Review article

Cardiac Myosin Heavy Chains

Abstract

Myosin is defined as a mechano-enzyme molecule which converts the chemical energy stored as adenosine triphosphate (ATP) into mechanical energy (muscle contraction). Moreover, the cardiac muscle has different types of myosin heavy chain when it separated with the one dimensional electrophoresis; in addition to their structural difference cardiac myosin isozymes have different contractile functions.

Key words: Myosin heavy chains, myosin isozymes, alpha myosin heavy chain, beta myosin heavy chain

Cardiac myosin isozymes

Based on electrophoretic mobility, Hoh et al 1978 *discovered* that there are five distinct components of cardiac myosin isozymes. Two of them present in the atrial muscle named A1 & A2 and *the other three are* in the ventricular muscle *designated* V1, V2 & V3. These ventricular myosin *chains* have been differentiated by their speed of migration and subsequently on their molecular weights into V1 which is the fastest one and the slower one was *detected to be* V3 myosin isozyme while V2 was intermediate between V1 & V3. The two atrial components A1 & A2 migrate faster than the fastest ventricular myosin isozyme V1 (Hoh et, al 1978).

In comparison with mammals, ventricular myosin of the amphibian hearts has somewhat different electrophoretic properties. Depending on the species. There are only one or two myosin components in the ventricle. Ventricular isozymes of Urodelan amphibians display mobility similar to V2 or V1 of the rat ventricular isozymes and the ventricular myosin of the Anurans migrates faster than V1 (Karasinski et al, 1986).

Cardiac myosin molecule is a hexamer (figure 1) *which is comprised of two* heavy chains and two pairs of light chain (Mcnally et al, 1989). The myosin isozymes differ in their heavy chains structure (Hoh et al, 1979) while their light chains not being different in molecular size or stoichiometry (Hoh et al, 1978) thus the difference only in their heavy chains.

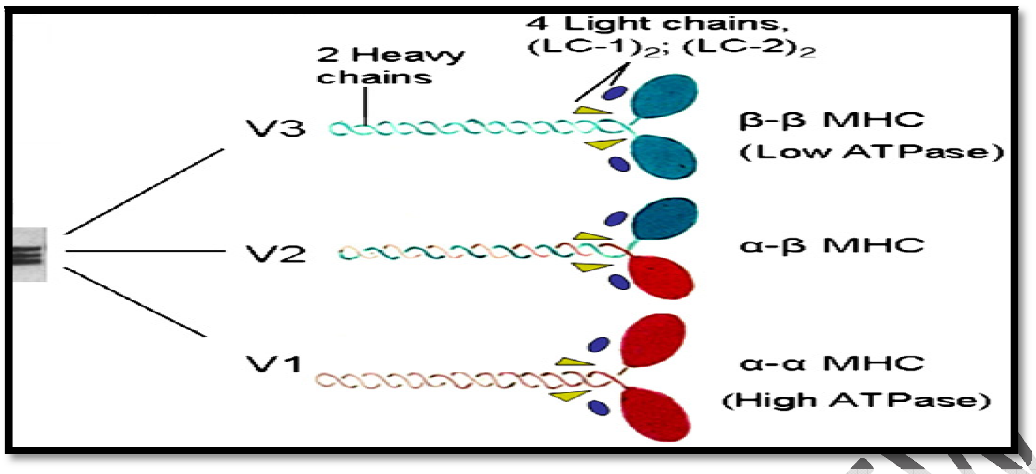

Figure 1: MHC structure (Gupta et al, 2007)

In contrast to skeletal muscle which expresses multiple myosin heavy chain genes, the heart expresses only two myosin heavy chain genes which produce the Alpha & Beta myosin heavy chains (Mahdavi et al, 1982). Therefore the structural component of the ventricular myosin isozymes according to their heavy chains is as the following: V1 isozyme is homodimer consisting of two alpha myosin heavy chains, V3 isozyme is also homodimer consisting of two Beta heavy chains while V2 isozyme is hetrodimer formed by one alpha & one beta heavy chains (Hoh e al, 1979) see figure1.

Analysis of the Calcium – activated myosin ATPase activity revealed that A1, A2 & V1 isozymes have about the same activity while V3 has the lowest activity and V2 has intermediate activity (Hoh et al, 1978). The V1 which has a much higher Calcium ATPase activity resembles fast- twitch skeletal muscle myosin while V3 behaves like slow – twitch skeletal muscle myosin (Pope et al, 1980).

