Influence of gender on the response to hemodynamic overload after myocardial infarction

MOHIT JAIN,1 RONGLIH LIAO,1 BRUNO K. PODESSER,1 SOEUN NGOY,1 CARL S. APSTEIN,1 AND FRANZ R. EBERLI2

1Cardiac Muscle Research Laboratory; Boston University School of Medicine, Boston, Massachusetts 02118; and 2Swiss Cardiovascular Center Bern, University Hospital, 3010 Bern, Switzerland

Received 15 April 2002; accepted in final form 28 July 2002

Influence of gender on the response to hemodynamic overload after myocardial infarction. Am J Physiol Heart Circ Physiol 283: H2544–H2550, 2002. First published August 1, 2002; 10.1152/ajpheart.00338.2002.—After myocardial infarction (MI), the left ventricle (LV) undergoes ventricular remodeling characterized by progressive global dilation, infarct expansion, and compensatory hypertrophy of the noninfarcted myocardium. Little attention has been given to the response of remodeling myocardium to additional hemodynamic overload. We therefore determined 1) structural and functional consequences of superimposing hemodynamic overload (systemic hypertension) on remodeling myocardium after a MI and 2) the potential influence of gender on this remodeling response. Male and female Dahl salt-sensitive and salt-resistant rats underwent coronary ligation, resulting in similar degrees of MI. One week post-MI, all rats were placed on a high-salt diet. Four groups were then studied 4 wk after initiation of high-salt feeding: MI female, MI female + hypertension, MI male, and MI male + hypertension. Hypertension-induced pressure overload resulted in additional comparable degrees of myocardial hypertrophy in both females and males. In females, hypertension post-MI resulted in concentric hypertrophy with no additional cavity dilation and no measurable scar thinning. In contrast, in males, hypertension post-MI resulted in eccentric hypertrophy, further LV cavity dilation, and scar thinning. Physiologically, concentric hypertrophy in post-MI hypertensive females resulted in elevated contractile function, whereas eccentrically hypertrophied males had no such increase. Female gender influences favorably the remodeling and physiological response to hemodynamic overload after large MI.

hypertension; hypertrophy; remodeling; Dahl rat

After myocardial infarction (MI), the left ventricle (LV) undergoes ventricular remodeling, characterized by progressive global dilation, infarct expansion, and increased interstitial fibrosis (2, 36, 38). To compensate for the loss of contracting heart muscle, the noninfarcted myocardium initially undergoes a process of compensatory hypertrophy with subsequent supracontractile function (13). Whereas it is well established that the heart maintains a remarkable degree of plasticity, or ability to withstand and compensate for a large range of stresses, little attention has been given to the response of remodeling myocardium to additional hemodynamic overload. It has been suggested that after MI, the noninfarcted portion of the myocardium has limited ability to further hypertrophy in the presence of additional hemodynamic load (11, 12, 33). Furthermore, previous studies of hemodynamic overload after MI have detailed both a reduction as well as an exacerbation in infarct expansion (27, 32). Functional consequences of post-MI hemodynamic overload have also been unclear, because cardiac function has been shown to decline (32) as well as remain unchanged (1, 11, 32).

Both experimental and clinical studies have indicated that gender may influence remodeling and the response to both MI and hemodynamic overload. Females exhibit increased left ventricular hypertrophy secondary to hypertension and aortic stenosis (3, 5, 21). Furthermore, females may have an increased cardiac reserve, with augmented preservation of cardiac function during stressed conditions, and slowed transition to heart failure (3, 5, 9, 41, 44).

We have previously shown in Dahl salt-sensitive (DS) rats that 4 wk of hypertension results in the development of stable, well-compensated left ventricular hypertrophy, marked by concentric wall thickening and enhanced cardiac function (29, 30). By using this model, we determined 1) the structural and functional consequences of superimposing hemodynamic overload (systemic hypertension) on remodeling myocardium post-MI and 2) the potential influence of gender on this remodeling response.

