Myofilament calcium sensitization delays decompensated hypertrophy differently between the sexes following myocardial infarction

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Shioura KM, Farjah M, Geenen DL, Solaro RJ, Goldspink PH. Myofilament calcium sensitization delays decompensated hypertrophy differently between the sexes following myocardial infarction. Am J Physiol Regul Integr Comp Physiol 300: R361–R368, 2011. First published November 24, 2010; doi:10.1152/ajpregu.00321.2010.—Contractile dysfunction is common to many forms of cardiovascular disease. Approaches directed at enhancing cardiac contractility at the level of the myofilaments during heart failure (HF) may provide a means to improve overall cardiovascular function. We are interested in gender-based differences in cardiac function and the effect of sarcomere activation agents that increase contractility. Thus, we studied the effect of gender and time on integrated arterial-ventricular function (A-V relationship) following myocardial infarction (MI). In addition, transgenic mice that overexpress the slow skeletal troponin I isoform were used to determine the impact of increased myofilament Ca2+ sensitivity following MI. Based on pressure-volume (P-V) loop measurements, we used derived parameters of cardiovascular function to reveal the effects of sex, time, and increased myofilament Ca2+ sensitivity among groups of post-MI mice. Analysis of the A-V relationship revealed that the initial increase was similar between the sexes, but the vascular unloading of the heart served to delay the decompensated stage in females. Conversely, the vascular response at 6 and 10 wk post-MI in males contributed to the continuous decline in cardiovascular function. Increasing the myofilament Ca2+ sensitivity appeared to provide sufficient contractile support to improve contractile function in both male and female transgenic mice. However, the improved contractile function was more beneficial in males as the concurrent vascular response contributed to a delayed decompensated stage in female transgenic mice post-MI. This study represents a quantitative approach to integrating the vascular-ventricular relationship to provide meaningful and diagnostic value following MI. Consequently, the data provide a basis for understanding how the A-V relationship is coupled between males and females and the enhanced ability of the cardiovascular system to tolerate pathophysiological stresses associated with HF in females.

arterial-ventricular relationship; sex; myofilament calcium sensitivity

NORMAL CARDIOVASCULAR FUNCTION depends on the cycle of contraction and relaxation of cardiac myocytes and is influenced by numerous factors such heart rate, venous return, systemic resistance, contractile state, and arterial and ventricular elastance. However, following events resulting in cardiac myocyte death, such as myocardial infarction (MI), the remaining myocytes are unable to generate adequate force despite being provided with calcium and increased preload. Consequently, the decline in cardiac output represents a transition into heart failure (HF), which has serious implications for the cardiovascular system and the other organ systems of the body.

Sex-related differences in cardiovascular function are of great clinical interest, because postmenopausal women tend to suffer more diverse symptoms and poorer clinical outcomes compared with age-matched men following-MI (12, 42). Several factors are thought to contribute, including sex hormones, sex-specific cardiac function, difference in body size, and risk factors such as age or coexisting disease. However, despite the apparent sexual dimorphism that exists in the clinical outcomes data, the pathophysiologic basis for sex-related differences are not well understood.

Assessment of cardiac function in both the clinical and experimental context is often defined by parameters such as stroke volume, ejection fraction, cardiac output, and the maximum first derivative of pressure change with time (5, 6). Based on these parameters, additional diagnostic indices can be derived such as cardiac index (CI), which relates cardiac output to body surface area. Likewise, vascular function can be estimated by arterial elastance (Ea), as a measure of net resistance imposed on the left ventricle (LV) by the arterial system (15, 20, 29). Previously, we have reported both time- and sex-related changes in cardiac function in post-MI mice in commonly used hemodynamic and contractile variables derived from pressure-volume (P-V) loop analysis (30, 31). Although significant cardiac dysfunction was noted using these preferred measures, the sex-related differences were subtle and did not relate the severity of LV dysfunction to overall cardiovascular function (3, 31, 43).

