Familial hypertrophic cardiomyopathy (FHC) is inherited as an autosomal dominant trait that is characterized by myocardial hypertrophy in the absence of identifiable precipitating hemodynamic factors.1,2 The diagnostic hallmark of FHC is asymmetric hypertrophy of the interventricular septum; however, the distribution and severity of hypertrophy are variable.3,4 Affected individuals may present with symptoms ranging from dizziness and palpitations to sudden death. Molecular genetic studies have demonstrated that FHC is genetically heterogeneous; 10 disease genes have been identified.2,5 All 10 of these genes encode sarcomere proteins expressed in cardiac muscle. We and others have demonstrated that individuals bearing some sarcomere protein gene mutations have better prognoses than individuals bearing other mutations,6–8 but the basis for this correlation has not been elucidated.

To further investigate factors determining the clinical response to a sarcomere protein gene mutation, we have created two strains of mice, using homologous recombination in embryonic stem cells that bear precise analogues of FHC-causing mutations. Individuals bearing the β-cardiac myosin heavy chain (MHC) gene Arg403Gln missense mutation have an earlier disease onset and a shorter life expectancy than individuals bearing mutations in the cardiac myosin binding protein C (MyBP-C) gene.7,8 Transgenic mice expressing cDNAs encoding mutant forms of both MyBP-C and MHC 403/ were constructed as murine FHC models using homologous recombination in embryonic stem cells. We have compared cardiac structure and function of these mouse strains by several methods to further define mechanisms that determine the severity of FHC. Both strains demonstrated progressive left ventricular (LV) hypertrophy; however, by age 30 weeks, αMHC403/ mice demonstrated considerably more LV hypertrophy than MyBP-C(-/ mice. In older heterozygous mice, hypertrophy continued to be more severe in the αMHC403/ mice than in the MyBP-C(-/ mice. Consistent with this finding, hearts from 50-week-old αMHC403/ mice demonstrated increased expression of molecular markers of cardiac hypertrophy, but MyBP-C(-/ hearts did not demonstrate expression of these molecular markers until the mice were >125 weeks old. Electrophysiological evaluation indicated that MyBP-C(-/ mice are not as likely to have inducible ventricular tachycardia as αMHC403/ mice. In addition, cardiac function of αMHC403/ mice is significantly impaired before the development of LV hypertrophy, whereas cardiac function of MyBP-C(-/ mice is not impaired even after the development of cardiac hypertrophy. Because these murine FHC models mimic their human counterparts, we propose that similar murine models will be useful for predicting the clinical consequences of other FHC-causing mutations. These data suggest that both electrophysiological and cardiac function studies may enable more definitive risk stratification in FHC patients. (Circ Res. 2001;88:383-389.)

Key Words: cardiomyopathy • hypertrophy • genetics • myosin • cardiac myosin binding protein C
and MHC have been produced previously. These mice are of limited value for directly comparing the consequences of FHC-causing mutations because the amount and temporal pattern of mutant cDNA expression, even when controlled by a cardiac specific promoter, varies even between different strains of mice bearing the same mutant transgene. We have previously created a mouse bearing the Arg403Gln mutation in one allele of the α-cardiac MHC gene, the murine analogue of the human β-cardiac MHC gene. Heterozygous Arg403Gln α-cardiac MHC (αMHC<sup>403Gln</sup>) mutant mice have been shown to develop physiological and histological features typical of human FHC. Recently, we created a strain of mice bearing a neomycin resistance gene inserted in the cardiac MyBP-C gene. This mutant allele encodes a truncated MyBP-C protein that closely resembles the truncated MyBP-C protein that causes FHC in some individuals (Family NN in Figure 1A and Reference 14); heterozygous mice bearing the mutant allele were designated MyBP-C<sup>t</sup>/<sup>t</sup> mice. Although we have previously demonstrated that both homoyzogous αMHC<sup>403Gln</sup> and MyBP-C<sup>t</sup>/<sup>t</sup> mice produce mutant polypeptides and develop dilated cardiomyopathy, the cardiac phenotype of older heterozygous mice bearing these mutations has not been compared.

