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Distribution pattern of α and β myosin in normal and diseased human ventricular myocardium*)

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Summary: All fibers in three normal, four dilated, and two ischemic human ventricles were classified according to their myosin content using three sets of monoclonal antibodies each specific for one myosin heavy chain isoform (α, β and β'). Numerous fibers contained only β myosin heavy chain (denoted as β fibers), others contained either α and β, or β and β' myosin heavy chain (denoted as αβand ββ' fibers, respectively). The percentages of αβ fibers were systematically determined along the walls of seven homologous regions of the ventricular myocardium.

In all ventricles, there was an αβ-fiber transmural gradient, with less αβ fiber in the subendocardium than in the subepicardium. More αβ fibers were found in the right than in the left ventricular wall but there was no difference between the mid-portion and the apex of the free wall of each ventricle. The diseased ventricles contained a lower αβ fiber percentage than the normal hearts. ββ' fibers were very rare in the normal ventricles (less than 5%) and almost inexistent in pathological hearts. The correlation between the mean αβ fiber percentages of the diseased hearts and their cardiac indices ($r = 0.88$, $P < 0.05$) suggests that the small amount of α myosin distributed in a large number of ventricular fibers could play a role in the contractile performance of the heart. In conclusion, this study provides evidence for 1) an αβ fiber transmural gradient, and 2) a lower α myosin ratio in diseased than in normal human ventricle.

Key words: anatomy, human, monoclonal antibody, myosin, ventricle

Introduction

Myosin polymorphism in human ventricles has been conclusively evidenced in histoenzymatic (1, 27), histoimmunological (1, 11, 19, 24, 28, 32), and genetic studies (22). The different human myosin isoforms have been designated with reference to the α and β isoforms of myosin heavy chains present in rat ventricles (13). In human ventricles, the β myosin heavy chain isoform is largely predominant, whereas the α myosin heavy chain isoform is only present in small amounts (11, 19). Another myosin heavy chain isoform

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related to the main β myosin heavy chain isoform, and designated as β', has also been detected in scarce normal human fibers scattered throughout both ventricles (1). The differences between the histological adenosine thriphosphatase activities observed in different human ventricular fibers could correspond to the different in vitro adenosine triphosphatase activities of each myosin isoform, as demonstrated in rat ventricels (21, 31). Since the different human ventricular myosin isoforms have not yet been isolated, their respective in vitro adenosine triphosphatase activities are still unknown. It should be noted that a clear-cut correlation between the maximum velocity of muscle shortening and the isomyosin activity patterns has been demonstrated in rat ventricles (8, 25).

In contrast with beef, rabbit, and rat ventricles (9,23), no obvious regional or transmural variations in the distribution of the minor α myosin has until now been observed in normal or pathological human ventricles. It has been proposed that the changes in myosin composition induced in human ventricular myocardium by chronic pressure overload (α-to-β-transition) are obscured by the considerable intra- and inter-individual variability and could be quantitatively negligible due to the great prevalence of the β-myosin isoform (19).

In a recent study (2), using monoclonal antibodies specific for each human atrial myosin isoform, we were able to identify the atrial myosin variants, to classify the atrial fibers according to their myosin content, and to quantify the fiber-type distribution within the different regions in normal and diseased hearts. In the present work, we use three sets of monoclonal antibodies specific for α, β, and β' ventricular myosin heavy chain isoforms, to study myosin dispersion and distribution within the ventricles of three normal and six diseased human hearts.

Materials and Methods

Patients

Six adult human diseased hearts were obtained either from recipients of cardiac transplants (denoted as hearts P1 to P5; Cardiological Hospital of Lyon) or from a patient who died in hospital (denoted as heart P6; Cardiological Department, St. Eloi Hospital, Montpellier). Three normal human hearts were included in this study (denoted as hearts N1, N2, and N3; Nephrology and Urology Departments, St. Charles Hospital, Montpellier). Informed consent was obtained either from the patient or from the patient's family.

Clinical data for some of the patients have been presented in a previous publication (Table 1 of (2); patients P1, P2, P5, and P6 were denoted A, B, C and D, respectively). Patients P1 to P4 had primary dilated cardiomyopathy with progressive congestive heart failure temporarily counterbalanced by appropriate therapy. Patient P5 had two posterior myocardial infarctions (most recently one year before transplantation). Eleven years before his death, patient P6 underwent a resection of an aneurysm related to a massive anterior apical myocardial infarction. Clinical, echocardiographic, and hemodynamic data providing information on their ventricular function are summarized in Table 1.

