Susceptibility to systolic dysfunction in the myocardium from chronically infarcted spontaneously hypertensive rats

Gavin R. Norton,1 Demetri G. A. Veliotes,1 Oleg Osadchii,1 Angela J. Woodiwiss,1 and D. Paul Thomas2

1Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, University of the Witwatersrand, Johannesburg, South Africa; and 2Division of Kinesiology and Health, University of Wyoming, Laramie, Wyoming

Submitted 5 September 2007; accepted in final form 6 November 2007

Norton GR, Veliotes DG, Osadchii O, Woodiwiss AJ, Thomas DP. Susceptibility to systolic dysfunction in the myocardium from chronically infarcted spontaneously hypertensive rats. Am J Physiol Heart Circ Physiol 294: H372–H378, 2008. First published November 9, 2007; doi:10.1152/ajpheart.01024.2007.—We explored whether the hypertensive heart is susceptible to myocardial dysfunction in viable noninfarcted tissue post-myocardial infarction (MI), the potential mechanisms thereof, and the impact of these changes on pump function. Six to seven months after the ligation of the left anterior descending coronary artery, left ventricular (LV) myocardial systolic function, as assessed from the percent shortening of the noninfarcted lateral wall segmental length determined over a range of filling pressures (ultrasonic transducers placed in the lateral wall in anesthetized, open-chest, ventilated rats) and the percent thickening of the posterior wall (echocardiography), was reduced in infarcted spontaneous hypertensive rats (SHR-MI) (P < 0.05) but not in normotensive Wistar-Kyoto (WKY-MI) animals compared with corresponding controls [SHR-Sham operations (Sham) and WKY-Sham]. This change in the regional myocardial function in SHR-MI, but not in WKY-MI, occurred despite a similar degree of LV dilatation (increased LV end-diastolic dimensions and volume intercept of the LV end-diastolic pressure-volume relation) in SHR-MI and WKY-MI rats and a lack of difference in LV relative wall thinning, LV wall stress, apoptosis [terminal deoxynucleotidyl transferase biotin-dUTP nick-end labeling (TUNEL)], or necrosis (pathological score) between SHR-MI and WKY-MI rats. Although the change in regional myocardial function in the SHR-MI group was not associated with a greater reduction in baseline global LV chamber systolic function [end-systolic elastance (LV Ees)] and endocardial fractional shortening determined in the absence of an adrenergic stimulus], in the presence of an isoproterenol challenge, noninfarct-zone LV systolic myocardial dysfunction manifested in a significant reduction in LV Ees in SHR-MI compared with WKY-MI and SHR and WKY-Sham rats (P < 0.04). In conclusion, these data suggest that with chronic MI, the hypertensive heart is susceptible to the development of myocardial dysfunction, a change that cannot be attributed to excessive chamber dilatation, apoptosis, or necrosis, but which in turn contributes toward a reduced cardiac adrenergic inotropic reserve. pressure-overload hypertrophy; remodeling; myocardial systolic function; cardiac reserve

THE PRESENCE OF HYPERTENSIVE cardiac hypertrophy is a well-recognized risk factor for myocardial infarction (MI) and may predispose to a greater reduction in pump function post-MI (6a, 7, 10, 11, 23, 24). The impact of hypertension and associated cardiac hypertrophy on pump dysfunction post-MI could be attributed in part to an impact of elevated afterload on infarct size (25, 30) or adverse cardiac remodeling in noninfarcted tissue (10–12, 23). However, what has not been explored is whether the chronically infarcted hypertensive heart is susceptible to a decrease in systolic function in the remaining noninfarcted and chronically remodeled viable myocardium. In this regard, in normotensive animals, some studies have demonstrated the importance of a decrease in regional systolic dysfunction measured in noninfarcted and remodeled myocardial tissue remote from a MI (4, 6, 17–19, 21, 35, 40), changes that may be related to a number of mechanisms (9, 35). Because hypertensive hearts compared with normotensive hearts are more susceptible to alterations in viable-tissue adrenergic-signaling post-MI (14) and to apoptosis in general (36), this may increase the chances of myocardial systolic dysfunction occurring in remote cardiac tissue. The aim of the present study was, therefore, to assess whether the hypertensive heart compared with the normotensive heart is more susceptible to the development of myocardial dysfunction in viable cardiac tissue post-MI and the potential mechanisms thereof and whether this effect contributes toward global pump dysfunction.