We have characterized cardiac structure and function of αMHC<sup>403Gln</sup> and MyBP-C<sup>t</sup>/<sup>t</sup> mice at several ages to define the development of hypertrophic cardiomyopathy in these mice. We demonstrate in the present study that both mutations cause cardiac hypertrophy. However, αMHC<sup>403Gln</sup> mice develop hypertrophy much earlier than MyBP-C<sup>t</sup>/<sup>t</sup> mice consistent with the pathologies observed in humans bearing these mutations. In addition, we demonstrate that hearts bearing truncated MyBP-C polypeptide have normal cardiac function and do not demonstrate inducible ventricular tachycardia whereas age-matched hearts bearing α-cardiac MHC Arg403Gln missense polypeptide have significant deficits in cardiac and electrophysiological function. We speculate that deficits in cardiac function, rather than increased cardiac hypertrophy, are responsible for the more severe symptoms observed in individuals with the Arg403Gln missense mutation.

### Materials and Methods

#### Animals

Mice bearing the MyBP-C<sup>(Neo)</sup> allele were generated using homologous recombination techniques and a targeting construct containing exons 28 to 32 of the murine cardiac MyBP-C gene with a 2-kb neomycin gene insertion in exon 30 as described. Heterozygous mice bearing the MyBP-C<sup>(Neo)</sup> allele are designated MyBP-C<sup>t</sup>/<sup>t</sup>. The structure of mutant-derived MyBP-C-RNA was defined by reverse transcription–polymerase chain reaction (RT-PCR) amplification and DNA sequencing of RNA derived from homozygous mice bearing the mutant allele were designated MyBP-C<sup>t</sup>/<sup>t</sup> mice. Although we have previously demonstrated that both homoyzogous αMHC<sup>403Gln</sup> and MyBP-C<sup>t</sup>/<sup>t</sup> mice produce mutant polypeptides and develop dilated cardiomyopathy, the cardiac phenotype of older heterozygous mice bearing these mutations has not been compared.

We have characterized cardiac structure and function of αMHC<sup>403Gln</sup> and MyBP-C<sup>t</sup>/<sup>t</sup> mice at several ages to define the development of hypertrophic cardiomyopathy in these mice. We demonstrate in the present study that both mutations cause cardiac hypertrophy. However, αMHC<sup>403Gln</sup> mice develop hypertrophy much earlier than MyBP-C<sup>t</sup>/<sup>t</sup> mice consistent with the pathologies observed in humans bearing these mutations. In addition, we demonstrate that hearts bearing truncated MyBP-C polypeptide have normal cardiac function and do not demonstrate inducible ventricular tachycardia whereas age-matched hearts bearing α-cardiac MHC Arg403Gln missense polypeptide have significant deficits in cardiac and electrophysiological function. We speculate that deficits in cardiac function, rather than increased cardiac hypertrophy, are responsible for the more severe symptoms observed in individuals with the Arg403Gln missense mutation.

#### Cardiac Physiology and Pathology

Cardiac tissues from male mice were subjected to histological examination using methods described previously. A single experienced pathologist who was unaware of the mouse genotype reviewed all histological specimens.

Echocardiographic studies were performed on male mice using a 12-MHz linear array probe with a Sonos 5500 ultrasonograph (Hewlett-Packard) as described. Left ventricular (LV) end-diastolic and end-systolic (LVDD) chamber dimensions and wall thickness were obtained from M-mode tracings using measurements averaged from 3 separate cardiac cycles. LV fractional shortening (%) was derived as follows: (LVDD – LVDD)/LVDD X 100. A single observer, who did not know the mouse’s genotype, made all echocardiographic measurements. Heart rates were determined from electrocardiographic recordings performed during echocardiography.

LV hemodynamic studies were performed in male mice as described previously. In brief, anesthetized mice were intubated, artificially ventilated, and real-time LV pressure-volume relationships were measured using a newly developed miniaturized impedance/micromanometer catheter (Millar Instruments). Aortic flow was measured using an ultrasound perivascular probe (Transonic, 1RB) placed around the thoracic aorta. Pressure-volume signals were recorded at steady state and during transient reduction of cardiac preload achieved by inferior vena cava occlusion. Data were digitized at 2 kHz for subsequent analysis.