Preparation of tissue

Seven tissue were systematically excised from the ventricular myocardium of each heart: three came from the right ventricle, three from the left ventricle (from the mid-proportion, from the region near the apex of the free wall, and a complete papillary muscle from both ventricles). The seventh sample was from the mid-portion of the interventricular septum. All samples were comprised of the total width of the ventricular wall. Each tissue sample was carefully oriented so that a transmural surface was in the sectioning plane. Papillary muscles were oriented so that the longitudinal surface was in the sectioning plane. The border of the infarcted myocardium in the two ischemic hearts was also systematically excised. Finally two to four tissue samples were also randomly excised from other areas in each ventricle.

Table 1. Cardiac characteristics of patients.

Patients	P1	P2	P3	P4	P5	P6
Age	43	50	51	33	55	62
Echocardiographic data						
LVD (mm)	82/74	75/69	66/58	70/63	80/73	74/60
Hemodynamic data						
RVSP (mm Hg)	30	45	60	30	–	30
RVEDP (mm Hg)	5	12	15	3	–	5
LVSP (mm Hg)	110	100	160	–	–	120
LVEDP (mm Hg)	36	12	15	–	–	35
CI (l/min/m^2)	2.4	2.2	1.8	2.4	–	2.5
Heart weight (g)	560	640	520	380	440	480
Diagnosis	PDC	PDC	PDC	PDC	IHD	IHD

All patients are male.
Abbreviations: CI: cardiac index; IHD: ischemic heart disease; LVD: left ventricular dimension; PDC: primary dilated cardiomyopathy; LVEDP and RVEDP: left and right ventricular end-diastolic pressure, respectively; LVSP and RVSP: left and right ventricular systolic pressure, respectively.

Tissue samples were frozen in precooled isopentane or directly in liquid nitrogen, as previously described (1, 2).

Monoclonal antibodies

Three groups of monoclonal antibodies whose specificity has already been described (1, 2, 5, 6, 7, 17) were used in this study. According to their reactivity with rat myosin, they were referred to as anti-α and

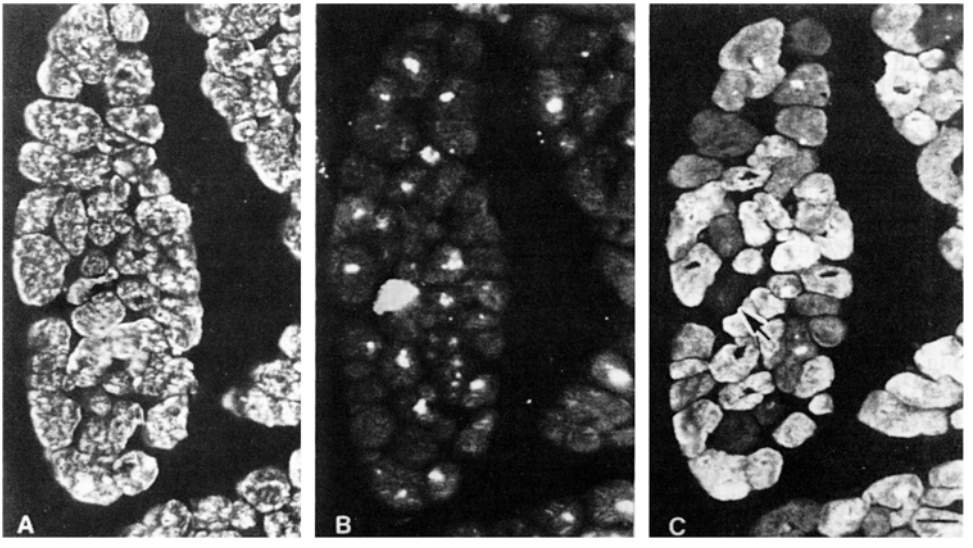

Fig. 1. Three serial sections of the left posterior wall of the normal heart were stained with anti-β (a), anti-β′ (b), and anti-α (c) myosin heavy chain monoclonal antibodies. Fibers labeled by the anti-β′ antibody (b) were not labeled by the anti-α antibody (arrow in c). Initial magnification: 100 ×. Bar 20 μ.

anti-β myosin. Initially, two to three different monoclonal antibodies of each group were used to carry out the fiber typing and the preliminary fiber counting. Since similar results were obtained with all three antibodies of each group, the complete fiber counting was performed with only one antibody of each group.