METHODS

Models and groups. This study was approved by the Animal Ethics Screening Committee of the University of the Witwatersrand (approval numbers 2004:43:4 and 2004:59:4). To induce MI, young postpubescent male spontaneous hypertensive rats (SHR) and Wistar-Kyoto (WKY) control rats were subjected to the ligation of the left anterior descending coronary artery ~4 mm from its emergence at the inferior border of the left atrium, as previously described (32). This approach resulted in only a moderate-sized MI and, hence, is not subject to a high postoperative mortality (32). Control rats were subjected to sham operations (Sham) (SHR-Sham and WKY-Sham) (32). To optimize postoperative mortality rates, a number of adaptations were employed. To ensure that spontaneous breathing postsurgery was appropriate, anesthesia was induced with ketamine and medetomidine and reversed with atipamezole-HCl immediately before the removal of the endotracheal tube. All surgery was performed under sterile conditions. The rats were placed in 100% O2 in a 36°C room, and 1 ml of Ringer lactate solution and 5 mg enrofloxacin antibiotic were injected subcutaneously during recovery. The rats were fed a nutritionally enriched supplement (Ensure) for 1 wk postoperatively to ensure adequate nutrition. Under these conditions, no postoperative mortality occurred during the first week post-MI. Although in our hands homogenous infarct sizes obtained in normotensive rats have previously allowed us to study sample sizes of five to six per group (41), before the present study we were uncertain as to

Address for reprint requests and other correspondence: A. J. Woodiwiss or G. R. Norton, Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Univ. of the Witwatersrand Medical School, 7 York Rd., Parktown, 2193, Johannesburg, South Africa (e-mail: angela.woodiwiss @wits.ac.za or gavin.norton@wits.ac.za).

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.
whether similar effects would be noted in SHR; hence, we studied a larger sample of SHR than WKY. To assess the degree of hypertrophy of the viable myocardium, the area of scar tissue, the degree of left ventricular (LV) dilatation, and systolic chamber and regional myocardial function, all sham-operated rats and only those rats with distinct evidence of pallor of the myocardium, akinesis, and “ballooning” of the LV wall after coronary artery ligation were followed for a period of 6 to 7 mo after surgery. During the 6-to-7 mo follow-up period, only one rat died (SHR-MI). One rat from each of the SHR and WKY groups that underwent coronary artery ligation was excluded from the analysis at the end of the study since the surgically induced infarct scar was determined to be nontransmural.

**Echocardiography.** To determine the degree of LV dilatation, systolic chamber and myocardial dysfunction, and increases in LV wall stress in noninfarcted myocardium post-MI in vivo, two-dimensionally targeted M-mode echocardiography together with simultaneous invasive carotid blood pressure assessments was employed in ketamine-xylazine anesthetized rats, as previously described (26). Echocardiography was performed using a 7.5-MHz transducer and a Hewlett Packard Sonos 2500 sector scanner to measure LV end-diastolic (LVED) diameter (LVEDD) and LV end-systolic (LVES) internal diameter (LVESD) and LVESD posterior wall thickness (PWT) (5, 26). Simultaneous carotid artery blood pressure measurements were determined from a fluid-filled catheter system, as previously described (26). The LV endocardial fractional shortening (FSend) (FSend = LVEDD − LVESD/LVEDD × 100) and LV relative wall thickness [wall thickness-to-radius ratios (b/r)] were calculated as previously outlined and used as an in vivo assessment of global systolic chamber function and the degree of hypertrophy of viable myocardium, respectively (4, 26). The percent thickening of the LV posterior wall from diastole to systole (LVES PWT − LVED PWT/LVED PWT × 100) was used as an in vivo assessment of regional systolic myocardial (as opposed to global chamber) function in remote noninfarcted myocardium (18). From carotid end-systolic blood pressures (dicrotic notch), LV internal diameters measured at end systole, and LV PWT measured at end systole, LV posterior wall end-systolic stress was estimated as previously described (26).