To examine the interdependence between pump function and vascular control, the arterial-ventricular (A-V) relationship can be estimated from the Ea divided by LV contractility, assessed by the end-systolic pressure volume relationship (ESPVR) or maximal elastance (6, 27, 29, 45). Increases in the A-V relationship have been noted with age where vascular stiffening is known to occur in tandem with increased ventricular stiffness and termed “coupling disease” (14). However, less is known regarding the A-V relationship with respect to cardiovascular disease. This may hold great value since this relationship is an important determinant of the mechanoenergetics of the heart, which is strongly correlated with the oxygen cost of performing stroke work (38).

Given that cardiac contractility is depressed following MI, we are interested in determining whether modifications at the level of the myofilaments can improve global cardiovascular function. Cognizant of the clinical use of calcium myofilament sensitizing agents in HF patients (16), we examined the effectiveness of increasing the myofilament sensitivity to calcium due to overexpression of slow skeletal troponin I (ssTnI) on contractile function. This particular isoform is only expressed...
during development and is the basis of enhanced myofilament calcium sensitivity in the neonatal heart (33, 34). Transgenic overexpression in the adult heart is associated with a lower sensitivity to ischemia and acidosis (2, 40, 44). Therefore, our goal was to determine whether the A-V relationship could serve as a sensitive diagnostic index of integrated cardiovascular function to examine the impact of sex and myofilament sensitivity on the pathophysiological changes following MI.

**MATERIALS AND METHODS**

The experiments were approved by the Institutional Animal Care and Use Committee in accordance with the National Institutes of Health guidelines.

**Animals.** Two separate studies were conducted to examine sex-related and enhanced myofilament sensitivity on A-V coupling following various times post-MI. In the first study, 108 young (3–4 mo) and male B6SJL mice were used. Twenty mice were designated as controls, and 88 underwent coronary artery ligation. Overall, there were 10 experimental groups comprised of females and males at different times post-MI (control, 2, 4, 6, and 10 wk), with n = 10 per group.

In the second study, 130 mature (6–8 mo) and male nontransgenic (NTG) and ssTnI transgenic (TG) mice on a CD-1 background were used. Expression of the ssTnI isoform is driven by the α-myosin heavy chain promoter and has been shown to effect a full replacement of the cardiac isoform in the heart. Consequently, myocytes isolated from ssTnI TG hearts have a significantly greater Ca\(^2+\) sensitivity of tension as indicated by a leftward shift in the tension-[–log(Ca\(^{2+}\)M\(^{-1}\))] (pCa) relationship, an increased pCa50 and no change in the pCa-tension relationship after PKA treatment (9). Therefore, ssTnI mice were used to examine the impact of enhanced myofilament Ca\(^2+\) sensitivity on cardiovascular function following MI. Overall, there were 12 experimental groups comprised of NTG and TG females and males at different times post-MI (control, 2 wk and 10 wk) with n = 10 per group. All mice were kept in a temperature- and humidity-controlled environment with standard chow and water given ad libitum and on a 12:12-h light-dark cycle.

**Surgical preparation.** Mice were initially anesthetized with 3% isoflurane inhaled in a closed chamber followed by an intraperitoneal injection of atropine (10 mg/kg). Mice were intubated and connected to a rodent ventilator with a stroke volume of 0.2–0.4 ml/min and with a respiration rate of 135 breaths/min. A plane of anesthesia for surgery was regulated by delivery of 1.5% isoflurane through a vaporizer with 100% oxygen. Body temperature was maintained by placing the animal on a heated surgical pad at 40°C.

**MI.** A left thoracotomy was performed, and the left main coronary artery ligated with 8–0 prolene suture 1–2 mm below the ostium (30, 31). Myocardial blanching indicated a lack of perfusion. The chest cavity was subsequently closed in three layers (intercostal muscles, pericardium, and skin) with 6-0 silk sutures. Mice were gradually weaned off the ventilator and once spontaneous respiration resumed, the endotracheal tube removed and the mice placed in a heating cage until fully conscious. The postsurgical procedure survival rate was ~90% in both studies.

