Human cardiac myosin heavy chain isoforms in fetal and failing adult atria and ventricles

PETER J. REISER, MICHAEL A. PORTMAN, XUE-HAN NING, AND CHRISTINE SCHOMISCH MORAVEC. Human cardiac myosin heavy chain isoforms in fetal and failing adult atria and ventricles. Am J Physiol Heart Circ Physiol 280: H1814–H1820, 2001.—The goal of this study was to test the hypothesis that the relative amounts of the cardiac myosin heavy chain (MHC) isoforms MHC-α and MHC-β change during development and transition to heart failure in the human myocardium. The relative amounts of MHC-α and MHC-β in ventricular and atrial samples from fetal (gestational days 47–110) and nonfailing and failing adult hearts were determined. The majority of the fetal right and left ventricular samples contained small relative amounts of MHC-α (mean < 5% of total MHC). There was a small significant decrease in the level of MHC-α in the ventricles between 7 and 12 wk of gestation. Fetal atria expressed predominantly MHC-α (mean > 95%), with MHC-β being detected in most samples. The majority of adult nonfailing right and left ventricular samples had detectable levels of MHC-α ranging from 1 to 10%. Failing right and left ventricles expressed a significantly lower level of MHC-α. MHC-α comprised ~90% of the total MHC in adult nonfailing left atria, whereas the relative amount of MHC-α in the left atria of individuals with dilated or ischemic cardiomyopathy was ~50%. The differences in MHC isoform composition between fetal and nonfailing adult atria and between fetal and nonfailing adult ventricles were not statistically significant. We concluded that the MHC isoform compositions of fetal human atria are the same as those of nonfailing adult atria and that the ventricular MHC isoform composition is different between adult nonfailing and failing hearts. Furthermore, the marked alteration in atrial MHC isoform composition, associated with cardiomyopathy, does not represent a regression to a pattern that is uniquely characteristic of the fetal stage.

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different isoenzymes observed on native gels consisted of different heavy chains and/or myosin light chains was not always clear in these previous studies. Conceivably, small but important amounts of MHC-α could not be detected in previous studies in which the large hexameric myosin was studied electrophoretically. Doubts concerning the results from these previous electrophoretic studies are supported by recent findings (15, 22) suggesting that the human myocardium expresses substantial levels of α-myosin mRNA, which decreases during transition to heart failure. These findings suggested that similar expression patterns occur at the protein level, which are subject to developmental and contractile state. Detectable levels of MHC-α protein in nonfailing human ventricles from measurements based on a denaturing gel electrophoretic protocol have been recently reported (19). We examined MHC-α and MHC-β protein patterns in human left atrial and right and left ventricular samples from adult nonfailing hearts and those from adults with dilated or ischemic cardiomyopathy in an attempt to confirm the presence of significant amounts of MHC-α in nonfailing human ventricles. We also utilized a denaturing gel electrophoretic protocol that yields sufficient separation of MHC-α and MHC-β for reliable quantitation of the relative amounts of these two isoforms in a given sample (24). Human fetal atria and ventricles were also analyzed to determine whether developmental transitions occur in the MHC isoform expression of these chambers. Our results indicate that normal as well as dilated and ischemic cardiomyopathic adult human ventricles express predominantly MHC-β and very low levels of MHC-α but that the level of MHC-α is lower in failing ventricles. Furthermore, although MHC-α predominates in fetal atria, MHC-β clearly predominates in fetal ventricles at all ages examined. We concluded that adult human ventricular myosin isoform expression changes during the development of cardiomyopathy. The results of the present study also indicate that there is a much greater relative amount of the MHC-β isoform in the failing compared with nonfailing left atrium. Furthermore, this study provides quantitative information on human cardiac myosin isoform expression over ~25% of the gestational period and indicates that a small significant change in myosin expression occurs in fetal ventricles between gestational weeks 7 and 12.

METHODS

Tissue preparation. Fetal heart tissue was obtained from the Laboratory for the Study of Embryology at the University of Washington. The tissue was obtained under informed consent and under a protocol that was conducted in compliance with state and federal guidelines and approved by the Institutional Review Board of the University of Washington Medical Center. Twelve whole fetal hearts (gestational ages 47–110 days), obtained from electively terminated pregnancies, were immediately immersed and stored in iced saline. Within 2–3 h, cardiac chambers were identified and separated under a dissecting microscope. Right atrial samples from three fetuses and left atrial samples from two fetuses were not obtained. Free wall portions of each chamber were then immersed in liquid nitrogen for storage until analyzed for MHC composition.