**Regional systolic function at controlled filling pressures.** Regional (segmental) systolic function was also assessed in viable (noninfarcted) myocardium using techniques previously described and validated (33, 37) in ketamine-xylazine anesthetized rats (26). Regional systolic function was assessed from the percent shortening of the segmental length (LVED length − LVES length/LVED length × 100) in the long axis of the lateral wall of the LV as determined over a range of LVED pressures (LVEDPs) in anesthetized, ventilated, open-chest rats (33, 37). The segmental length changes were measured using piezoelectric ultrasonic transducers connected to the arms of a hinge with two 30-gauge needles attached at the opposite ends of each arm inserted into the myocardium (33, 37). Ultrasonic signals were transmitted through an ultrasonic medium suspended between the needles on the opposite end of the hinge (33, 37). LVESD was measured using a fluid-filled catheter system with an amplitude-frequency response uniform to 10 Hz. The filling pressures were modified using an isovolumetric, isotonic solution injected via a carotid cannula and also using inferior vena cava occlusion. The percent shortening at LVEDP values below 4 mmHg could not be obtained in three rats (2 SHR-Sham and 1 WKY-MI) because of the induction of spontaneous extrastolic beats. Hence, only data obtained above an LVEDP of 4 mmHg are shown.

**Isolated, perfused heart studies.** After the collection of hemodynamic data in vivo, LV remodeling, as well as systolic chamber function, was determined ex vivo under controlled conditions in isolated, isovolumic, retrograde-perfused, constant-flow heart preparations, as previously outlined (26, 38). LV developed- and end-diastolic pressures were measured over a range of filling volumes via a balloon-tipped catheter inserted through the mitral orifice into the LV both in the absence and then again in the presence of isoproterenol (10⁻⁸ M; Sigma). Isoproterenol rather than dobutamine was employed as an inotrope in the present study, since we have previously demonstrated inotropic effects of both β1 (dobutamine) and β2 (salbutamol)-adrenoreceptor agonists in this preparation (28) and, hence, greater inotropic responses to the nonselective β-adrenoreceptor agonist isoproterenol than to dobutamine (26a). LV remodeling and systolic chamber function were assessed by constructing LVED and LVES pressure-volume relations, respectively. LV pressures were measured at 0.005 to 0.01-ml increments in filling volume using a micromanipulator to fill the LV balloon (26, 38). To assess chamber systolic function, LVES elastance (LV Ees) was compared between groups (26, 38). LV Ees was determined from β-coefficients of relationships found to best fit the LVES pressure-volume relation (27). LV volumes were expressed either as absolute values or per 100 g body wt to account for differences in body size between SHR and WKY rats and the impact of body size on filling volumes (39). LV Ees, as opposed to other indexes of LV systolic chamber function, was employed in the present study since LV Ees is both preload and afterload independent and, hence, closely reflects contractile function (26). For statistical comparisons of the degree of LV dilatation produced by MI, the volume intercepts either with or without adjustments for differences in body size at an LVEDP of 0 mmHg (LV V0) were compared (26, 27, 38).

**Scar tissue size.** A discrete border between the scar tissue and viable myocardium 6-to-7 mo posturgery allowed for a clear separation between these areas. Scar tissue size was determined from the area of scar tissue expressed as an absolute value and a percentage of the area of the endocardial surface of viable myocardium obtained from hearts arrested in diastole with a high-K⁺ solution (8 mmol/l) without Ca²⁺. After scar tissue was separated from the viable myocardium, both the scar tissue and the viable LV myocardium were placed on a flat surface, the outer borders were delineated, and the area within the borders was quantified using planimetry.