**P-V loop analyses.** Under the same anesthetic regimen, a standard 1.4-French pressure-conductance catheter with 4.5-mm signal electrode spacing (model SPR-839; Millar Instruments, Houston, TX) was inserted into the right carotid artery to measure baseline arterial pressure. It was then advanced retrograde into the LV to record baseline hemodynamics in the closed-chest configuration with the ARIA Pressure Volume Conductance System (Millar Instruments, Houston, TX). A small incision in the diaphragm was then made, and baseline open-chest hemodynamics obtained. Transient occlusions of the thoracic inferior vena cava were made to vary venous return during recording of ventricular pressures. Subsequently, parallel conductance was determined by a 10-µl injection of 15% saline into the right femoral vein to establish the offset due to the conductivity of structures external to the blood pool (30, 31). The mice were euthanized with an overdose of 5% isoflurane, the hearts were removed, and infarct size quantified.

All data were analyzed with the PVAN 3.4 software package from Millar Instruments (Houston, TX). Volume was calibrated by submerging the P-V catheter into heparin-treated murine blood in a series of six volume-calibrated cylinders (1.5–4 mm in circumference and 1-cm deep). The volume of each loop was calculated as the slope of 3.213/relative volume units + intercept of –8.867.

The load-dependent hemodynamic variables were measured in the closed-chest configuration. Total peripheral resistance (TPR), was derived by dividing mean arterial pressure by cardiac output (29, 45). CI was derived by the ratio of cardiac output divided by body weight. LV contractility variables were obtained during transient inferior vena cava occlusion and were used to derive the A-V relationship. The effective Ea was the ratio of the end systolic pressure over stroke volume (15, 29, 45). The A-V relationship was the ratio of Ea divided by ESPVR (25, 27, 29). CCE was the ratio of external work over the pressure volume loop area corrected for parallel conductance.

**Infarct quantification.** Duplicate 1-mm mid-LV sections were cut and incubated with 1% triphenyltetrazolium chloride for 20 min at 37°C and then fixed in 10% buffered formalin. Infarct size was determined by planimetry of the infarct zone (white) and expressed as a percent of the total LV area on digital images at ×10 magnification (Advanced SPOT Diagnostic Instruments) (30, 31).

**Statistical analysis.** Descriptive statistics were derived using SigmaStat 3.1. Two-way ANOVA of two independent attributes (infarct and sex) was used to analyze sex-related responses post-MI. Three-way ANOVA of three independent attributes (infarct, sex, and ssTnI transgene) was used to study the effect of increased myofilament sensitivity post-MI. Post hoc analysis was performed using the Holm-Sidak multiple comparisons method to test for statistical significance (P < 0.05).

**RESULTS**

In post-MI mice, infarct size did not reach statistical difference among the experimental groups based upon triphenyltetrazolium chloride staining (Fig. 1A). In the first study group of young adult mice, infarct size ranged from 42 to 46% for both male and female mice. In the second study group of mature adult mice, infarct size ranged from 46 to 50% for NTG and TG females and males. Cardiac hypertrophy was also comparable between male and female mice at all times post-MI (Fig. 1B). Similarly, there was a significant increase in heart weight-to-body weight ratio in both male and female NTG and TG mice post-MI. There were signs of attenuated hypertrophy at all time points in the TG mice, which was significant in 10-wk-old post-MI males (Fig. 1B).

Cardiovascular function derived from P-V loops was significantly depressed in all post-MI mice compared with their respective controls (Tables 1 and 2). Overall, there were no apparent sex-related differences in either study group except TPR was significantly elevated in males at various times post-MI compared with females.

Cardiac performance in post-MI mice significantly deteriorated over time compared with control mice. Expressed as percent of control, the initial decline in CI was similar between females and males. However, at 6 and 10 wk post-MI the females tended to stabilize, whereas males showed a trend to decline further (Fig. 2A). Preload-recruitable stroke work (PRSW) indicated stronger LV contractility in control males compared with females (females = 70.3 ± 3.2 vs. males = 90.7 ± 1.8 mmHg/ml, P < 0.05). In post-MI mice, LV
contractility was significantly better in females than males at both 2 and 10 wk post-MI relative to their respective controls, indicating a greater decline in males (Fig. 2B).