Surface resting electrocardiograms and electrophysiological studies were performed in anesthetized male wild-type and αMHC<sup>403Gln</sup> mice as described. Standard procedures for pacing and extra-stimulus testing were used to assess baseline conduction parameters and arrhythmia induction. The PR, QRS, RR, and QT intervals were measured in 6 surface limb ECG leads by two independent observers who were blinded to mouse genotype. Inducible ventricular tachycardia was assessed as described previously.

#### RNA and Protein Analyses

Northern blot analyses were performed as described previously. Total RNA was isolated from the left ventricle using Trizol (Gibco BRL) and analyzed by standard Northern blot procedures. MyBP-C RNA was detected using 32P-labeled insert from a 2.9-kb mouse MyBP-C cDNA plasmid clone designated pMyBPC. The MyBP-C cDNA probe consisted of a 1584-bp segment encoding amino acid residues 582 to 1110. Other RNAs were detected using 32P-labeled oligonucleotide probes and hybridized to nylon membranes using standard hybridization conditions. The oligonucleotides used as transcript specific probes were as follows: atrial natriuretic factor: 5′-AATGGCAAGTCGGGACACCAAAAGGCTAGATTGGAC-3′; brain natriuretic factor: 5′-CAGCTGAGATATGCTGCTGTGC-3′; α-skeletal actin: 5′-TGCTTAACTGCTCAAGTTTTCATTTTCCCAATTTCCCATTTCCACAG-GG-3′; GAPDH: 5′-GGACCATGAGACTCATCCATTGAGGTCAC-3′.

The hybridization signal for each oligonucleotide probe was quantified using ImageQuant software (Molecular Dynamics) and normalized to the signal intensity observed with an oligonucleotide specific for GAPDH RNA. MyBP-C polypeptides were identified by Western blot analyses using antibody raised against chicken cardiac MyBP-C.

#### Statistical Analysis

The statistical significance of differences between groups of wild-type, MyBP-C<sup>t</sup>/<sup>t</sup>, and αMHC<sup>403Gln</sup> mice in continuous variables was determined by one-factor ANOVA and the unpaired Student’s t test. Differences in categorical variables were assessed with the χ<sup>2</sup> test. Data are expressed as mean±SD. A value of P<0.05 was considered significant.
Results

Expression and Structure of RNAs and Proteins Expressed in MyBP-C<sup>C<sup>C<sup>++</sup></sup> and αMHC<sup>403<sup>+/−</sup></sup> Hearts

MyBP-C mRNA expressed from the MyBP-C(Neo) allele was characterized by Northern blot analyses of heterozygous MyBP-C<sup>C<sup>++</sup></sup> cardiac RNA (Figures 1A and 1B). The 4.5-kb MyBP-C RNA transcript was found in the left ventricle of both wild-type and MyBP-C<sup>C<sup>++</sup></sup> mice; however, MyBP-C mRNA expression in MyBP-C<sup>C<sup>++</sup></sup> mice (n = 6) was 49.2 ± 16.6% the level of expression in wild-type mice (n = 6).

MyBP-C (150 kDa) protein was identified in myofibrillar extracts from cardiac left ventricles of wild-type and MyBP-C<sup>C<sup>++</sup></sup> mice. MyBP-C (mutant and wild type) protein expression in MyBP-C<sup>C<sup>++</sup></sup> left ventricles (n = 4) was 89.9 ± 8.5% the level found in wild-type left ventricles. Because the mutant MyBP-C(Neo) allele produces a reduced amount (10% of wild type) of truncated MyBP-C peptide, we hypothesize that the heterozygous MyBP-C<sup>C<sup>++</sup></sup> hearts contain ~90% wild-type MyBP-C and 10% truncated peptide.

Myocardial Histopathology

Previous studies demonstrated that hearts from 15-week-old αMHC<sup>403<sup>+/−</sup></sup> mouse hearts have mild myocyte hypertrophy, interstitial fibrosis, and myofibrillar disarray that become much more severe by 30 to 50 weeks of age. No histological abnormalities were observed in 50-week-old MyBP-C<sup>C<sup>++</sup></sup> mouse hearts. Histological sections obtained from >125-week-old MyBP-C<sup>C<sup>++</sup></sup> mouse hearts demonstrated myocyte hypertrophy, interstitial fibrosis, and myofibrillar disarray in ~50% of mutant animals. However, similar histological abnormalities were observed in a comparable proportion of hearts from age-matched wild-type mice (Figure 2 and data not shown).