MATERIALS AND METHODS

Animal model. The DS rat is an inbred genetic hypertensive rat strain that when fed a high-salt diet develops hypertension at low renin and low aldosterone levels, whereas

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: F. R. Eberli, Cardiovascular Center, Univ. Hospital Zurich, Rämistr. 100, 8091 Zurich, Switzerland (E-mail: franz.eberli@dim.usz.ch).
Dahl salt-resistant (DR) rats remain normotensive on high-salt diet. Male and female inbred DS and DR rats were obtained from Harlan Sprague Dawley. Rats were received at 8 wk of age, weight 250 g, and were fed a low-salt diet (0.12% NaCl) for 1 wk for acclimatization.

After 1 wk, MI was induced by coronary ligation as previously described (19). All animal handling and procedures strictly adhered to the regulations of Boston University Animal Care and the Guide for the Care and Use of Laboratory Animals (DHEW Publication No. (NIH) 85-23, Revised 1996. Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20205).

One week after MI, all animals were fed a high-salt diet (7.8% NaCl) and water ad libitum for 4 wk (5 wk post-MI). Systemic blood pressures were measured by the tail-cuff method (35) in unanesthetized rats at 30°C at the time point of study.

Experimental groups and mortality. Four infarcted groups of animals were utilized in this study: MI female, MI male, MI male + hypertension, MI female + hypertension. Animals had a perioperative mortality of 32%, with female animals experiencing a slightly greater (37%) perioperative mortality than males (27%). After 24 h postinfarction and until time of study, mortality was minimal with one animal dying in each group, except the female + hypertension group, which had no deaths. At the time of study, 5 wk postinfarction, animals studied were as follows: MI female (n = 11), MI female + hypertension (n = 12), MI male (n = 12), and MI male + hypertension (n = 8).

Whole heart perfusion protocol. Hemodynamic studies were performed in isolated isovolumically beating (balloon-in LV) erythrocyte-perfused hearts, as previously described (19, 30). Perfusate consisted of cow erythrocytes resuspended in Krebs-Henseleit buffer and 4 g/dl bovine serum albumin at a final hematocrit of 40%. The heart’s coronary perfusion was maintained at a constant pressure of 80 mmHg for normotensive animals and 100 mmHg for hypertensive animals to produce similar coronary blood flow per gram heart weight (30). Hearts were paced at 5 Hz via epicardial electrodes. A collapsed polyethylene balloon was inserted in the LV via the left atrium and secured in place. The balloon was connected to a pressure transducer (Gould-Statham model P23 Db; Gould, Oxnard, CA) for constant monitoring of left ventricular pressure. Coronary flow was measured by timed collection of venous effluent.

Pressure-volume analysis. After an equilibration period of 30 min, active pressure-volume relationships were then generated. From a balloon volume of 0, the balloon was filled in increments of 0.05 ml, and subsequent pressures were recorded. Diastolic pressure-volume analysis was derived as previously described (19). End-diastolic pressures at incremental volumes were plotted, and a best-fit exponential curve was generated for each rat (DeltaGraph Pro 3). Values at a given pressure were averaged for animals in each group, and a final pressure-volume exponential relationship was obtained. Contractile function was assessed by systolic pressure-volume analysis, wherein developed pressure was plotted versus preload, defined here as end-diastolic wall stress. Mean midventricular diastolic wall stress was estimated according to the equation (wall stress = pressure × chamber radius/wall thickness), where chamber radius was defined as the mean radius of the midsection of the heart and wall thickness was defined as the mean viable wall thickness at this section. Curves of developed pressure versus diastolic wall stress were generated for each heart and the best fit logarithmic curve (DeltaGraph Pro 3) was derived. From the derived logarithmic equations, corresponding developed pressures were determined at preloads from 5 to 60 dynes/cm² in increments of 5 dynes/cm² for each heart. Developed pressure at each diastolic wall stress was averaged for hearts within each group, and a final contractility relationship was determined.