**Myocardial apoptosis and necrosis.** A longitudinal slice of the LV from the apex to the base through the LV posterior wall viable tissue was obtained from all rats for histology. The LV tissue was stored, prepared, and sectioned as previously described (34) and stained with van Gieson stain. A pathological grade was assigned to each slice, as previously described (34). The degree of apoptosis was quantified on myocardial tissue sections obtained from the same tissue blocks used to assess the pathological score. For each tissue block, 5-μm-thick sections were stained and evaluated. Nuclear deoxyribonucleic acid (DNA) fragments in the tissue sections were detected using a nonradioactive in situ apoptotic cell death detection kit (DeadEnd Colorimetric TUNEL system; Promega, Madison, WI) (27). Terminal deoxynucleotidyl transferase (TdT) was used to incorporate biotinylated nucleotide at the 3′-OH DNA ends. Horseradish peroxidase-labeled streptavidin was then bound to the biotinylated nucleotides, which subsequently stained dark brown in response to hydrogen peroxide and diaminobenzidine. Both positive (DNase treated) and negative (no addition of TdT) control tissue sections were incorporated in each assay. The number of apoptotic cardiomyocyte nuclei and the total number of cardiomyocyte nuclei (hematoxylin and eosin stain) in each slide were counted on 10 evenly spaced fields from the apex to the base using a computer-based image acquisition and analysis system at ×400 magnification (Axiovision 3; Carl Zeiss, Gottingen, Germany). Apoptotic nuclei were expressed as a percentage of the total number of nuclei.

**Data analysis.** Regression analysis was used to determine the lines of best fit for the cardiac function and other relations. The differences between groups were assessed by a two-way ANOVA to test for significant main and interaction effects. All values in the text are represented as means ± SE. P < 0.05 was considered to be significant.
RESULTS

Cardiac structural characteristics. Table 1 summarizes the LV and right ventricular weights and scar tissue size. Sham-operated SHR had a marked increase in LV weight and LV weight per 100 g body wt compared with sham-operated WKY controls (Table 1). Scar tissue weight and scar tissue inner surface areas expressed as a proportion of the inner surface areas of viable tissue were similar between SHR-MI and WKY-MI groups (Table 1). Viable myocardial tissue LV weight per 100 g body wt was reduced post-MI in SHR and WKY groups (Table 1). Viable myocardial tissue weight was nevertheless still greater in SHR compared with WKY rats after MI (Table 1).

LV remodeling. Table 1 also shows the effect of MI on LV dimensions, and Fig. 1 shows the effect of MI on LVED pressure-volume relations in SHR and WKY rats. Sham-operated SHR had a reduced LVEDD and LVEDSD (Table 1), a left shift in the LVED pressure-volume relation (Fig. 1), and a reduced LV V₀ (Table 1) compared with sham-operated WKY rats, changes that may be accounted for by either the smaller body size of SHR or concentric LV remodeling or both. After the LV cross-sectional area (Table 1) and LV volumes (Fig. 1, bottom, and Table 1 for LV V₀) were adjusted for body weight differences, no substantial differences in internal dimensions or diastolic volumes were noted in SHR-Sham rats compared with WKY-Sham rats.

Six to seven months after coronary artery occlusion, marked increases in LV dimensions (Table 1), cross-sectional area (Table 1), a substantial right shift in LVEDD pressure-volume relations (Fig. 1), and an increase in LV V₀ (Table 1) were noted in both WKY-MI and SHR-MI groups. Importantly, after normalizing data to 100 g body wt were adjusted, LV cross-sectional area (Table 1) and volume (Fig. 1, bottom, and Table 1 for LV V₀) were no different between SHR-MI and WKY-MI groups. Although MI increased LV internal diameters (Table 1), the relationship between LVED PWT and the internal radius remained unchanged in either SHR-MI or WKY-MI rats (Table 1).