The derived systolic A-V relationship based on $E_a$ over ESPVR (assuming its linearity), highlighted the difference between the sexes, particularly during the decompensated stages post-MI. The A-V relationship revealed a greater degree of cardiovascular dysfunction in males than females at 6 and 10 wk post-MI (6 wk, 2.9 vs. 4.2-fold and 10 wk, 3.1 vs. 4.1-fold), which was significantly different (Fig. 2C). To understand the basis of the difference in the A-V relationship between the sexes, both $E_a$ and TPR were examined. Initially, $E_a$ increased to a similar degree in females and males but then declined in females. In males, $E_a$ remained elevated at 6 and 10 wk post-MI (Table 1). TPR was significantly elevated in post-MI females and males relative to control, but to a greater extent in males and was sustained. This was also reflected in a lack of correlation between $E_a$ and TPR changes in females ($R = 0.502$), while in males there was a significant correlation ($R = 0.921$, $P < 0.05$). Since the vascular response differed, we examined whether CCE could explain the difference in the A-V relationship between the sexes following MI. CCE demonstrated a similar profile with an overall 30% decline in both females and males post-MI (Fig. 2D). Together, these data suggest that the decline in the A-V relationship in females occurs largely as a result of LV dysfunction independent of vascular changes. In males, a congruent decline in LV function and increased vascular resistance occurs particularly during the decompensated stages following-MI.

To highlight the difference in cardiovascular function between the sexes, the A-V relationship was plotted against CCE at 2 and 10 wk post-MI (Fig. 3). This was particularly revealing and shows that the decompensated stage in males is associated with a decline in both CCE and vascular function. Conversely, while a comparable decline in CCE occurred in females, the vascular response serves to unload the heart and delays the decompensated stage.

Table 1. Time-dependent deterioration of cardiovascular function based on pressure-volume (P-V) loop measurements collected in the closed-chest configuration and during the transient occlusions of thoracic vena cava in mice post-myocardial infarction (post-MI)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>2 wk post-MI</th>
<th>4 wk post-MI</th>
<th>6 wk post-MI</th>
<th>10 wk post-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>HR</td>
<td>521 ± 20</td>
<td>615 ± 17</td>
<td>631 ± 19#</td>
<td>539 ± 18#</td>
<td>541 ± 25</td>
</tr>
<tr>
<td>SV</td>
<td>18.6 ± 2.5</td>
<td>17.0 ± 0.7</td>
<td>10.1 ± 0.8#</td>
<td>10.0 ± 0.9#</td>
<td>11.4 ± 0.8#</td>
</tr>
<tr>
<td>$E_a$</td>
<td>5.0 ± 0.2</td>
<td>5.4 ± 0.4</td>
<td>8.0 ± 0.8</td>
<td>7.7 ± 0.5</td>
<td>7.7 ± 0.5</td>
</tr>
<tr>
<td>TPR</td>
<td>7.9 ± 0.1</td>
<td>6.9 ± 0.2</td>
<td>9.3 ± 0.2#</td>
<td>a115 ± 0.4#</td>
<td>9.4 ± 0.4#</td>
</tr>
<tr>
<td>ESPVR</td>
<td>19.2 ± 0.7</td>
<td>21.2 ± 0.7</td>
<td>9.6 ± 0.4#</td>
<td>9.5 ± 0.6#</td>
<td>9.7 ± 0.6#</td>
</tr>
</tbody>
</table>

Data are means ± SE. HR, heart rate (beats/min); SV, stroke volume (µl); $E_a$, effective arterial elastance (mmHg/µl); TPR, total peripheral resistance (mmHg·ml⁻¹·min⁻¹); ESPVR, end-systolic pressure volume relationship (mmHg/µl). $*P < 0.05$; $**P < 0.01$ changes due to MI in comparison with their respective controls and sex-related effect.