The ventricular myosin isoforms have different distribution according to the age & species. In all species during the fetal life the ventricular myosin isoforms is essentially V3 (ββ) while the V1 (αα) appears around the time of birth (Lompre et al, 1981). There are species differences; in adult mice and rats V1 (αα) myosin isozyme remain the predominant one but in rabbit and pigs return to V3 (ββ) myosin isozyme after three weeks of age see figure 2. Adult dog, beef & human ventricular myosins are also formed by V3 (ββ) isoform only (Lompre et al, 1981).

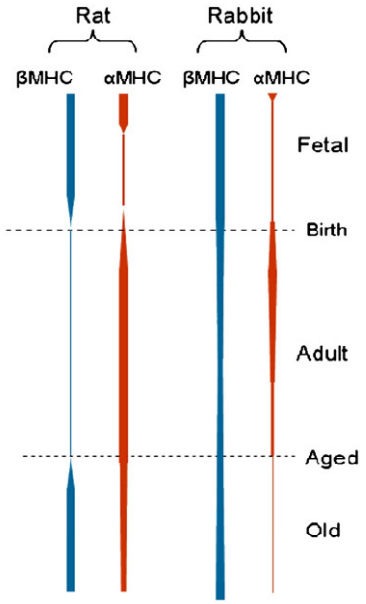

Figure 2:- Effect of age on the cardiac MHC in rat and rabbit (Gupta et al, 2007)

Expression of myosin isoforms (V1 & V3) depends on the location of cardiomyocytes in the heart. V1 myosin isozyme is present predominantly in the ventricular papillary and epicardium muscle layers while the V3 myosin isozyme is distributed predominantly in the ventricular endocardium muscle layer (Litten et al, 1985). Also V1 myosin isozyme is present predominantly in the ventricular conductive system which is reflected by the higher concentration of the alpha myosin heavy chain in the ventricular conductive system (Komuro et al, 1987).

Cardiac myosin heavy chains

There are two genes encoding the alpha and beta cardiac myosin heavy chains (Mahdavi et al, 1982). Interestingly the complete sequences of alpha & beta cardiac myosin heavy chain nucleotides and amino acids have been determined in 1989 (Mcnally et al, 1989). The complete alpha myosin heavy chain cloned DNA is 5930 base pairs and encodes a protein of 1938 amino acid residues in length with predicted molecular mass of 223,511 Daltons. The complete beta myosin heavy chain cloned DNA is 5925 base pairs and encodes a protein of 1935 amino acid residues in length with predicted molecular mass of 223,172 Daltons. The alpha and beta myosin heavy chain nucleotide sequences are 92% identical and the amino acid sequences of the alpha and beta myosin heavy chains are 93% identical (Mcnally et al, 1989).

The two myosin heavy chains are different in the concentration of two amino acids in their structure. Methionine is found in higher concentration in alpha myosin heavy chain while Arginine amino acid is found in higher concentration in beta myosin heavy chain (Hoh et al, 1979).

Some functional difference has been found to be correlated with these structural differences. The Calcium – activated ATPase activity of the alpha myosin heavy chain is higher than that of the beta myosin heavy chain (Hoh et al, 1978). In guinea pig hearts, the beta myosin heavy chain is about five times more economical than the alpha myosin heavy chain (Van der et al, 1998). Recently, Narolska et al 2005 observed that human ventricular muscle consists of beta myosin isozyme while the human atrial muscle consists of both alpha and beta myosin isozyme. Also they have observed that human ventricular muscle which is beta myosin heavy chain is fivefold more economical in force development and nine times slower than atrial muscle (Narolska et al, 2005). Functionally, it has been recently found that the activity of the two cardiac myosin heavy chains alpha and beta can be increased by the reversible lysine acetylation (Samant et al, 2011).