Immunofluorescence

Tissue samples and cryostat sections (6 to 8μ) were kept frozen at −80 °C until use. Control experiments and indirect immunofluorescence processing (fluorescein goat antimouse IgG specially prepared from human tissue) (Nordic Immunological Laboratories, Tilburg, The Netherlands) were done as previously described (1, 2). Sections were examined with a Leitz microscope equipped with epifluorescence optics.

Fiber counting

We quantified the percentages of ventricular fibers labeled with anti-α antibody on photomicrographs taken from different regions: the subepicardial and subendocardial layers of the right ventricular free wall. The subepicardial, middle third and subendocardial layers of the left ventricular free wall, and the right side, middle third, and left side of the interventricular septum. Longitudinal sections of papillary muscles were also divided arbitrarily into four regions from apex to base. More than 500 labeled and unlabeled fibers were counted with a point-counting method (30) in 10 to 15 non-serial sections from each region. Since this procedure involves discrimination between only two types of fiber (labeled and unlabeled fibers) the difference between the percentages obtained by observers was reduced to less than 3 %.

Morphometry

The fiber diameter of each fiber type (see results) was calculated by measuring the short axis at the level of the nucleus on cross or oblique sections in the tissue samples excised from the ventricular walls. In order to account for the transmural variability of ventricular fiber diameters (14), an identical number of each fiber type was measured in each layer of the ventricular walls.

Statistical analysis

Statistical analyses were performed using two-way analyses of variance, Student's t-test, and a correlation study. Percentages of αβ fibers obtained from the pont-counting method were expressed as mean $\pm \sqrt{pq/n}$; p and q are the numbers of αβ and β fibers, n is the total number of counted fibers (p+q).

Results

Fiber typing

When processed with either one of three anti-β monoclonal antibodies, all fibers in all sections of the normal human ventricles were labeled intensely and homogeneously (Fig. 1a). On the other hand, the anti-β' monoclonal antibodies stained very few ventricular fibers interspersed among unstained fibers (Fig. 1b). The anti-α monoclonal antibodies stained numerous fibers but the staining intensity differed from one fiber to another (Fig. 1c). The use of serial sections demonstrated that the fibers labeled by the anti-α or anti-β' monoclonal antibodies were also labeled by the anti-β monoclonal antibodies. Thus, these fibers contained two different isoforms of myosin heavy chains. No fiber stained by the anti-β' monoclonal antibodies was stained by the anti-α monoclonal antibodies (Fig. 1b and arrow in Fig. 1c). Finally, some fibers were stained by anti-β antibodies but neither by anti-α nor by anti-β' antibodies. Consequently, three types of fiber were distinguished in the ventricles:

1) Fibers labeled by the anti-α and anti-β monoclonal antibodies which are here designated as αβ fibers;
2) Fibers labeled by the anti-β and anti-β' monoclonal antibodies which are here designated as ββ' fibers;
3) Fibers labeled by the anti-β monoclonal antibodies but neither by the anti-α nor the by anti-β' monoclonal antibodies which are here designated as β fibers.

This terminology is not related to the homo- or heterodimeric structure of the myosin molecules, but only to the reactivity of the fibers with our antibodies. The same three sets of monoclonal antibodies were used to identify the same myosin isoforms in diseased ventricles, and the same fiber classification (αβ, ββ', and β) was obtained.

Distribution of αβ fibers within the ventricular wall

Observation of ventricular sections of tissue excised from the three normal and six diseased hearts revealed that αβ fibers were not homogeneously distributed within the ventricular wall. In order to evaluate these variations precisely, we measured the percentage of αβ fibers in each layer of each tissue sample with a point-counting method using a test-grid on photomicrographs (30). In order to be consistent, the same anti-α and anti-β monoclonal antibodies were used to stain all the samples although the other antibodies from each group gave the same results on several samples.