Fig. 1. A: representative image of 1-mm sections cut from control (CTL) and infarcted hearts at 2 (2w MI) and 10 wk (10w MI) incubated with 1% triphenyltetrazolium chloride (scale bar: 3 mm). B: heart weight-to-body weight ratio in female and male mice at different times postmyocardial infarction (post-MI). C: heart weight-to-body weight (Hw/Bw) ratio in female and male non-transgenic (NTG) and slow skeletal troponin I (ssTnI) transgenic (TG) mice, 2 and 10 wk post-MI. $*P < 0.05$ compared with control and $**P < 0.05$ ssTnI TG-related effect.
Since declining contractility was common to both female and male mice but the vascular response differed, we examined the impact of increased myofilament Ca$^{2+}$/sensitivity on cardiovascular function. In the second study, infarcts were created in both female and male TG that express the ssTnI isoform and compared with NTG. We focused on the 2- and 10-wk time points post-MI because they correspond to the early hypertrophic and decompensated stages post-MI in the murine model (30).

CI was significantly higher in females than males in both NTG and TG control mice (Fig. 4A). However, the significant decline post-MI relative to each control did not differ between females and males at 2 wk. A gender difference was apparent at 10 wk post-MI, whereby males were significantly lower than females regardless of transgene expression (Fig. 4A). This measurement was influenced by significantly higher body weights in NTG and TG control males and greater fluctuations in their body weight post-MI, despite the same age. This appeared to be more of a confounding factor in this particular inbred stain of mice compared with the outbred strain in the first study.

There was a significant deterioration in LV contractility represented by PRSW in both NTG and TG post-MI mice. However, compared with the first cohort of mice there were no significant sex-related differences post-MI or difference in control NTG mice, despite males showing a greater PRSW (females $= 73 \pm 3.9$ vs. males $= 87.9 \pm 3.3$ mmHg/$\mu$L). This may be attributed to slightly older mice or background strain variability. Overall, contractility was better in females than males with a trend to greater deterioration occurring in NTG compared with TG mice compared with their respective controls (Fig. 4B). The A-V relationship revealed a greater magnitude of change due to the effect of ssTnI transgene expression and sex in post-MI mice (Fig. 4C). In NTG females vs. TG females, the A-V relationship was similar at 2 and 10 wk post-MI. However, the greatest difference occurred between TG and NTG males. The A-V relationship was similar at 2 wk post-MI, but significantly better in TG males compared with NTG males at 10 wk post-MI (Fig. 4C). This improvement resulted in no statistical difference in the A-V relationship between the sexes of TG mice at 10 wk post-MI, which was apparent in NTG mice and in the first study with young adult mice.

Changes in vascular function were similar in NTG and TG females where both $E_a$ and TPR peaked at 2 wk post-MI before
declining. However, in both NTG and TG males $E_a$ and TPR showed a greater tendency to peak at 2 wk and remain elevated at 10 wk post-MI (Table 2). CCE showed there was a tendency for it to be better in the TG 10 wk post-MI mice compared with their respective NTG (Fig. 4D). Both TG female and male mice showed better CCE compared with their respective NTG cohorts at 10 wk post-MI. To examine further the differences in cardiovascular function between the sexes as a result of increased myofilament sensitization, the relationship between the A-V relationship and CCE post-MI was analyzed (Fig. 5). In TG females, increased myofilament sensitivity provided a slight overall functional benefit at 10 wk post-MI mainly due to an improvement in CCE. This, coupled with the inherent vascular response in females, lead to an improved cardiovascular function in TG females during the decompensation stages compared with NTG females (Fig. 5A). Interestingly, in TG males the impact of increased myofilament sensitivity on CCE was comparable to that as TG females at 10 wk post-MI, but ameliorated the decline in the A-V relationship giving rise to improved cardiovascular function in TG males compared with NTG males (Fig. 5B). Thus, in the context of the A-V relationship these data indicate that increased myofilament sensitivity to calcium has a more pronounced effect in males and delays decompensation, whereas the delayed decompensation in females occurs principally due to inherent vascular unloading of the heart.

