation (AFib), the atria lose coordinated contraction and undergo chaotic, high- frequency electrical activity. The α-MHC fibers no longer engage in organized periodic contraction. This functional disuse promotes atrophy and phenotypic change toward the slower fiber Type 1 β-MHC. The high firing rate causes intracellular calcium overload

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which is especially harmful to the α-MHC fibers. Mitochondrial dysfunction, oxidative stress, and myofibrillar degeneration lead to myocyte structural damage. Expression of slow β-MHC increases while fast α-MHC decreases. The damaged α-MHC fibers undergo apoptosis or necrosis, and are replaced by interstitial fibrosis. This disrupts conduction further perpetuating the Afib (Afib begets Afib). The atria become mechanically weaker, losing their ability to augment ventricular filling. Remodeling of the atrial myocardium develops progressively. Even if sinus rhythm is restored, recovery of α-MHC fibers may be incomplete, especially in chronic Afib. This may help explain why atrial contractile stunning persists after cardioversion, and why there can be recurrences of Afib [5-8].

The shift from α to β is associated with decreased ATPase activity and cross-bridge cycle rate, resulting in a slower myocardial shortening and relaxation. This process increases with aging.

In the healthy adult, ventricular contraction is slow but powerful, and optimized for sustained output. However, in cardiomyopathy this shift from α to β makes overall contraction less efficient. This is due to such factors as reduced Vmax, altered calcium handling, and the above mentioned reduced myosis ATPase activity, with decreased cross-bridge cycling, resulting in an increased ATP cost per unit of work [9-10]

In Afib with cardiomyopathy the damages can be more severe. The atria dilate further due to increased ventricular end-diastolic stress leading to further fibrosis, remodeling, and decreased contractility/relaxation [11].

Discussion:

The transformation of α-MHC to β-MHC increases with age. At the same time, the risk of Afib doubles every decade over 50. For people over 40, the lifetime risk is 25%. Although the transformation has not been proven to cause Afib, its association with structural and biochemical abnormalities seen in Afib, and Afib with cardiomyopathy, suggest that it is a part of this pathologic process. It is not known if preventing this transformation from α to β in some way might delay the onset or lessen the severity of such conditions. It seems reasonable then that at the present time, detecting and maintaining cardiac health, including treating such conditions as hypertension, valvular disease, sleep apnea, diabetes, coronary disease, weight gain, and such, may in some way slow this transformation and its associated sequelae. Further studies of this transformation may be of considerable interest [12].

Conclusion:

Transformation of cardiac α-MHC to β-MHC fibers appears to be an important pathophysiologic process which may lead to significant cardiovascular abnormalities. Further studies are needed.

Table 1: Age related changes in Myosin Heavy Chain isoform expression in the normal heart

	Age	%α-MHC	%β-MHC
Left Atrium	20-30	65-70%	30-35%
	50-60	45-55%	45-55%
	>75	25-35%	65-75%
Right Atrium	20-30	60-65%	35-40%
	50-60	40-50%	50-60%
	>75	20-30%	70-80%
Left Ventricle	20-30	7-10%	90-93%
	50-60	3-5%	95-97%
	>75	<2%	>98%
Right Ventricle	20-30	8-10%	90-92%
	>75	2-3%	97-98%

Table 2: Structural and molecular changes in Atrial fibrillation

Early Afib	sarcomere disorganization	decreased contractile speed reversible
Sustained Afib	myolysis, mitochondrial damage, shift from α to β-MHC	loss of fast phenotype contractile stunning
Afib/Cardiomyopathy	myocyte death, fibrosis, fetal-gene re-expression	permanent lost of fast fibers stiff, hypocontractile, left atrium

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CITATION

Robert M.P. (2025). Transformation of Cardiac Muscle Isoforms. Global Journal of Research in Medical Sciences, 5(6), 42–44. https://doi.org/10.5281/zenodo.17602553