Cardiac Morphology of Mutant and Wild-Type Mice

Cardiac hypertrophy in mutant and wild-type mice was assessed using transthoracic echocardiography (Table 1). Neither 10- to 20-week-old male MyBP-C<sup>C<sup>++</sup></sup> or αMHC<sup>403<sup>+/−</sup></sup> hearts contain similar amounts of disarray, fibrosis, and hypertrophy.
TABLE 1. Echocardiographic Characteristics of Wild-Type, MyBP-C<sup>−/−</sup>, and αMHC<sup>403/+</sup> Mice Aged 10 to 20, 30 to 50, and >125 Weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10–20-Week-Old Mice</th>
<th>30–50-Week-Old Mice</th>
<th>&gt;125-Week-Old Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+/+</td>
<td>MyBP-C&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>αMHC&lt;sup&gt;403/+&lt;/sup&gt;</td>
</tr>
<tr>
<td>No. studied</td>
<td>4</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>BW, g</td>
<td>26.9±2.5</td>
<td>30.7±7.0</td>
<td>27.2±3.2</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>439±20</td>
<td>448±67</td>
<td>411±41</td>
</tr>
<tr>
<td>LVAW, mm</td>
<td>0.87±0.10</td>
<td>0.91±0.05</td>
<td>0.91±0.07</td>
</tr>
<tr>
<td>LVPW, mm</td>
<td>0.87±0.08</td>
<td>0.89±0.06</td>
<td>0.89±0.08</td>
</tr>
<tr>
<td>LVDD, mm</td>
<td>2.88±0.09</td>
<td>2.66±0.32</td>
<td>2.89±0.09</td>
</tr>
<tr>
<td>LVSD, mm</td>
<td>1.44±0.06</td>
<td>1.51±0.35</td>
<td>1.32±0.13</td>
</tr>
<tr>
<td>LVFS, %</td>
<td>49±2</td>
<td>44±8#</td>
<td>54±5*</td>
</tr>
<tr>
<td>LA, mm</td>
<td>1.51±0.01</td>
<td>1.58±0.06*</td>
<td>1.55±0.02*</td>
</tr>
</tbody>
</table>

LVAW indicates left ventricular anterior wall thickness; LVDD, left ventricular end-diastolic diameter; LVFS, left ventricular fractional shortening; LVPW, left ventricular posterior wall thickness; LVSD, left ventricular systolic diameter; LA, left atrium; and HR, heart rate.

*Significant difference (P<0.05) compared with wild-type (+/+); †significant difference (P<0.05) between MyBP-C<sup>−/−</sup> and αMHC<sup>403/+</sup> mice.

Figure 3. LVAW of age-matched MyBP-C<sup>−/−</sup> and αMHC<sup>403/+</sup> mice. Wall thickness was evaluated in wild-type, MyBP-C<sup>−/−</sup>, and αMHC<sup>403/+</sup> mice at 10 to 20 and 30 to 50 weeks of age and wild-type and MyBP-C<sup>−/−</sup> mice at >125 weeks of age using transthoracic echocardiography. LVAW >1.0 mm, in mice 10 to 50 weeks of age, is considered to be hypertrophied. ○, Wild-type mice; ●, αMHC<sup>403/+</sup> mice; and □, MyBP-C<sup>−/−</sup> mice.