Histology and infarct size measurement. After pressure-volume experiments, hearts were arrested in diastole with KCl at a final distending pressure of 5 mmHg. Hearts were then perfusion fixed with 200 ml of 10% buffered formalin acetate (Fisher Scientific). After paraffin embedding, the heart was tomed and sections (6-μm thick) from each of six equally spread levels (base through apex) were stained with trichrome and picrosirius red. Infarct size was determined as the mean percentage of epicardial and endocardial circumference occupied by scar tissue averaged for all of the ventricular levels. Similarly, by using digital imaging (Scan Pro 4; Sigma), morphometric analysis was performed on histology sections at the level of the midventricle. Morphometric measurements were made as indicated. Anterior and posterior wall thickness measurements were made remote to the infarct region and were averaged together and presented as one value (anterior/posterior wall thickness). Endocardial midseptum-to-free wall and anterior-to-posterior wall diameters were similarly averaged and presented as one value (LV diameter).

Statistics. Statistical analysis was conducted by using a two-factor repeated-measures ANOVA, or simple ANOVA as appropriate, with the least-significant difference post hoc test. All data are presented as means ± SE.

**RESULTS**

Animal characteristics. Infarct size was comparable among groups (Table 1) and was unaffected by gender or by hemodynamic overload. The degree of hemodynamic overload was also similar in hypertensive female and male rats, as determined in vivo systolic blood pressure measurements. Female rats were significantly smaller than male animals as assessed by body weight.

### Table 1. Animal characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Percent Infarct</th>
<th>SBP, mmHg</th>
<th>Body Wt, g</th>
<th>Tibia, mm</th>
<th>Heart Wt, g</th>
<th>Heart Wt/Tibia, g/cm</th>
<th>Lung, wet/dry wt</th>
<th>Liver, wet/dry wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI female</td>
<td>11</td>
<td>47 ± 3</td>
<td>130 ± 7</td>
<td>216 ± 5</td>
<td>3.65 ± 0.04</td>
<td>1.37 ± 0.03</td>
<td>3.75 ± 0.08</td>
<td>4.81 ± 0.10</td>
<td>3.34 ± 0.03</td>
</tr>
<tr>
<td>MI female + hypertension</td>
<td>12</td>
<td>46 ± 3</td>
<td>177 ± 5*</td>
<td>237 ± 5*</td>
<td>3.67 ± 0.05</td>
<td>1.58 ± 0.04*</td>
<td>4.33 ± 0.13*</td>
<td>4.76 ± 0.07</td>
<td>3.37 ± 0.03</td>
</tr>
<tr>
<td>MI male</td>
<td>12</td>
<td>48 ± 3</td>
<td>148 ± 4</td>
<td>346 ± 14†</td>
<td>3.96 ± 0.03*</td>
<td>1.81 ± 0.05†</td>
<td>4.56 ± 0.11†</td>
<td>4.95 ± 0.10</td>
<td>3.31 ± 0.06</td>
</tr>
<tr>
<td>MI male + hypertension</td>
<td>8</td>
<td>46 ± 2</td>
<td>182 ± 6†</td>
<td>368 ± 8†</td>
<td>4.07 ± 0.04*</td>
<td>2.19 ± 0.05†</td>
<td>5.39 ± 0.13†</td>
<td>4.94 ± 0.08</td>
<td>3.44 ± 0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats; MI, myocardial infarction; SBP, systolic blood pressure; Body wt, body weight; heart wt, heart weight. *P < 0.05 vs. MI female; †P < 0.05 vs. MI female + hypertension; ‡P < 0.05 vs. MI male.
weight and tibia length. Body weight was increased in females with hypertension relative to normotensive females, although no increase in tibia length, an index of growth independent of body fat, muscle mass, or fluid homeostasis was observed. No differences of body weight or tibia length were observed in male animals with hemodynamic overload relative to same sex controls.