Table 2 shows the percentages of αβ fibers determined within two layers of the mid-portion of the right ventricular free wall, three layers of the interventricular septum, and three layers of the mid-portion of the left ventricular free wall of the nine hearts. Two-way analysis of variance showed that the variability of percentages reflected a heterogeneity between the hearts ($F^8_{56} = 119.2$, $p < 0.001$, as well as between the layers of each heart ($F^7_{56} = 13.5$, $p < 0.05$). Since the normal ventricles had higher percentages of αβ fibers than the diseased ventricles, we separated the study of normal and diseased ventricles. In normal as well as in diseased ventricles, the subendocardial layers contained significantly lower amounts of αβ fibers than the epicardial counterpart of right and left ventricles (see Table 2). Furthermore, the right and left endocardial side of the interventricular septum contains a similar αβ fiber percentage as does the endocardial layer of the right and left ventricular free wall, respectively. Interestingly, the papillary muscles of these ventricles also exhibited a longitudinal gradient of αβ fibers: the apex of the papillary muscle where the chordae tendinae are connected contained fewer αβ fibers than the endocardial layer of the ventricular wall. The proportion of αβ increased progressively along the papillary muscle axis; at mid-height, it attained the percentage of αβ fibers observed in the endocardial layer. At the base of the muscle, the percentage of αβ fibers was comparable to that observed in the mid-layer of the homologous ventricle.

Thus, normal as well as diseased ventricles have a transmural gradient of αβ fiber distribution with more αβ fibers in the epicardium than in the endocardium of the right as well as of the left ventricle.

Regional variation of the percentages of αβ fibers

To study the regional variation of the αβ fibers percentage within the ventricle, we compared all samples available (see "Materials and Methods") using the same statistical approach as above (Two-way analysis of variance and t-test). Since a transmural gradient was observed in all samples, we accounted for it by counting the same number of fibers in each layer. The final percentage of each sample was obtained by pooling αβ and β fibers of all layers (1000 to 2000 fibers for each sample) (Table 3).

Table 2. Percentage of αβ fiber evaluated in eight homologous layers of three normal and six diseased hearts.

	RVFW		IVS			LVFW		
	SEP	SEN	R	M	L	SEN	M	SEP
N1	98 ± 0.6	84 ± 1.6	75 ± 1.9	80 ± 1.8	52 ± 2.2	58 ± 2.2	88 ± 1.5	70 ± 2.1
N2	52 ± 2.2	26 ± 2.0	29 ± 2.0	30 ± 2.1	16 ± 1.6	20 ± 1.8	28 ± 2.0	39 ± 2.2
N3	65 ± 2.2	48 ± 2.2	46 ± 2.2	53 ± 2.2	30 ± 2.0	29 ± 2.0	56 ± 2.2	44 ± 2.2
N	72 ± 14	52 ± 17	50 ± 13	54 ± 14	33 ± 10	36 ± 11	57 ± 17	51 ± 10
	0.02		0.10	0.01		0.05	NS	
P1	15 ± 1.6	9 ± 1.3	12 ± 1.5	19 ± 1.8	2 ± 0.6	2 ± 0.6	9 ± 1.3	13 ± 1.5
P2	25 ± 1.9	22 ± 1.9	15 ± 1.6	19 ± 4.4	5 ± 1.0	6 ± 1.1	11 ± 1.4	13 ± 1.5
P3	18 ± 1.7	12 ± 1.5	10 ± 1.3	16 ± 1.6	4 ± 0.9	9 ± 1.3	12 ± 1.5	15 ± 1.6
P4	20 ± 1.8	12 ± 1.5	25 ± 1.9	32 ± 2.1	9 ± 1.3	8 ± 1.2	10 ± 1.4	20 ± 1.8
P5	6 ± 1.1	2 ± 0.6	2 ± 0.6	4 ± 0.9	0 ± 0	0 ± 0	1 ± 0.4	2 ± 0.6
P6	22 ± 1.9	18 ± 1.7	14 ± 1.6	30 ± 2.0	8 ± 1.2	9 ± 1.3	17 ± 1.7	22 ± 1.9
P	18 ± 3	13 ± 3	13 ± 3	20 ± 4	5 ± 1	6 ± 2	10 ± 2	14 ± 3
	0.001		0.02	0.01		0.02	NS	

– Numbers correspond to percentages ± $\sqrt{pq/n}$ obtained by counting more than 500 fibers in 10 to 15 non-serial sections from each region (see Materials and Methods).