mouse hearts demonstrated significant differences from age-matched wild-type mouse hearts (Table 1). By 30 to 50 weeks, both MyBP-C<sup>−/−</sup> and αMHC<sup>403/+</sup> mice were beginning to demonstrate signs of their mutations. MyBP-C<sup>−/−</sup> mice displayed significantly enlarged atria and a slight increase in LV wall thickness compared with wild-type mice (0.96±0.08 versus 0.87±0.05 mm; P<0.05). However, αMHC<sup>403/+</sup> mice demonstrated significantly increased left atrial dimensions and much greater LV wall thickness than either MyBP-C<sup>−/−</sup> or wild-type mice (compare left ventricular anterior wall thickness [LVAW] of αMHC<sup>403/+</sup> mice, 1.12±0.07 mm versus LVAW of wild-type, 0.87±0.06 mm, and MyBP-C<sup>−/−</sup>, 0.96±0.08 mm, mice; P<0.05; Table 1). In addition, only 32% (6 of 19) of the MyBP-C<sup>−/−</sup> mice had developed cardiac hypertrophy (>1.0 mm) by 50 weeks of age (Figure 3) compared with 92% (11 of 12) αMHC<sup>403/+</sup> mice. However, LVAW of >125-week-old MyBP-C<sup>−/−</sup> mice was significantly greater than age-matched wild-type mice (1.39±0.10 versus 1.08±0.05 mm, P<0.001; Table 1), demonstrating that cardiac hypertrophy is late onset in heterozygous MyBP-C mutant mice. The fractional shortening was not significantly different in MyBP-C<sup>−/−</sup> mice (55±4%) compared with age-matched wild-type mice (52±5%) at >125 weeks. Heart rates during echocardiographic studies were similar in all groups of mice (Table 1 and data not shown). (The different heart rates of age- and strain-matched mice reported in Tables 1 and 2 are due to differences in anesthesia used in different studies.)

LV Pressure-Volume Analyses

Previous studies have demonstrated that 8- to 20-week-old αMHC<sup>403/+</sup> mice have impaired cardiac function compared with age-matched wild-type mice.12 We demonstrate in the present study that 30- to 50-week-old αMHC<sup>403/+</sup> mice, like 20-week-old αMHC<sup>403/+</sup> mice, exhibited altered LV diastolic kinetics with delayed pressure relaxation and chamber filling (Table 2). Thirty to 50-week-old αMHC<sup>403/+</sup> mice also had altered elevated LV systolic pressure (Table 2).

Cardiac function of wild-type and MyBP-C<sup>−/−</sup> mice at 30 to 50 weeks and >125 weeks were assessed by in vivo cardiac catheterization (Figure 4). Thirty to 50-week-old MyBP-C<sup>−/−</sup> mice had normal systolic and diastolic LV function when compared with age-matched wild-type mice (Table 2 and data not shown). Similarly, cardiac function of >125-week-old MyBP-C<sup>−/−</sup> mice was indistinguishable from that of age-matched wild-type mice but significantly better than cardiac function of 30- to 50-week-old αMHC<sup>403/+</sup> mice (Figure 4, Table 2, and data not shown).

Electrophysiology

Baseline recordings in 30- to >125-week-old MyBP-C<sup>−/−</sup> mice showed the same electrocardiographic interval conduction times and axes as observed in age-matched wild-type mice (data not shown). Neither MyBP-C<sup>−/−</sup> nor αMHC<sup>403/+</sup> mice exhibited PR prolongation, AV block, or abnormally long atrioventricular conduction block coupling intervals. Normal atrial and ventricular conduction parameters and refractory periods were also demonstrated in both strains of mice (data not shown and Reference 20). Using a standard murine pacing and programmed electrical stimulation protocol,15,18,19 inducible arrhythmias were elicited in significantly more (8 of 15) 30- to 50-week-old αMHC<sup>403/+</sup> mice than...
Figure 4. LV pressure-volume relations and the first derivative of ventricular pressure (dP/dt) in 125-week wild-type (A and D), 125-week MyBP-C<sup>C<sup>+</sup></sup> mice (B and E), and αMHC<sup>403</sup>/+ mice (C and F) aged 30 to 50 weeks.

age-matched wild-type (0 of 10) or MyBP-C<sup>C<sup>+</sup></sup> (1 of 9) mice. Similar proportions of >125-week-old MyBP-C<sup>C<sup>+</sup></sup> (2 of 6) and wild-type (2 of 4) mice demonstrated inducible arrhythmias.