Heart weights and heart weight normalized for tibia length were significantly higher in MI male animals relative to MI female animals. Superimposed hemodynamic overload resulted in an increase in heart weights and heart weight-to-tibia length ratios in both MI females and MI males of ~15 and 20%, respectively. Lung and liver wet/dry weight ratios were similar among the groups, suggesting an absence of additional pulmonary or hepatic congestion.

**Patterns of LV remodeling.** Despite the similar degree of ventricular hypertrophy in post-MI females and males with additional hemodynamic overload, the patterns of muscle mass were markedly different. Illustrative examples are given in Fig. 1. MI females had a significantly thinner septum and anterior/posterior walls than MI males (Table 2). However, hemodynamic overload in MI females resulted in substantial septal wall thickening and anterior/posterior wall thickening, whereas MI male + hypertension hearts exhibited only a moderate increase in anterior/posterior wall thickness. Hemodynamic overload in infarcted male hearts also resulted in thinning of the infarct wall. Midventricular LV endocardial diameter and cavity area were reduced in MI female + hypertension animals relative to same-sex normotensive controls, resulting in a decrease in the LV diameter-to-septum thickness ratio (Table 2). Midventricular LV cavity dimensions did not significantly increase statistically in MI male + hypertension (Table 2).

To further assess ventricular cavity dimension, we generated a diastolic pressure-volume relationship (Fig. 2). MI caused a rightward shift of the diastolic pressure-volume relationship relative to animals without MI (data not shown), indicating LV dilation in females and males. In males, hypertension post-MI caused a further rightward shift in the pressure-volume curve relative to normotensive males post-MI, indicating further global LV dilation. In contrast, in females post-MI hypertension resulted in no significant shift of the diastolic pressure-volume relationship relative to normotensive females post-MI.

**Table 2. Cardiac morphometry**

<table>
<thead>
<tr>
<th>Group</th>
<th>Septal Thickness, mm</th>
<th>Ant-Post Thickness, mm</th>
<th>Infarct Wall Thickness, mm</th>
<th>LV Diameter, mm</th>
<th>LV Area, mm²</th>
<th>LV Diameter/Septum</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI female</td>
<td>1.18 ± 0.05</td>
<td>1.60 ± 0.06</td>
<td>0.62 ± 0.11</td>
<td>7.84 ± 0.16</td>
<td>47.5 ± 1.7</td>
<td>6.77 ± 0.33</td>
</tr>
<tr>
<td>MI female + hypertension</td>
<td>1.97 ± 0.08*</td>
<td>2.17 ± 0.16*</td>
<td>0.86 ± 0.16</td>
<td>6.95 ± 0.30*</td>
<td>37.2 ± 3.2*</td>
<td>3.61 ± 0.24*</td>
</tr>
<tr>
<td>MI male</td>
<td>1.62 ± 0.08*</td>
<td>1.87 ± 0.06*</td>
<td>0.99 ± 0.14</td>
<td>8.80 ± 0.25†</td>
<td>60.5 ± 3.4†</td>
<td>5.62 ± 0.40†</td>
</tr>
<tr>
<td>MI male + hypertension</td>
<td>1.67 ± 0.11*</td>
<td>2.24 ± 0.14*</td>
<td>0.53 ± 0.06†</td>
<td>8.89 ± 0.28†</td>
<td>63.1 ± 3.8†</td>
<td>5.84 ± 0.31†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Ant-Post Thickness, anterior wall and posterior wall thickness; LV, left ventricular. *P < 0.05 vs. MI female; †P < 0.05 vs. MI female + hypertension; ‡P < 0.05 vs. MI male.
Additional hemodynamic overload post-MI therefore resulted in a pattern of eccentric hypertrophy and infarct expansion in males, marked by LV cavity dilation and infarct wall thinning, without change in the diameter-to-septum ratio. In contrast, hemodynamic overload in females resulted in a pattern of concentric hypertrophy, as shown by substantial noninfarct wall thickening and a reduction of the LV diameter-to-septum ratio. Hypertension post-MI also caused scar thinning in males, but not in females.