– Abbreviations: IVS: interventricular septum; L: left ventricular side; LVFW: left ventricular free wall; M: middle third; N1 to N3: normal ventricles; N: mean ± standard deviation of the mean of normal hearts, below are indicated the results of t test; P1 to P4: primary dilated cardiomyopathy; P5 and P6: ischemic heart disease; P: mean ± standard deviation of the mean of diseased ventricles; R: right ventricular side; RVFW: right ventricular free wall; SEN: subendocardium; SEP: subepicardium.

Table 3. Percentage of αβ fiber evaluated in seven different areas of three normal and six diseased ventricles.

	RV			IVS	LV		
	AW	PM	AP		PW	PM	AP
N1	91 ± 0.7	88 ± 1.5	93 ± 1.1	69 ± 1.2	72 ± 1.2	70 ± 2.0	89 ± 1.4
N2	39 ± 1.3	21 ± 1.8	24 ± 1.9	25 ± 1.1	29 ± 1.2	23 ± 1.9	17 ± 1.7
N3	57 ± 1.3	39 ± 2.2	43 ± 2.2	43 ± 1.3	43 ± 1.4	39 ± 2.2	49 ± 2.2
P1	12 ± 0.8	18 ± 1.7	20 ± 1.8	11 ± 0.8	8 ± 0.7	12 ± 1.5	16 ± 1.6
P2	24 ± 1.1	12 ± 1.5	14 ± 1.6	13 ± 0.9	10 ± 0.8	9 ± 1.3	15 ± 1.6
P3	15 ± 0.9	7 ± 1.1	11 ± 1.4	10 ± 0.8	12 ± 0.8	8 ± 1.2	10 ± 1.3
P4	16 ± 0.9	10 ± 1.3	8 ± 1.2	22 ± 1.1	13 ± 0.9	15 ± 1.6	20 ± 1.7
P5	4 ± 0.5	2 ± 0.6	3 ± 0.8	2 ± 0.4	1 ± 0.3	3 ± 0.8	2 ± 0.6
P6	20 ± 1.0	14 ± 1.6	16 ± 1.6	18 ± 1.0	16 ± 1.0	25 ± 1.9	22 ± 1.8

– Numbers correspond to percentages ± $\sqrt{pq/n}$ obtained by counting 1000 to 2000 fibers in each region; p, q and n as in Table 2.
– Abbreviation: AP: apex; AW: anterior wall; PM: papillary muscle; PW: posterior wall, IVS, LV, N_1 to N_3, P_1–P_5, and RV as in Table 2.

There was, not surprisingly, heterogeneity between the different hearts so that we further separated the study of normal and diseased hearts. In both groups, there was a weak heterogeneity between the samples ($0.10 < p < 0.05$). Furthermore, we evidenced a higher fiber percentage in the right ventricular free wall than in the left one ($p < 0.05$) (see Fig. 2), but no significant difference between the mid-portion and the apex region of each ventricu-

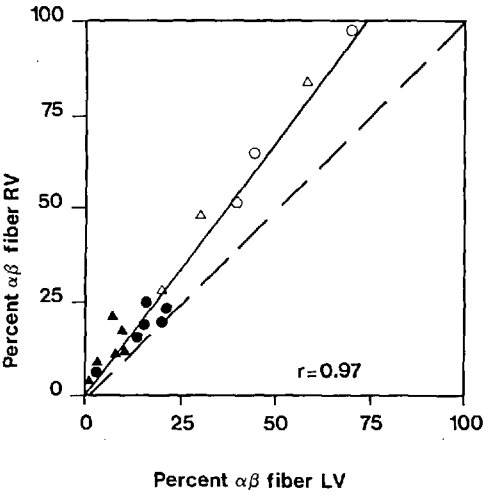

Fig. 2. Correlation of αβ fiber percentages from different ventricular regions. The αβ fiber percentage was determined as described in Methods. Plotted are: percent αβ fibers in the right ventricles vs the left ventricles in subendocardial (▲, △) or subepicardial (●, ○) layers. The solid line represents the least squares linear regression lines with correlation coefficients of 0.97. The steep slope of the line corresponds to the predominance of αβ fibers in the right ventricles. Open signs = normal hearts, solid signs = diseased hearts. Normal ventricles have a noticeably higher percentage of αβ fibers than diseased ventricles.