RNA Expression Associated With Cardiomyopathy

Atrial natriuretic factor, brain natriuretic factor, and α-skeletal actin mRNAs, which are induced in other models of cardiac hypertrophy, were measured in mutant mice at 10 to 20, 30 to 50, and >125 weeks of age by Northern blot analyses. The amounts of atrial natriuretic factor, brain natriuretic factor, and α-skeletal actin RNA transcripts in 10- to 20-week-old αMHC<sup>403</sup>/+ and MyBP-C<sup>C<sup>+</sup></sup> hearts were the same as in age-matched wild-type hearts (data not shown). However, by 50 weeks, αMHC<sup>403</sup>/+ left ventricles demonstrated increases in atrial natriuretic factor (4.9±1.0-fold), brain natriuretic factor (2.5±0.3-fold), and α-skeletal actin (1.9±0.2-fold) RNAs compared with 50-week-old wild-type left ventricles (Figure 5). Left ventricles from 50-week-old MyBP-C<sup>C<sup>+</sup></sup> mice had the same amounts of these RNAs as left ventricles from age-matched wild-type mice. However, left ventricles of >125-week-old MyBP-C<sup>C<sup>+</sup></sup> mice demonstrated significant increases in atrial natriuretic factor (3.1±0.4-fold), brain natriuretic factor (2.3±0.2-fold), and α-skeletal actin (3.3±0.7-fold) RNAs compared with left ventricles from age-matched wild-type hearts (Figure 5).

Discussion

We demonstrate that both αMHC<sup>403</sup>/+ and MyBP-C<sup>C<sup>+</sup></sup> mice, two strains of mice bearing different FHC-causing mutations, develop LV hypertrophy, but age-matched αMHC<sup>403</sup>/+ mice have much more LV hypertrophy than MyBP-C<sup>C<sup>+</sup></sup> mice. Mice bearing the Arg403Gln missense mutation in the α-cardiac MHC gene have impaired cardiac function (Figure 4 and References 11 and 12) and some have electrophysiological abnormalities. However, no difference in cardiac function of mice expressing the truncated cardiac MyBP-C gene and wild-type mice was detected (Figure 4 and Table 2) and neither demonstrated inducible arrhythmias. These observations may explain the different clinical features observed in humans bearing different sarcomere protein gene mutations. Although the mechanisms by which these mutations cause hypertrophy remain uncertain, some insights into this process can be gained by considering the effects of these different mutations on cardiac function and LV morphology.

Both heterozygous αMHC<sup>403</sup>/+ and MyBP-C<sup>C<sup>+</sup></sup> mice develop LV hypertrophy, whereas homozygous αMHC<sup>403</sup>/+ and

<p>| TABLE 2. Left Ventricular Function of Wild-Type, MyBP-C&lt;sup&gt;C&lt;sup&gt;+&lt;/sup&gt;&lt;/sup&gt;, and αMHC&lt;sup&gt;403&lt;/sup&gt;/+ Mice Aged 30 to 50 Weeks and Wild-Type and MyBP-C&lt;sup&gt;C&lt;sup&gt;+&lt;/sup&gt;&lt;/sup&gt; Mice Aged &gt;125 Weeks |</p>
<table>
<thead>
<tr>
<th>Genotype</th>
<th>30–50 Weeks</th>
<th>&gt;125 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of mice</td>
<td>+/+</td>
<td>MyBP-C&lt;sup&gt;C&lt;sup&gt;+&lt;/sup&gt;&lt;/sup&gt;</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>621±65</td>
<td>652±83</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>4.38±2.39</td>
<td>3.75±1.07</td>
</tr>
<tr>
<td>LVEDV (arbitrary unit)</td>
<td>24.10±7.75</td>
<td>22.71±6.27</td>
</tr>
<tr>
<td>Stroke volume, μL</td>
<td>14.32±7.12</td>
<td>15.40±1.50</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>58±14</td>
<td>72±20</td>
</tr>
<tr>
<td>Cardiac output, mL/min</td>
<td>8.91±4.82</td>
<td>9.51±2.38</td>
</tr>
<tr>
<td>dP/dt&lt;sub&gt;max&lt;/sub&gt;, mm Hg/s</td>
<td>1285±4749</td>
<td>15416±3651</td>
</tr>
<tr>
<td>dP/dt&lt;sub&gt;min&lt;/sub&gt;, mm Hg/s</td>
<td>−11.673±3155</td>
<td>−15.947±2430</td>
</tr>
<tr>
<td>dP/dt ratio (maximum/minimum)</td>
<td>1.06±0.28</td>
<td>1.02±0.26</td>
</tr>
<tr>
<td>Stroke work, mm Hg</td>
<td>1575±852</td>
<td>2073±371</td>
</tr>
<tr>
<td>Time to peak filling, ms</td>
<td>28.22±7.62</td>
<td>31.75±5.95</td>
</tr>
<tr>
<td>τ, ms</td>
<td>4.97±1.19</td>
<td>4.46±0.49</td>
</tr>
<tr>
<td>Pressure one-half time, mm Hg</td>
<td>4.34±0.64</td>
<td>4.17±0.28</td>
</tr>
</tbody>
</table>