Redistribution of the cardiac myosin heavy chains

There are many factors that could cause redistribution of the cardiac MHC isoforms (table 1): these factors can be classified into physiological (Lompre et al, 1981, Rupp et al 1989,and Rupp et al 1981), environmental (Horowitz et al, 1986), metabolic (Morris et al 1989), pathological factors (Yazaki et al 1989, Zang et al 2003, and Naroska et al 2005), and the redistribution due to drugs administration. Some of these factors affecting redistribution of the cardiac MHC isoforms are associated with cardiac hypertrophy, while other factors are not (Rupp et al 1989,and Rupp et al 1981).

The physiological factors affecting cardiac MHC isoforms redistribution are age and routine physical exercise. The effect of age on cardiac MHC isoforms redistribution is not associated with heart hypertrophy (Lompre et al, 1981). This redistribution depends on species; in mice and rats the amount of alpha MHC isoform increases with age, while the amount of beta MHC isoform decreases with age (Lompre et al, 1981). Similarly the distribution of MHC due to hypertrophy depends on type of exercise at least in rat. Hypertrophy after swimming exercise shows that MHC is shifted toward alpha while hypertrophy after running exercise is not associated with changes in the cardiac MHCs distribution ((Lompre et al 1981, Rupp et al 1989,and Rupp et al 1981).

The effect of adaptation to heat stress has been demonstrated by Horowitz et al 1986 ; they found that there is an alteration in cardiac myosin isozyme distribution as an adaptation to chronic environmental heat stress in rats. Chronic environmental heat stress causes down regulation of V1 (αα) myosin isozyme and up regulation of V3 (ββ) myosin isozyme (Horowitz et al, 1986). The redistribution of the myosin heavy chains due to acclimatization to hot weather is associated with a decrease in thyroid hormone level (Horowitz et al, 1986).

The metabolic factors that can cause cardiac MHC redistribution is demonstrated by food restriction & Carbohydrate rich meal replacement. In food restricted rats there were downregulation of alpha MHC isoform and upregulation of beta MHC isoform but this shifting can be prevented by

carbohydrate rich meal replacement. The shifting in MHC isoforms is correlated with reduction in heart weight in food restricted rats (Morris et al, 1989).

There are multiple pathological factors associated with the redistribution of the myosin heavy chains of the heart. Rupp et al 1981 showed in the case of cardiac hypertrophy due to renal hypertension (Goldblatt II) there was a shift on the ventricular myosin isozyme toward V3 (ββ) myosin isoform. This was reinforced in 1989 by the observation of Yazaki et al 1989 where they demonstrated that the left ventricular hypertrophy was evident from 3 days after pressure loading and the isozymic transition of myosin heavy chain from the alpha MHC isoform to the beta MHC isoform was detected within 24 hours after aortic constriction. Thus pressure overload led to MHC shift toward beta MHC isoform.

In some cardiac pathological conditions like myocardial infarction there is change in the cardiac MHCs toward V3 (ββ) myosin isoform, but this change can be inhibited by administration of Losartan (an angiotensin II blocker) (Zhang et al, 2003). Similarly atrial fibrillation was accompanied by a significant shift from the alpha MHC isoform to the beta MHC isoform in the atrial tissue (Narolska et al, 2005). Also the alpha MHC isoform in the heart decreases in diabetes mellitus to a significant level (Rundell et al, 2004).

The correlation between sex hormone and the distribution of the cardiac MHCs is shown in experiments on the effect of gonadectomy & sex hormone replacement on the cardiac MHCs in the spontaneously hypertensive rats. Lengsfeld et al 1988 showed that the male gonadectomy causes shift in the myosin isozyme pattern toward V3 (ββ) myosin isozyme while testosterone hormone replacement leads to myosin isozyme pattern in favor of V1 (αα) myosin isoform. This observation was supported recently by Jazbutyte .V et al 2006 who reported that ; in spontaneously hypertensive female rat, the ovariectomy decreases the alpha myosin heavy chain in the heart and shift the MHC ratio toward beta MHC accumulation. While estrogen substitution in ovariectomized young spontaneously hypertensive rat results in an increase in alpha MHC isoform.

Administration of thyroid hormone makes the cardiac MHC to redistribute in favor of V1 (αα) myosin isozyme which is associated with heart hypertrophy. While decreasing the thyroid hormone level in the blood has the reverse effect, it changes the cardiac MHC ratio toward the beta MHC isoform (Hoh et al 1979 and Rundell et al 2005). Similarly dexamethazone (a synthetic glucocorticoid drug) administration has the same effect of thyroid hormone on the cardiac MHCs. This drug induces cardiac hypertrophy and makes a change in the cardiac MHCs toward the fast alpha MHC isoform (Muangmingsuk et al, 2000).