Tissue from failing adults was obtained from the transplant program at the Cleveland Clinic Foundation, and nonfailing adult tissue was obtained from the unmatched hearts of organ donors. Consent from the next of kin was obtained before collecting samples from the nonfailing hearts. Adult left atrial and right and left ventricular samples were obtained from the hearts of 14 nonfailing individuals (10 men, 38–64 yr; 4 women, 26–62 yr) without any signs of cardiovascular disease, 12 individuals with ischemic cardiomyopathy (10 men, 48–68 yr; 2 women, 43 and 56 yr), and 12 individuals with dilated cardiomyopathy (9 men, 17–68 yr; 3 women, 37–60 yr). Atrial samples were not available from five of the individuals with nonfailing hearts. Ventricular samples were not available from one individual with a nonfailing heart. Samples from the left atrium and right and left ventricle from all other adult individuals were examined. Failing heart tissue was obtained from the explanted hearts of cardiac transplant recipients at the Cleveland Clinic Foundation. This protocol was approved by the Institutional Review Board of the Cleveland Clinic Foundation. The entire heart was obtained in the operating room after cardiopulmonary arrest. The heart was transported immediately to the laboratory while immersed in the same cardioplegic solution. The average time between explant and arrival in the laboratory was 30 min. After a brief pathological examination, the heart tissue was separated by chamber and immediately frozen in liquid nitrogen or −80°C until MHC analysis. Nonfailing human heart tissue was obtained from the unmatched hearts of organ donors through cooperation of Life Banc of Northeast Ohio (Cleveland, OH). No hearts used in this study had been rejected for cardiac function. All nonfailing hearts were transported from the donor institution to the laboratory at the Cleveland Clinic in cold cardioplegic solution. The duration from explant until arrival in the laboratory was 60–90 min for the nonfailing hearts due to the time in transit from the donor institution.

Protein analysis. The composition of gel sample buffer, preparation of gel samples, gel preparation and composition, and the gel running conditions were identical to those described by Reiser and Kline (24). Briefly, samples (25–40 mg) that were free of visible fat and connective tissue were prepared with homogenization after adding 30 μl of sample buffer per milligram of tissue. The tissues were heated to 95°C for 2 min and centrifuged for 5 min at 12,000 rpm in an Eppendorf centrifuge (model 5415). The supernatant was diluted 1:10 with sample buffer, and 3 or 4 μl, corresponding to 10–13 μg of tissue, were loaded. A set of molecular weight standards (Bio-Rad Laboratories; Hercules, CA) was loaded in one lane of two gels (Figs. 1 and 4) to verify the identification of the MHC bands. Assuming ~20% of tissue mass is protein, these loads corresponded to 2–3 μg of protein. Stacking gels contained 4% total acrylamide and 5% (vol/vol) glycerol. Separating gels contained 6% or 8% total acrylamide and 5% (wt/vol) glycerol. Gels were run for 19 h (6% gels) or 30 h (8% gels). All of the adult samples were run on an initial set of gels, which were stained with GelCode Blue Stain Reagent (Pierce; Rockford, IL). The gels were scanned with a GS3000 scanning densitometer (Hoefer Scientific; San Francisco, CA) to determine the relative amounts of MHC-α and MHC-β in those samples in which both bands were visible on the stained gels. The results from these gels suggested that the relative level of MHC-α was below detection in the majority of the ventricular samples. A subsequent set of gels, on which all of the adult ventricular and all of the fetal samples were run, were silver stained. The results from
this set of gels revealed that MHC-α was present in the majority of adult ventricular samples. The reported values of the relative amounts of MHC-α in all of the fetal samples and all of the adult ventricular samples were determined on silver-stained gels. The percentage of total MHC in a sample that was expressed as the α-isoform (or the β-isoform) is referred to as “the relative amount of MHC-α (or MHC-β).” The linearity of densitometric scanning of the stained gels was tested by loading onto one gel several volumes, ranging from 1 to 12 μl, of a sample that contained nearly equal amounts of MHC-α and MHC-β. The linear correlation coefficients between densitometric peak area and sample volume were 0.955 for MHC-α and 0.943 for MHC-β.