LV wall stress. LVES posterior wall stress in both SHR-MI and WKY-MI rats was increased to an equivalent extent compared with corresponding sham-operated controls (Table 1). This increase in LVES wall stress after MI was attributed to a decreased LVES hlr (data not shown). The decreased LVES hlr cannot be attributed to adverse LV-chamber remodeling because LV hlr at end diastole was maintained post-MI in SHR and WKY rats (LVED hlr in Table 1). Thus the decrease in LVES hlr and the consequent increase in LVES wall stress post-MI are likely to be a consequence of a reduced LV pump function.

Remote regional systolic function. Figure 2 shows the impact of MI on systolic function in regions distant to the scar as determined 6 to 7 mo after coronary artery occlusion. In intact animals, when we compared sham-operated groups, SHR-Sham rats had normal systolic function in the LV posterior wall (PWT determined using echocardiography) and in viable myocardial tissue in the LV lateral wall (percent shortening of viable tissue) as determined over a range of filling pressures. Six to seven months after MI, although WKY-MI rats still had a preserved systolic function in the posterior and lateral walls of the LV, MI in SHR resulted in a reduction in systolic function in both of these regions in the remaining viable LV myocardium (Fig. 2).

Systolic chamber function. Figures 3 and 4 illustrate the impact of MI on global LV chamber systolic function at baseline and in the presence of a β-adrenergic inotropic stimulus in both SHR and WKY groups. Six to seven months after MI, baseline global LV systolic chamber function assessed in vivo (FS.end) and ex vivo (LV Ees) was reduced in both SHR-MI and WKY-MI groups, and these changes were similar in both groups (Fig. 3). In contrast, however, 6 to 7 months after MI, global LV systolic chamber function (LV Ees) was assessed in the presence of an adrenergic inotropic stimulus

Table 1. LV and RV characteristics, blood pressures, and LV wall stress of normotensive WKY and SHR 6 to 7 mo after MI or sham operations