LVEDP indicates left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume.
*Significant difference (P<0.05) compared with age-matched wild-type (+/+ ) mice; †significant difference (P<0.05) compared between αMHC<sup>403</sup>/+ and MyBP-C<sup>C<sup>+</sup></sup> age-matched mice.
MyBP-C<sup>−/−</sup> mice develop dilated cardiomyopathy. Current models suggest that cardiac hypertrophy in MyBP-C<sup>−/−</sup> mice occurs because of a sarcomere dysfunction that causes cardiac dysfunction. We used these mice (Table 1 and Figures 3 and 4) to study whether cardiac dysfunction precedes or follows cardiac hypertrophy. We show that cardiac dysfunction occurs before cardiac hypertrophy. Thus, cardiac dysfunction precedes cardiac hypertrophy in MyBP-C<sup>−/−</sup> mice. The severity of dilated cardiomyopathy in MyBP-C<sup>−/−</sup> mice is the same as that observed in MyBP-C<sup>−/−</sup> mice. These findings suggest that cardiac dysfunction induces hypertrophy in these FHC models. Electrophysiological abnormalities might contribute to the more severe disease process observed in MyBP-C<sup>−/−</sup> mice. However, we do not know whether these abnormalities precede cardiac hypertrophy in mice. We have demonstrated that cardiac hypertrophy can occur in mice without causing electrophysiological abnormalities because >125-week-old mutant animals were no more susceptible to inducible arrhythmias than >125-week-old wild-type mice. Previous studies of individuals with hypertrophic cardiomyopathy have suggested that electrophysiological abnormalities are not a good prognostic indicator in this disease. The findings reported in the present study suggest that some FHC-causing mutations cause more electrophysiological abnormalities than other FHC-causing mutations. Why one sarcomere gene mutation causes such abnormalities and not another remains uncertain.

The prognostic value derived from identification of FHC-causing mutations has been debated for the past several years. Physicians have recognized for the past two decades that some FHC-causing mutations cause more severe disease than others. However, when a new mutation is identified in an individual, predicting whether this mutation will cause severe or mild disease in other family members is difficult. Characterization of murine FHC models suggests that one approach to this problem may be to introduce mutations into otherwise genetically identical mice and then study the phenotype of these murine models. We suggest that the strong correlation between murine phenotypes and clinical features observed in humans bearing analogous FHC-causing mutations will be observed in mice bearing other FHC-causing mutations. Further production and evaluation of other mouse strains bearing FHC-causing mutations should help to define the predictive value of these murine FHC models. Eventually, characterization of other murine FHC models will provide important prognostic information to patients and physicians. Another approach to the problem of predicting the severity of an FHC-causing mutation in humans is suggested by the results in the present study. Based on the two murine models, mutations that cause significant deficits in cardiac function cause severe disease whereas mutations that cause less impairment of cardiac function cause milder disease. Cardiac function of genetically affected family members should provide a good indicator of the clinical consequences of an FHC-causing mutation.

Acknowledgments

The Howard Hughes Medical Institute supported these studies. J.M. and M.H. were recipients of Sarnoff Foundation fellowships. C.S.
References


Comparison of Two Murine Models of Familial Hypertrophic Cardiomyopathy

doi: 10.1161/01.RES.88.4.383

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/88/4/383

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/