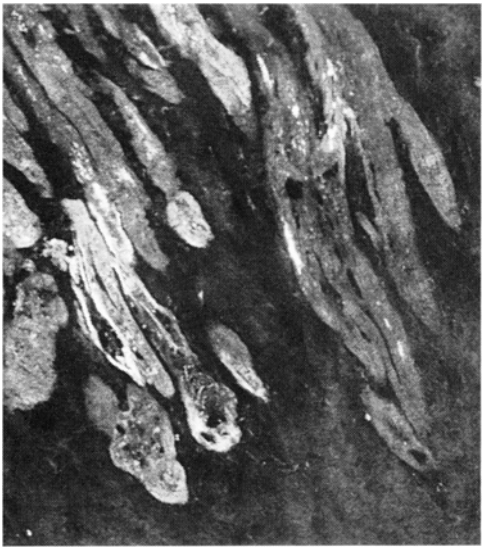

Fig. 3. A section of a tissue sample excised from the border of the necrosis in heart P5 is labeled with the anti-α monoclonal antibody. αβ and β fibers are very close to one another.

lar free wall of both ventricles. Lastly, at the edges of necroses (heart P5 and P6), a moderate percentage of αβ fibers was observed, together with the predominant β fibers (Fig. 3).

Comparison of normal and diseased ventricles and correlation of αb fiber percentage to the cardiac index

Very few αβ fibers were intensely stained with the anti-α antibodies in diseased ventricles compared to normal ones. In addition, diseased ventricles contained significantly less αβ fibers than normal ventricles ($p < 0.001$). This result was demonstrated by comparing either homologous layers or pooled data of each ventricle of normal and diseased hearts (see Table 2 and 3, and Fig. 2). Moreover, the global mean percentage of the diseased hearts (13.9 ± 4.3, 13.9 ± 5.0, 10.4 ± 2.6, 14.9 ± 5, 18.7 ± 3.9, for P1, P2, P3, P4, and P6, respectively) correlated with the cardiac index ($r = 0.88$, $n = 5$, $p < 0.05$), but not with the left ventricular systolic or diastolic dimensions, nor with the ejection fraction of these diseased hearts. The cardiac index is also correlated with the mean αβ fiber percentage of the left ventricle (mid-portion and apex of the posterior wall + papillary muscle) $r = 0.74$. These correlations would be reinforced by including the three normal hearts and P5. P5 who had the lowest αβ fiber percentage (2.4 ± 1.0), had no hemodynamic measurement before his heart transplantation because of a rapid and dramatic deterioration of his cardiac function.

Comparison of αβ and β fiber diameters

To compare the diameters of the αβ and β fibers, we measured the diameters of 20 fibers of each type in two or three layers of each ventricular wall. αβ and β fibers did not differ significantly with respect to their fiber diameter: 21.8 ± 4.8 μ for αβ fibers and 22.9 ± 5.1 μ for β fibers in normal hearts ($n = 3$) as well as in diseased hearts 27.9 ± 8.0 μ and 28.0 ± 7.0 μ ($n = 6$), respectively, although diseased ventricles had significantly larger fibers than normal ventricles ($p < 0.01$).

Percentages of ββ' fibers

In contrast to αβ fibers, ββ' fibers were always rare. The mean percentages of ββ' fibers in the tissue samples from normal ventricles varied from less than 1 % to no more than 5 % of the total fibers; they were practically absent in the diseased hearts (less than 1 %). These fibers, which were found either isolated or in small clusters, did not show a clear-cut distribution pattern in the myocardium. Their diameters did not differ from those of the other fiber types.

Discussion

The heterogeneity of myosin in the human heart has already been evidenced either with mono- or polyclonal antibodies (11, 16, 19, 32). Each isoform has been related to α and β isoforms according to Hoh (13). Myosin heavy and light chain variants have also been shown to exist in beef and human ventricles, respectively, as demonstrated from amino acid sequence studies (10, 15). We have previously isolated and characterized the α and β myosin isoforms in the human atrium (5) but none of these isoforms have so far been isolated and characterized in the human ventricle. The myosin heavy chains were probed at several different locations by the 3 monoclonal antibodies of each set since these antibodies have different epitopes as evidenced by different affinities against various myosin preparations (17), western blot assays of myosin peptide fragments (1, 5), and immunoelectron microscopy (5, 7). Thus, it seems unlikely that this heterogeneity of the ventricular myofibers and its variation in diseased hearts could be related to the interference of a binding protein or a change in the myosin light chains. (12).