<table>
<thead>
<tr>
<th></th>
<th>WKY-Sham</th>
<th>WKY-MI</th>
<th>SHR-Sham</th>
<th>SHR-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>6</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Body wt, g</td>
<td>400 ± 17</td>
<td>436 ± 11</td>
<td>360 ± 5*</td>
<td>360 ± 7.5*</td>
</tr>
<tr>
<td>Viable LV weight, g</td>
<td>0.94 ± 0.03</td>
<td>0.86 ± 0.05</td>
<td>1.20 ± 0.03*</td>
<td>1.01 ± 0.04†</td>
</tr>
<tr>
<td>Viable LV weight/body wt × 100</td>
<td>0.24 ± 0.007</td>
<td>0.20 ± 0.009†</td>
<td>0.33 ± 0.009*</td>
<td>0.28 ± 0.01†</td>
</tr>
<tr>
<td>RV weight, g</td>
<td>0.30 ± 0.02</td>
<td>—</td>
<td>0.32 ± 0.02</td>
<td>0.34 ± 0.02</td>
</tr>
<tr>
<td>Scar tissue weight, g</td>
<td>—</td>
<td>0.17 ± 0.02</td>
<td>—</td>
<td>0.17 ± 0.02</td>
</tr>
<tr>
<td>%Scar tissue area</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>85.85 ± 0.01</td>
<td>95.03 ± 0.03†</td>
<td>72.2 ± 0.02*</td>
<td>84.01 ± 0.04†</td>
</tr>
<tr>
<td>LVEDD/100 g body wt</td>
<td>0.135 ± 0.004</td>
<td>0.173 ± 0.009†</td>
<td>0.124 ± 0.009</td>
<td>0.170 ± 0.008†</td>
</tr>
<tr>
<td>LVEDS, cm</td>
<td>47.01 ± 0.01</td>
<td>66.60 ± 0.04†</td>
<td>0.34 ± 0.02*</td>
<td>0.54 ± 0.02†</td>
</tr>
<tr>
<td>LV V₀, ml</td>
<td>0.27 ± 0.006</td>
<td>0.37 ± 0.05†</td>
<td>0.24 ± 0.006*</td>
<td>0.33 ± 0.02†</td>
</tr>
<tr>
<td>LV V₀, ml/100 g body wt</td>
<td>0.060 ± 0.004</td>
<td>0.091 ± 0.013†</td>
<td>0.071 ± 0.002</td>
<td>0.092 ± 0.007†</td>
</tr>
<tr>
<td>LVESD, ml</td>
<td>36.0 ± 0.02</td>
<td>34.0 ± 0.04</td>
<td>0.54 ± 0.04*</td>
<td>0.57 ± 0.03*</td>
</tr>
<tr>
<td>LVESD, hlr</td>
<td>120 ± 129</td>
<td>141 ± 5/102 ± 5</td>
<td>181 ± 4/120 ± 4*</td>
<td>161 ± 6/117 ± 3*</td>
</tr>
<tr>
<td>LVES stress, g/cm²</td>
<td>43 ± 4</td>
<td>62 ± 2*</td>
<td>42 ± 3</td>
<td>62 ± 2*</td>
</tr>
<tr>
<td>LV pathological score</td>
<td>1.10 ± 0.37</td>
<td>1.54 ± 0.16</td>
<td>1.63 ± 0.24</td>
<td>1.71 ± 0.21</td>
</tr>
<tr>
<td>%LV apoptotic/normal nuclei</td>
<td>0.11 ± 0.03</td>
<td>0.14 ± 0.09</td>
<td>0.13 ± 0.02</td>
<td>0.12 ± 0.02</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = number of rats. LV, left ventricular; RV, right ventricular; WKY, Wistar-Kyoto rat; SHR, spontaneously hypertensive rat; MI, myocardial infarction; Sham, sham operations; LVEDD, LV end-diastolic (LVED) diameter; LVEDSD, LV end-diastolic (LVED) diameter; LV V₀, volume intercepts of LV diastolic pressure-volume relations depicted in Fig. 1; SBP, systolic blood pressure; DBP, diastolic blood pressure; %Scar tissue area, scar tissue area/viable tissue area; LVED hlr, LVED wall thickness (h)-to-radius (r) ratio from echocardiography; %LV apoptotic/normal nuclei, apoptotic nuclei expressed as a percent of the number of normal nuclei. *P < 0.05 vs. WKY groups; †P < 0.05 vs. WKY or SHR-Sham.
was reduced in the SHR-MI group to values lower than those noted in WKY-MI rats (Fig. 4).

Myocardial apoptosis and necrosis in noninfarcted tissue.
Table 1 also shows terminal deoxynucleotidyl transferase biotin-dUTP nick-end labeling (TUNEL)-positive nuclear scores and pathological scores in adjacent areas of noninfarcted tissue in SHR-MI and WKY-MI and in similar regions of the heart in sham-operated SHR and WKY rats. Neither excessive TUNEL-positive scores nor increased pathological scores were a feature of SHR-Sham rats at this age. MI failed to promote increases in TUNEL-positive or pathological scores in these tissue regions in either infarcted group.

DISCUSSION

The main findings of the present study are as follows. First, 6 to 7 mo after a moderate-sized LV anterolateral wall MI (~25% of the LV), SHR but not WKY rats had reduced regional myocardial systolic function in both the posterior (echocardiography) and lateral (over a range of filling pressures as determined with ultrasonic transducers) walls of viable tissue of the LV. Second, regional myocardial systolic abnormalities in SHR did not translate into a reduced global LV systolic chamber function at baseline but could explain a reduced global systolic chamber function in the presence of an adrenergic inotropic stimulus. Third, regional myocardial systolic abnormalities in SHR-MI rats were not associated with an increased scar tissue-viable tissue surface area, an enhanced degree of LV dilatation or relative wall thinning, alterations in viable tissue wall stress, or excessive apoptosis or necrosis in viable tissue.