Statistical analysis. Analysis of variance was conducted separately on the atrial samples (fetal right and left atria and nonfailing left atria and failing left atria) and the ventricular samples (fetal and nonfailing and failing adult right and left ventricles). Both analyses indicated that significant differences exist among the sets of atrial samples and among the sets of ventricular samples. Student’s two-tailed t-test was employed to test whether the means of two atrial sets differed significantly. Fisher’s exact test was used for the ventricles because many of the individual values for the failing right and left ventricles were 0% MHC-α. The level of significance was set at \( P < 0.05 \). The results obtained from the samples prepared from two fetal hearts (gestational ages 47 and 54 days) were not included in the calculation of mean values or in the statistical analyses because right and left chambers could not be distinguished from each other during sample preparation. The ventricular samples from the 47- and 54-day-old fetuses were included when testing, with linear regression, whether there is a significant change in ventricular myosin expression during fetal development. Results are expressed as an individual value, range, or means ± SE.

RESULTS

Representative gels on which fetal and adult atrial and ventricular samples were analyzed are shown in Figs. 1, 3, and 5. The mean relative amounts of MHC-α in all of the fetal and adult samples are presented in Table 1.

Fetal atria. MHC-α was the predominant isoform in fetal right and left atria (Fig. 1). The relative levels of MHC-α in the atrial samples from the 47- and 54-day-old fetuses (right and left atrial samples from these fetuses were not distinguished from each other, see METHODS) were 96 and 97%, respectively. There was no change in the pattern of MHC isoform expression within the fetal atria over the gestational age range included in this study as tested with linear regression (\( P > 0.05 \)).

Fetal ventricles. MHC-β predominated in fetal right and left ventricles (Fig. 1). The relative levels of MHC-β in the ventricular samples from the 47- and 54-day-old fetuses were 93 and 90%, respectively. Two papillary muscles isolated from two fetal left ventricles contained 98 and 100% MHC-β. All of the fetal right ventricular samples contained low levels of MHC-α. Seven of ten fetal left ventricles contained low levels of MHC-α, whereas this isoform was not detected in the remaining three fetal left ventricular samples. When analyzed separately, neither the right nor left ventricle underwent a significant change in the level of MHC-α expression between gestational days 82–110. However, a significant decline with increasing fetal age in the relative amount of MHC-α in the ventricular samples was detected when the relative MHC-α values from all (\( n = 22 \)) of the ventricular samples, including those from the 47- and 54-day-old fetuses, were regressed linearly against gestational age (Fig. 2).

Nonfailing adult atria. Relatively large amounts of MHC-α were detected in all of the nonfailing adult left atrial samples. The mean relative amount of MHC-α in the adult nonfailing left atrial samples was not different from those in fetal right or left atria.

Failing adult atria. The mean relative amounts of MHC-β in the ischemic cardiomyopathic left atria and in the dilated cardiomyopathic left atria were significantly higher than the nonfailing left atrial value (Fig. 3 and 4). The variation in the amount of MHC-β in the failing adult left atria was not correlated (\( P > 0.05 \)) with age when tested with linear regression. Furthermore, the amount of MHC-β in the failing left atria was not correlated with ejection fraction, heart weight, drug therapy, or the presence or absence of previous surgery among the patients included in this study. Four of five female cardiomyopathic left atria had relatively high levels of MHC-β (i.e., low levels of MHC-α; Table 2); however, a gender difference was not statis-

Table 1. Summary of MHC-α composition of all samples

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>LA</th>
<th>RV</th>
<th>LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal</td>
<td>92 ± 3 (84–100)</td>
<td>95 ± 3 (76–100)</td>
<td>4 ± 0.6 (1–8)</td>
<td>2.8 ± 1.4 (0–15)</td>
</tr>
<tr>
<td>Nonfailing adult</td>
<td>86 ± 3 (71–100)</td>
<td>5 ± 0.8 (0–10)</td>
<td>2.5 ± 0.7 (0–6)</td>
<td></td>
</tr>
<tr>
<td>DCM adult</td>
<td>48 ± 5* (24–73)</td>
<td>1.8 ± 1.3+ (0–15)</td>
<td>0.3 ± 0.2a (0–2)</td>
<td></td>
</tr>
<tr>
<td>ICM adult</td>
<td>50 ± 7* (7–87)</td>
<td>1.1 ± 0.6+ (0–5)</td>
<td>1.3 ± 0.5+ (0–2)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. The values represent the relative amount of myosin heavy chain (MHC-α) as a percentage of total MHC; value in parentheses are the range. Values for the right (RV) and left ventricles (LV) do not include the results obtained from the 47- and 54-day-old fetuses in which the 2 ventricles could not be distinguished from each other. RA, right atrium; LA, left atrium; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy. *Significantly different from nonfailing adult, \( P < 0.05 \). †Significantly different from fetal RV, \( P < 0.05 \).
tically evaluated due to the relatively small number of samples from adult females in this study.