Our purpose was to classify human ventricular fibers according to their myosin isoform content and to quantitate the dispersion level of the α myosin isoform within different regions of normal and diseased human ventricles. Only three fibers types, each containing the β isoform (αβ, ββ and ββ') out of six possible fiber types, exist in human ventricular fibers. No fiber containing either pure α or pure β' or αβ' myosin isoform was detected.

The distribution pattern of ventricular αβ fibers takes the form of a transmural gradient (the αβ fiber percentage was lower in the subendocardial layer of both ventricles than in the subepicardial layer) and a slightly higher αβ fiber percentage in the right ventricle than in the left. Thus, human myocardium is similar to the myocardium of other mammals (9, 18, 23). Small animals, which predominantly express the α myosin have more β myosin in the subendocardium than in the subepicardium; larger animals, whose ventricles, like those of humans, predominantly express the β myosin, have less α myosin in the subendocardium than in the subepicardium. Finally, rabbit (9, 23) and bovine (23) heart express also a higher ratio of α myosin in the right than in the left ventricle. From this point of view, our results differ from those of Gorza (11) who did not find any difference between the right and the left ventricle in humans. The apparent discrepancy could be explained by the fact that some diseases involve one ventricle more than the other (e.g. valvular disease, congenital malformation, myocardial infarction). However, it is interesting to note that after myocardial infarction, which induces a reorientation of the fiber stress, there are still αβ fibers at the border of necrosis. In any case, these results underline the necessity to analyze numerous tissue samples of the ventricle to assess the mean αβ fiber percentage, or to compare homologous regions of different hearts.

Another interesting result was that diseased hearts have fewer αβ fibers than normal hearts. Hypertrophy in humans is associated with the appearance of an "atrial-like" myosin light chain (12) and a decrease of α myosin. The drop of αβ fibers in diseased hearts and the

correlation of the mean αβ fiber percentage with the cardiac index suggests that small amounts of α myosin isoform may possibly be important for the hemodynamic performance of the ventricle. However, the cardiac index is not strictly related to the cardiac contractility since it depends also on the pre- and afterload. Other indexes have been proposed to characterize the cardiac contractility (4). The lack of some hemodynamic data prevents in this study the comparison of the isomyosin fiber pattern to the velocity of circumferential fiber shortening at maximum wall tension, or the left ventricular wall stress that are indices more closely related to the fiber contractility and load on myofibers, respectively. α myosin has been experimentally found to be associated with a high speed of myocardial contraction (8, 25). Nevertheless, in these latter studies cardiac fibers were exclusively composed of α myosin. This is not the case in human ventricular myocardium since all fibers contain β myosin. The mechanism of action of these scarce α myosin molecules is still hypothetical but it is possible that non-randomly distributed α myosin within the thick filament could markedly modify the overall contractile efficiency. The assumption that myosin plasticity is part of a whole phenomenon involved in heart adaptation to changing hemodynamic and physiologic conditions, is further reinforced by the fact that birth corresponds in human ventricles to the appearance of α myosin (3). It is more difficult to predict the differential role (if any) of subgroups of isoforms such as our β' or the β 2 isoform recently found by Tsuchimochi (29). These β myosin isoforms could be encoded by the same alternatively spliced gene (22).

In this study, there is no striking difference between the ventricles of primary dilated cardiomyopathy and ischemic heart disease. This observation suggests that both diseases trigger, directly or indirectly, a drop in α myosin expression, although it is not possible to rule out the hypothesis that primary dilated cardiomyopathy could actually be induced by a decrease in α myosin expression. Any disruption in the process that leads to α myosin expression would result in the progressive disappearance of this molecule from the myocytes. The loss of this "high energetic" myosin could not be compensated by an increased production of the "low energetic" β myosin. In fact, the therapy could also participate in the α-to-β shift since digitoxin has been shown to have such a property in normal rat ventricle (26). The elucidation of the molecular mechanism that result in the preferential expression of these isoforms needs work and it may open a new field of research therapy that would be aimed at controlling the expression level of these isoforms.

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