The present study is the first to explore whether the hypertensive heart is susceptible to alterations in regional myocardial systolic function in tissue adjacent and remote from an infarct. In this regard, previous studies have focused on the role of regional myocardial systolic dysfunction remote from an infarct in the normotensive heart after a MI. Although some studies have reported on a decreased systolic function in isolated cardiomyocytes (4, 17, 35, 40), papillary muscle (19, 21), isolated trabeculae (6), and regional tissue (18) from the viable myocardium remote from infarcted tissue in normotensive hearts after a MI, in keeping with the present study, not all studies have reproduced these findings in normotensive animals (1a, 2, 9, 13, 15, 16, 20, 31). A number of factors could explain the discrepancies between studies including the size of the MI produced, where a MI that is larger may result in...
regional viable tissue systolic abnormalities (18) compared with a smaller MI where viable tissue systolic abnormalities are not noted (9, 13), or species differences between studies (2, 13, 35). Irrespective of discrepancies in normotensive hearts, the present study provides clear evidence that the hypertensive heart is susceptible to decreases in regional myocardial systolic function in tissue remote from an infarct post-MI. These data are in keeping with a reduced adrenergic inotropic response of the papillary muscle in SHR after a MI (14).

In the present study, a number of mechanisms were explored to attempt to explain an increased susceptibility of the hypertensive heart to decreases in regional myocardial systolic function in tissue remote from an infarct post-MI. In this regard, although the measurements of LV regional myocardial systolic function are load dependent, the reduction in posterior wall systolic function in SHR after a MI was associated with an estimated LVES wall stress comparable with WKY rats with a MI. Furthermore, the reduction in LV lateral wall systolic function in SHR after a MI occurred over a range of filling pressures. Thus the susceptibility of the hypertensive heart to decreases in LV regional myocardial systolic function in tissue adjacent to or remote from an infarct post-MI does not appear to be either afterload or preload dependent. However, these results do not exclude the possibility that complex interactions between the LV and large vessels may not contribute toward decreases in regional myocardial systolic function in tissue adjacent to or remote from an infarct post-MI in SHR.

Alterations in LV regional myocardial systolic function in noninfarcted tissue after a MI have previously been attributed to cardiac dilatation (18), producing an increase in LV wall stress and, hence, myocardial dysfunction. In this regard, a similar degree of LV dilatation and increases in LVES wall stress were noted in both SHR- and WKY-infarcted groups. Thus excessive cardiac dilatation is unlikely to contribute toward the increased susceptibility of SHR to developing LV regional myocardial systolic dysfunction in noninfarcted tissue after a MI compared with that in WKY rats.

Viable myocardium from SHR, but not WKY rats, with a MI has been previously reported to develop upregulated G protein, a change that may translate into a reduced contractile response to an adrenergic stimulus (14). This is consistent with the finding in the present study of a reduced LV systolic chamber function noted after a MI in SHR compared with WKY rats only in the presence of an adrenergic stimulus. Importantly, in contrast to a previous study where it was unclear whether similar changes occurred in WKY rats (14), the present study suggests that systolic function in the presence of an adrenergic stimulus is reduced in SHR compared with WKY rats post-MI. Moreover, in a previous study showing a reduction in systolic function in the presence of an adrenergic...

Fig. 3. Baseline LV systolic chamber function in SHR and WKY rats 6 to 7 mo after a MI or Sham. Fractional shortening was determined at the endocardial surface (FSend), and LV systolic elastance (LV $E_{es}$) was determined from the regression coefficient of the LV end-systolic (LVES) pressure-volume relations depicted. LV volume was normalized to 100 g body wt. *$P < 0.01$ vs. respective sham-operated groups. See Table 1 for sample sizes.