**Nonfailing adult ventricles.** The nonfailing adult right and left ventricular samples also contained predominantly MHC-β (Fig. 5 and Table 3). The majority (20 of 24) of nonfailing right and left ventricles were not distinguished from each other. Values obtained from the right and left, respectively, ventricles from other fetuses. The slope of the linear fit between all of the values and gestational age is significantly different from zero ($P < 0.04$). The correlation coefficient between all of the MHC-α values and age is 0.44.

**Failing adult ventricles.** The failing adult right and left ventricular samples contained predominantly MHC-β (Table 2). Only 7 of 24 failing (dilated and ischemic cardiomyopathic samples combined) right ventricles and 8 of 24 failing left ventricles had detectable levels of MHC-α. The differences between the adult nonfailing and failing right ventricle and between the adult nonfailing and failing left ventricle were significant. The cardiomyopathic right ventricles differed significantly from the fetal ventricles by expressing lower levels of MHC-α, but the cardiomyopathic adult left ventricles were not different from fetal left ventricle ($P = 0.054$).

**DISCUSSION**

Cardiac MHC isoform expression was examined at the protein level utilizing a recently described gel electrophoresis protocol (24). The results indicate that MHC-α predominates in fetal and nonfailing adult atria with coexpression of low levels of MHC-β, while the opposite pattern, with MHC-β predominating, exists in fetal and nonfailing and failing adult ventricles. The quantitative results obtained in this study are, overall, very consistent with the qualitative immunohistochemical results of Wessels et al. (31) and the electrophoretic results of Cummins and Lambert (5), two earlier studies focusing exclusively on nonfailing hearts. The SDS gel format has several advantages over the pyrophosphate gels that have been utilized by others to examine the hexameric myosin isoenzyme composition of human cardiac samples. First, it allows the comparison of multiple samples from several individuals on a single gel, thereby eliminating differences in running conditions and gel staining. Second, it provides a direct examination of, specifically, the heavy chain portion of myosin isoenzymes that is the myosin subunit with the most critical role in determining the rate of myosin ATPase activity and, therefore, cross-bridge cycling kinetics. A direct examination of MHC expression at the protein level, as in the present study, has an additional advantage over other studies that must draw inferences from mRNA levels, because mRNA levels do not necessarily reflect actual protein isoform composition. Quantitative differences in the relative amount of MHC-α were observed between different heart chambers (atrium vs. ventricle). Furthermore, large ranges in the relative amount of MHC-α in the left atrium of adults with either dilated or ischemic cardiomyopathy were detected.

This study also provides quantitative information on human cardiac myosin isoform expression over a period of fetal development that represents ~25% of the

![Fig. 2](image_url)
total normal gestational period. Although the observations of fetal hearts were confined to gestational days 47–110, the results indicate that over this period of development, there is no change in atrial MHC expression, whereas the relative level of MHC-α in the ventricles decreased with increasing gestational age. Furthermore, it appears that the adult level of MHC-α is established by approximately week 12 of fetal development and does not change subsequently.

The results of this study indicate that the level of expression of MHC-α is very low in fetal and adult human left and right ventricles, both nonfailing as well as ischemic and dilated cardiomyopathic. Cummins and Lambert (5) reported that MHC-β was the only MHC isoform expressed in the human ventricle at fetal, neonatal, and adult ages. The small level of MHC-α in human fetal and adult ventricles in the present study was detected with more sensitive gel stains (see METHODS) compared with the stain employed by Cummins and Lambert (5). The decrease in adult human ventricular contractility during failure (7, 8, 21) cannot, therefore, be attributed to a shift in the expression of MHC isoforms, consistent with the conclusion of Mercadier et al. (18). Hirzel et al. (9) also reported that the ventricular MHC content was not different between normal and cardiomyopathic patients.

A low level of MHC-α was detected in fetal right and left ventricles, which is in contrast to an earlier immunohistochemical study (29) in which this isoform was not detected in fetal human ventricles. The discrepancy is likely due to differences in sensitivity between the techniques employed in the present and previous studies.