**DISCUSSION**

One of the major objectives of this study was to examine integrated vascular and ventricular function based upon the systolic A-V relationship in mice in vivo. We found that the A-V relationship provided an integrated assessment of cardiovascular function and increased sensitivity over widely referred to independent LV and vascular functional parameters.

In support of previous reports of gender dimorphism of cardiac function following MI, the data from the P-V loop-derived parameters revealed stronger differences between sexes in relation to overall cardiovascular function (3, 31, 43). We compared both sex and time-dependent effects on the A-V relationship and noted a number of important findings. First, basal cardiovascular function is comparable between males and females. Despite well-known differences in heart weight, when adjusted for body weight, cardiac function is similar between the sexes as indicated by CI (18), even though this index is not particularly informative during the progression of HF post-MI. Second, the initial decline in cardiovascular function associated with MI is similar between the sexes, suggesting that short-term compensatory mechanisms, which include enhanced sympathetic stimulation, do not differ between genders. Third, basal CCE is also similar between the sexes. Despite well-known differences in heart weight, when adjusted for body weight, cardiac function is similar between the sexes as indicated by CI (18), even though this index is not particularly informative during the progression of HF post-MI. We found that the initial threefold increase in the A-V relationship was comparable between the sexes mainly due to a similar decline in ventricular contractility and an increase in vascular resistance. However, with time post-MI, the A-V relationship in males continued to increase, while it remained constant in females. This appears to be due to a worsening of both components of the relationship.
(an increase in vascular resistance and decrease in contractility) in males, whereas the vascular component remained relatively constant in females. While the vascular component of the relationship (Ea) is not a direct measure of any specific arterial property, it serves as an integrative index that incorporates the foremost elements of arterial load, TPR, and arterial compliance (38). Therefore, Ea can be considered a measure of the net arterial load that is imposed on the LV. Based upon our data, there is not a gender dimorphic difference in Ea under physiologic conditions, but females appear to utilize different mechanisms to restore Ea in response to pathologic stress. Consequently, sex hormone-induced stimulation of endothelium-dependent mechanisms of vascular relaxation and inhibition of smooth muscle contraction could contribute to the gender differences in vascular tone noted here in premenopausal females compared with males (24).

The A-V relationship is an important determinant of cardiac energetics (35). Total energy, consisting of stroke work (SW) and potential energy, can be estimated from the P-V area (PVA) of the P-V loops (36). Given that the amount of SW...
heart performs and the oxygen it consumes are strongly correlated with loading conditions and contractile state, the ratio of SW/PVA can be used to express CCE (35, 37). Alterations in myofilament protein function or composition are likely to affect the economy and efficiency of the contractile machinery. However, posttranslational modifications of the myofilaments are also known to influence the mechanoenergetics of the myofilaments. Stimulation of the PKA pathway increases the relaxation rate and crossbridge kinetics of the myofilaments via phosphorylation of cardiac troponin I (cTnI) (17). While this may serve as an initial compensatory mechanism to increase diastolic filling time, it is associated with a decrease in the myofilament response to calcium. Our data indicate that expression of the ssTnI isoform and associated increase in myofilament Ca\(^{2+}\) sensitivity appears to improve the contractile efficiency, but whether this is due to an improvement in the efficiency of the contractile machinery or the energy in handling Ca\(^{2+}\), is not determined. Mathematical modeling of myocardial Ca\(^{2+}\) handling suggests that Ca\(^{2+}\) sensitization of the myofilaments reduces the total Ca\(^{2+}\) handling energy of the sarcoplasmic reticulum required to maintain contractility (23). Thus, in the context of the infarcted heart, enhancing contractile efficiency may provide a means of lessening the overall cellular demand on energy production within the viable myocardium to slow progression of the decompensated stages.