Fig. 4. LV systolic chamber function in the presence of isoproterenol ($10^{-8}$ M Iso) in SHR and WKY rats 6 to 7 mo after MI or sham operations. Top: LVES pressures determined over a range of LV volumes (normalized to 100 g body wt). Bottom: LV $E_{es}$ determined from the regression coefficient of the relations depicted. *$P < 0.01$ vs. the sham-operated groups; †$P < 0.04$ vs. WKY-MI group. See Table 1 for sample sizes.
stimulus in SHR after MI, the reduction in systolic cardiac function may have been attributed to an enhanced degree of cardiac dilatation (14). In contrast, in the present study, the reduced LV systolic chamber function noted in the presence of an adrenergic stimulus in SHR-MI rats was not associated with an enhanced degree of cardiac dilatation and, hence, is more likely to be attributed to a depressed systolic function of viable myocardium.

After MI, an enhanced myocardial expression of inducible nitric oxide synthase (iNOS) occurs in stroke-prone SHR compared with WKY rats, and the blockade of iNOS is associated with an attenuated decline in systolic cardiac function post-MI in stroke-prone SHR (1). Thus changes in nitric oxide, in part through reactive oxygen species, could also explain the regional myocardial systolic abnormalities noted in SHR, but not WKY rats, in the present study. However, it is unclear whether iNOS-induced systolic functional abnormalities post-MI in stroke-prone SHR are due to an impact on infarct size, increases in chamber dimensions and, hence, wall stress, or decreases in myocardial function in viable tissue (1).

Although upregulated G-proteins (14) or an increased iNOS (1) could explain the reduced myocardial systolic function in remote viable tissue in SHR after a MI, alternative changes have been described in the remote tissue of normotensive hearts after MI, which could also explain these findings. These include alterations in Ca\(^{2+}\) handling, sarcoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA) expression, and the degree of troponin I phosphorylation or degradation (35). These potential mechanisms previously described (35) may be enhanced in the hypertensive heart post-MI, and this hypothesis requires further study. Moreover, an increased cardiomyocyte apoptosis has previously been shown to occur in the viable tissue of rats with a MI (9), a change that may promote regional myocardial systolic dysfunction. However, in the present study, neither excessive apoptosis nor necrosis was associated with regional myocardial dysfunction in SHR with a MI.

An inability of hypertension and cardiac hypertrophy to increase the susceptibility of the myocardium to infarct expansion and cardiac dilatation post-MI in the present study is in apparent contrast to previous studies (10–12, 23–25, 30). Importantly, cardiac dilatation was assessed 6 to 7 mo after MI in the present study, a time period over which maximal LV dilatation is expected to occur. Moreover, not all studies have demonstrated an increased susceptibility to infarct expansion and cardiac dilatation post-MI in the hypertensive heart (22, 39), and some have even shown a protective effect of hypertensive hypertrophy (22). A potential explanation for these apparent discrepancies may be related to the size of the infarct studied or differences between studies in the time period after coronary artery occlusion when cardiac dimensions were assessed. Previous studies have demonstrated that the hypertensive heart does not increase the degree of adverse chamber remodeling if infarct sizes are similar to that reported on in the present study (24). However, with much larger infarcts of ~50% of the LV, the hypertensive heart is more susceptible to adverse LV remodeling (24).

In conclusion, the present study suggests that, as assessed after an extended period post-MI, the hypertensive heart is more susceptible to a depressed LV regional myocardial systolic function in both the adjacent and remote noninfarcted LV myocardium subsequent to a left anterior descending MI but that these changes cannot be explained by excessive LV dilatation, relative wall thinning, an increased increase in wall stress, apoptosis (TUNEL), or necrosis. Although these LV regional myocardial systolic abnormalities in hypertension may not manifest as alterations in LV global dysfunction under baseline conditions, such as at rest, they could contribute toward a reduced global LV systolic chamber function in the presence of an adrenergic inotropic stimulus, such as that which occurs with exercise. These findings lend further insight into the mechanisms of pump failure after MI in the hypertensive heart.

REFERENCES