LV contractile function. To assess the physiological response of these very different patterns of hypertrophy, we generated Starling contractility curves in isolated hearts (Fig. 3). In these isolated heart studies, coronary blood flow per gram heart weight was similar among all groups (MI female 1.55 ± 0.5; MI male 1.61 ± 0.09; MI female + hypertension 1.5 ± 0.06; MI male + hypertension 1.5 ± 0.12 ml/g heart weight; P not significant). Male and female normotensive animals post-MI had similarly developed pressures at any given preload. In post-MI females, hypertension-induced concentric hypertrophy resulted in an increased contractile function relative to normotensive females post-MI (P < 0.05). In contrast, eccentric remodeling, seen in post-MI hypertensive males, did not alter LV contractile function.

**DISCUSSION**

The main findings of this study are that after a large anterior MI, hypertension-induced pressure overload results in 1) additional myocardial hypertrophy above the compensatory hypertrophy accompanying post-MI remodeling and 2) marked differences in the pattern of LV hypertrophy between female and male rats. In females, hypertension post-MI resulted in concentric hypertrophy with no additional cavity dilation and no measurable scar thinning. In contrast, in males, hypertension post-MI resulted in eccentric hypertrophy, further LV cavity dilation and scar thinning. Physiologically, concentric hypertrophy in post-MI hypertensive females resulted in elevated contractile function, whereas eccentrically hypertrophied males had no such increase.

Large infarcts, as in the present study, lead to LV dilatation, thinning of the ventricular wall, and systolic dysfunction (2, 38). LV dilatation is accompanied by myocyte thinning, and it has been suggested that once myocytes start to lengthen, the ability to thicken is lost (12, 33). Indeed, after a large MI, thinning of the septum and an inability to develop compensatory hypertrophy has been observed (10). Our findings, however, do not support this notion. Salt-induced hypertension resulted in additional LV hypertrophy above that of compensatory left ventricular hypertrophy post-MI in both female and male rats. In previous studies of hearts with coronary artery constriction (1) or moderately sized transmural infarctions (11), hypertension also resulted in a slight increase in LV mass and a further shift of myosin heavy chain isoenzymes, resulting in preserved contractile function despite further LV dilatation. Therefore, hearts post-MI seem to maintain their ability to hypertrophy as a mechanism to compensate for superimposed pressure overload.

No previous study has assessed gender differences in post-MI remodeling complicated by hypertension. Whereas hypertension post-MI induced eccentric hypertrophy in males, similar to a previous report (1), hypertensive female rat hearts post-MI did not further dilate and thus developed a more concentric hypertrophy. This observed gender difference is in accordance with previous clinical and experimental observations that have shown a more concentric LV remodeling secondary to pressure overload hypertrophy in females relative to males (3, 5, 9, 21, 44). Results observed in females, however, are quite different than those previously reported (32) in animals undergoing MI with preexisting hemodynamic overload, in which scar thinning and infarct expansion were observed. Importantly, in our experiments, a high-salt diet was started.
7 days post-MI and hearts were exposed to severe hypertension after ~12 days post-MI, when infarct healing and scar formation was almost complete (36, 38). Indeed, clinical studies examining exercise, an additional form of “cardiac overload,” have shown an important time-dependent remodeling response, i.e., initiation of exercise soon after infarction results in exacerbated dilation and increased mortality (10, 18), whereas exercise late after infarction results in more beneficial remodeling (19, 34).

The gender differences in LV remodeling after MI or increased afterload in experimental and human studies, might be due to differences in hemodynamics, neurohumoral factors, or most likely, a combination of both. Sex hormones might have indirectly affected loading conditions, because they affect LV preload and afterload, blood volume regulation, and arterial mechanics. Importantly, hypertension in the DS rat is not sex linked (20), and we and others observed no gender differences in the speed and extent of hypertension during 4 wk as judged by continuous or by biweekly blood pressure measurements (17). Accordingly, at the time of study, tail-cuff blood pressure was identical in female and male hypertensive animals.