Miyata et al. (19), with the use of the electrophoretic technique described by Reiser and Kline (24), reported that MHC-α is minimally expressed in the adult nonfailing ventricular myocardium. They suggested that the MHC-β band on silver-stained gels can obscure faint MHC-α bands. However, gels from our study (Figs. 1 and 2) demonstrated high resolution and clear separation of both the MHC-α and MHC-β bands when even minimal MHC-α expression is apparent. Thus the absence of MHC-α expression in the adult nonfailing and failing myocardium as well as in the fetal left ventricular myocardium was not due to technical limitations in this electrophoretic technique. The small differences between our study and the study by Miyata et al. (19), e.g., 2.5 versus 7% MHC-α in nonfailing left ventricles, might be due to technical differences involved in separation of these bands. Regardless, both studies show low levels of MHC-α expression in failing ventricles and extremely low expression in nonfailing ventricles.
The low level of MHC-α, or V1 myosin isoenzyme (12), protein in the adult human ventricle is consistent with the results of the majority of previous studies in which human ventricular MHC isoform composition has been examined with a variety of experimental approaches (e.g., Refs. 3, 10, and 29). Therefore, an option to increase the relative amount of MHC-β in adult human ventricles, which is near 100% normally, does not exist. This could otherwise result in a presumably slower than normal and a more economical mode of contraction during the progression to heart failure, as is observed in experimentally induced failure in smaller mammals (e.g., Refs. 4 and 28).

The results from several laboratories (reviewed in Ref. 25) have shown that increases in cardiac work load in several animal models (especially small mammals; e.g., Ref. 6) are associated with reexpression of a fetal gene program coding for growth factors, sarcomeric proteins, and products of protooncogenes in the hypertrophied heart. The results of the present study clearly indicate that the fetal pattern of MHC isoform expression in human ventricles is very similar to the adult pattern and that marked changes do not occur during the progression to failure, at least in individuals with dilated or ischemic cardiomyopathy. Furthermore, we conclude that there is no distinct “fetal pattern” of MHC isoform expression in the left atrium because no difference was detected between fetal and adult non-failing left atria. Thus the MHC isoform expression pattern in the left atrium of the failing myocardium is distinctive and does not recapitulate the fetal/non-failing pattern.

The results also indicate that there is a much higher level of MHC-α protein in the left atrium than the ventricles, consistent with the long recognized relatively greater level of V1 myosin isoenzyme in normal atria compared with ventricles (3). The results indicate that the relative level of MHC-α in the atria is not significantly different between fetal and adult ages. Cummins and Lambert (5) reported that the mean level of MHC-α in human fetal atria is less than one-half of that in adult atria, but whether the difference was statistically significant was not stated. The present results indicate that level of atrial MHC-α is significantly lower and to a similar extent in individuals with either dilated or ischemic cardiomyopathy. The relative amount of left atrial MHC-α also decreases during canine rapid pacing-induced heart failure (13). The results do not show whether the level of MHC-α in the left atrium decreases during cardiomyopathy (as an adaptive response) or is initially lower in those individuals that develop cardiomyopathy (as a factor that contributes to heart failure). An increase in the relative amount of MHC-β of the left atrium during the development of heart failure could be beneficial by increasing the economy of contraction (14). This could be especially important if the left atrium has a greater role in facilitating diastolic filling of the left ventricle in an effort to increase stroke volume and cardiac output. Alternatively, a lower level of MHC-α in the left atrium, as an antecedent to failure, is expected to result in a slower rate of atrial contraction, which in turn could lead to a slower rate of ventricular diastolic filling. This, in turn, could result in a smaller stroke volume and reduced cardiac output. The increase in the relative amount of left atrial MHC-β during cardiomyopathy is consistent with a reported greater atrial systolic function (work load) during heart failure in humans (16, 17) and in a canine model (13).

In conclusion, MHC-α is expressed at very low levels in fetal and adult human right and left ventricles, and small but significant changes in ventricular MHC isoform protein expression occur during adult human dilated and ischemic cardiomyopathies. Furthermore, there is a significantly greater relative amount of MHC-β in the adult human cardiomyopathic left atrium, which could have marked consequences on myocardial contraction and disease progression. Finally, MHC isoform expression in the atria and ventricles of the human fetus does not comprise a unique fetal pattern.

### Table 3. Characteristics of the nonfailing patient population

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Sex</th>
<th>%MHC-α in LA</th>
<th>%MHC-α in RV</th>
<th>%MHC-α in LV</th>
<th>Cause of Death</th>
<th>Drugs</th>
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<tr>
<td>1</td>
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<td>N/A</td>
<td>N/A</td>
<td>MI</td>
<td>N/A</td>
</tr>
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</table>

Drugs include those that the patient was given in the emergency room or intensive care unit before death. CVA, cerebrovascular accident; GSW, gun shot wound; MVA, motor vehicle accident; MI, myocardial infarct; LB, labetol; LP, levophed; NF, nifedipine; NM, nimodipine; NS, neosynephrine; PT, pitressin; T4, thyroxine.
REFERENCES