Rupp et al 1991 showed the effect of positive inotropic agents on myosin isozymes in cultured cardiac myocytes. Isoproterenol and Phenylephrine caused an increase in V1 native myosin isozyme. The isoproterenol made a shift in the cardiac MHC toward the alpha MHC (Rupp et al, 1991).

The only drug that causes a shift of cardiac MHC toward beta MHC is Cocaine (Henning et al, 2000).

Table 1: factors affecting ventricular MHC distribution**.**

Factor affecting MHCs distribution	**Shifting of MHC**	**references (Ref)**
Physiological factors	**Shifting of MHCs**	**(Ref)**
Increase age	In mice increase α & decrease β MHCs	Lompre et al, 1981
Hypertrophy after swimming exercise	Increase α MHC	Rupp et al, 1981 and Rupp et al, 1989
Hypertrophy after running exercise	No change	Rupp et al, 1981 and Rupp et al, 1989
Environmental factor	**Shifting of MHCs**	**Ref**
Adaptation to heat stress	Decrease α MHC& increase β MHC	Horowitz et al, 1986
Metabolic factors	**Shifting of MHCs**	**Ref**
Food restriction	Decrease α& increase β	Morris et al, 1989

CHO rich meal	Increase α & decrease β	Morris et al, 1989
Pathological factors	**Shifting of MHCs**	**Ref**
Hypertrophy due to renal hypertension	Increase β MHC	Yazaki et al, 1989 and Horowitz et al, 1986
Myocardial infarction	Increase β MHC	Zhang et al, 2003
Atrial fibrillation	Increase βMHC	Narolska et al, 2005
Gonadectomy	Decrease α and increase β MHCs	Lengsfeld et al, 1988 & Jazbutyte et al, 2006
Hypophesectomy	Increase β MHC	Carter et al, 1987 & Hoh et al, 1979
Change due to drug administration	**Shifting of MHCs**	**Ref**
Sex hormones	Increase α and decrease β MHCs	Lengsfeld et al, 1988 & Jazbutyte et al 2006
Thyroid hormone	Increase α MHC	Carter et al, 1987 & Hoh et al, 1979
Anti thyroid drugs	Increase β & decrease α MHCs	Carter et al, 1987 &

		Hoh et al, 1979
Dexamethasone	Increase α MHC	Muangmingsuk et al, 2000
Positive inotropic drugs like isoproterinol, forskolin, phenylephrine	Increase α MHC	Rupp et al, 1991
Cocaine	Increase β MHC	Henning et al 2000

Heart hypertrophy

The word hypertrophy derived from the Greek, hyper means above or more than normal, and Trophe means nutrition(Dorn et al, 2003).hypertrophy is defined as the enlargement or overgrowth of an organ or part due to an increase in size of its cells (Dorn et al, 2003). The heart hypertrophy has two phenotypes named as concentric hypertrophy and eccentric hypertrophy (Dorn et al, 2003). In both forms of hypertrophy the cardiac dry mass is increased (Dorn et al, 2003).

Concentric hypertrophy is due to pressure overload in which there is an increased thickness of ventricular wall with little or no change in chamber volume, with new sarcomeres added in parallel to existing sarcomeres (Dorn et al 2003, Mihl et al 2008). While the eccentric form of hypertrophy is due to volume overload in which there is an increased chamber volume with ventricular wall thickness increased in proportion to the chamber dimension (Dorn et al 2003, Mihl et al 2008). The increased thickness of the ventricular wall is by adding new sarcomeres in series to existing sarcomers (Mihl et al, 2008).

Factors promoting left ventricular hypertrophy

It is now appreciated that left ventricular hypertrophy is mediated not only by the mechanical stress of pressure overload, but also by various neurohormonal substances that independently exert trophic effects on myocytes and nonmyocytes in the heart (Richard et al, 2011). The trophic factors that promote left ventricular hypertrophy include angiotensin II, aldosterone, noradrenalin, and insulin

which directly promote myocyte hypertrophy and matrix deposition independent of their effects on systemic arterial pressure (Richard et al, 2011).

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