It is increasingly apparent that myofilament properties as well as changes in intracellular Ca\(^{2+}\) have a major role in the modulation of contractile function. A steady observation in various models of cardiac disease has been the transition of myofilament desensitization to a state of myofilament sensitization as the disease progresses (4, 10, 11, 21). However, the literature examining sexual dimorphism of myofilament Ca\(^{2+}\) sensitivity is contradictory. Isolated myocyte preparations from female hearts show that greater tension is generated at a given Ca\(^{2+}\), suggesting an enhanced Ca\(^{2+}\) sensitivity compared with males (28). Other studies, however, demonstrate the opposite effect and suggest female hearts are less sensitive to Ca\(^{2+}\) (7). Supporting this observation further is the report that ovariec-
tomy increases myofilament Ca\(^{2+}\) sensitivity (41). Neverthe-
less, under physiological conditions, these reported sexual dimorphisms do not appear to influence cardiac contractility as shown here and elsewhere (31).

Altered thin filament function plays an important role in the contractile dysfunction associated with HF, and as such, troponin I has garnered much attention. Phosphorylation of specific serine and threonine residues on cTnI by several different kinases represents a major mechanism by which the myofilament response to Ca\(^{2+}\) is altered (32). While a general consensus exists to the fact that cTnI phosphorylation is increased in HF, there is a paucity of data regarding site-specific phosphorylation and the temporal changes that occur during the progression of HF. With respect to ischemia, cTnI proteolysis has been shown to occur. The extent of proteolysis occurs initially at the COOH terminus, but with longer durations of ischemia and ischemia/reperfusion there is NH\(_2\)-terminal truncation, suggesting a mechanistic link between the severity of ischemia and reversible cardiac dysfunction (19, 22). While proteolysis of the cTnI isoform is likely to affect numerous myofilament protein interactions in the adult heart, this does not appear to be the case with the expression of the embryonic isoform (ssTnI) with its NH\(_2\)-terminal truncation in the heart.

In fact, the features associated with ssTnI expression, increased Ca\(^{2+}\) sensitivity, slower relaxation rates, and low sensitivity to acidosis all appear to be beneficial during embryonic development and neonatal life (8, 33, 34). Although the inotropic effects of ssTnI isofrom expression are well characterized, the ssTnI TG mice provide a useful model to study the effects of increased myofilament Ca\(^{2+}\) sensitivity on cardiovascular function in response to clinically relevant perturbations. Consequently, our study relates to a recent interest in the use of Ca\(^{2+}\) sensitizers, which directly influence the myofilament proteins to alter the way the intracellular Ca\(^{2+}\) signal is transduced into force production (1, 16, 39).

The data presented here suggest that strategies directed at increasing the myofilament sensitivity to Ca\(^{2+}\) are beneficial in the context of HF following MI. This appears to be more so for males than females. While the improvements in CCE were comparable between the sexes at 10 wk post-MI (~6% in females and 7% in males), the impact on the A-V relationship was greater in males than females. However, improvements in females due to increased calcium sensitivity may be masked by the inherent vascular response that serves to reduce afterload and decrease the Ea component of the A-V relationship. In males, the improvements in cardiac contractile function associated with increased myofilament Ca\(^{2+}\) sensitivity had a more profound effect on overall cardiovascular function. Since LV performance is influenced by arterial load, there is also a reciprocal influence of LV performance on arterial properties (38). While this interrelationship of vascular and ventricular function is necessary for normal physiologic function, its dysfunction contributes to the vicious cycle of HF. Consequently, we believe that our data illustrate a fundamental difference between the sexes as to how the A-V relationship is coupled under pathologic conditions.

**Perspectives and Significance**

Gender has long been considered a significant risk factor in the development of cardiovascular disease. Females tend to lose their advantage during menopause, which is associated with the decline in female sex hormones. While we acknowledge these studies were conducted in younger premenopausal mice, the rapid increase in obesity in young females and the development of cardiovascular disease associated with metabolic syndrome makes this study relevant (26). Thus, study of sex-related differences in genetically modified rodent models should contribute to our understanding of the ability of the cardiovascular system to tolerate pathophysiological stresses within the context of a number of disease paradigms (13). In addition, these data add to the growing appreciation of the need for gender-based therapies in the treatment of HF.

**GRANTS**

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

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MYOFILAMENT Ca SENSITIZATION AND ARTERIOVENTRICULAR COUPLING