In LV remodeling secondary to pressure overload, male animals repeatedly have been shown to exhibit accelerated LV dilation and more pronounced molecular remodeling, indicative of greater LV failure (9, 33, 43, 44). It is possible, therefore, that in both sexes, pressure overload post-MI initially resulted in concentric hypertrophy, followed by accelerated ventricular dilation in male animals, resulting in a more eccentric pattern of ventricular growth at the time of study. The short period of hypertension (for 3–4 wk), however, makes it unlikely that adaptive changes were already overwhelmed. Furthermore, none of the animals showed any signs of overt heart failure and lung and liver weights were similar among groups indicating that no left or right heart congestion had yet occurred.

Furthermore, in post-MI remodeling, infarct size is a key determinant of LV dilation and hemodynamic impairment. Estrogen treatment in female animals has been reported to both increase infarct size (40) as well as decrease infarct size (16). We, however, did not observe any change in peri-infarct mortality in female compared with male animals and our infarcts were homogeneously large and of similar size in normoten- sive and hypertensive animals of both sexes. It is, therefore, unlikely that unequal infarct sizes before the onset of hypertension contributed to any of the observed differences.

Gender differences are not only related to geometric or loading differences but also to differences in gene expression (44). These differences might be modulated by gonadal hormones, because testosterone and estrogen have both been found to modulate ventricular hypertrophy (4). Estrogen receptors have been identified in cardiac fibroblasts and myocytes in both males and females (14, 44). Estrogens have, therefore, the potential to influence gene expression of cardiac growth factors and cytokines that are upregulated post-MI and with pressure overload (14, 44). For example, estrogen has shown to decrease endothelin B receptors after MI, resulting in infarct expansion early after MI, but increased hypertrophy in the noninfarcted myocardium and decreased wall stress late after MI (40). Similarly, estrogen has been found to affect the renin-angiotensin system (31) and insulin-like growth factor-1 (IGF-1) (26, 28). IGF-1 and IGF-1 receptor expression and activity are upregulated during hypertension (8) and MI (39) and are believed to help mediate the hypertrophic response secondary to both pressure and volume overload. Estrogen mediated further expression of IGF-1 and increased IGF-1 receptor binding could contribute to favorable remodeling by a direct growth effect or by preventing apoptosis, an important mechanism in both remodeling after MI and pressure overload (6, 15, 22, 23).

Compensatory hypertrophy of the noninfarcted portion of the myocardium post-MI improves LV systolic function and limits cavity dilation and wall stress (2, 38). This physiological adaptation has been successfully enhanced by several experimental interventions, such as inhibition of long-chain fatty acid oxidation (25), growth hormone (7), and estrogen (40). Great caution should be applied by extrapolating our findings to clinical practice. In particular, the findings do not imply that female patients post-MI with hypertension have improved prognosis. Concentric hypertrophy, although beneficial for LV dilatation and systolic function, might nevertheless worsen diastolic dysfunction (24). Our observations that after large MIs, the noninfarcted myocardium retains compensatory mechanisms, which seem to be gender specific, might have an implication on future gender specific treatment of patients with coronary artery disease. Female patients have been found to have an increased mortality in the acute phase of a MI, but appear to have an improved long-term survival (42). On the other hand, females patients with LV dysfunction derived less benefit from afterload reduction with angiotension converting enzyme inhibitors than males (37). Our data may help explain some of the underlying mechanisms contributing to these puzzling clinical findings. They also alert one to the fact, that any pharmacological intervention in post-MI remodeling might have a different effect in male and female patients.

This study was supported by National Heart, Lung, and Blood Institute Grants HL-03377 (to R. Liao), HL-55995 (to C. S. Aptein), and K08-HL-03574 (to F. R. Eberli).

REFERENCES


AJP-Heart Circ Physiol • VOL 283 • DECEMBER 2002 • www.ajpheart.org


35. Vaccarino V, Krumholz HM, Berkman LF, and Horwitz RI. Sex differences in mortality after myocardial infarction. Is there
