Time course of right ventricular remodeling in rats with experimental myocardial infarction

MATTHIAS NAHRENDORF,1 KAI HU,1 DANIELA FRACCAROLLO,1 KARL-HEINZ HILLER,2 AXEL HAASE,2 WOLFGANG R. BAUER,1 AND GEORG ERTL1
1Department of Internal Medicine, 97080 Würzburg; and 2Department of Biophysics Experimentelle Physik, University of Würzburg, 97074 Würzburg, Germany
Submitted 28 June 2002; accepted in final form 9 September 2002

Nahrendorf, Matthias, Kai Hu, Daniela Fraccarollo, Karl-Heinz Hiller, Axel Haase, Wolfgang R. Bauer, and Georg Ertl. Time course of right ventricular remodeling in rats with experimental myocardial infarction. Am J Physiol Heart Circ Physiol 284: H241–H248, 2003.—Right ventricular (RV) remodeling is observed after large myocardial infarction (MI) in rats. RV weight increases dependent on time after MI. RV pressure-volume curves were shifted toward larger volumes 16 wk after MI. The ratios of β-myosin heavy chain (MHC) to α-MHC and skeletal to cardiac α-actin were determined for the RV and LV after large MI or sham operation. RV weight increased in rats with MI, as did RV volume. RV pressure-volume curves were shifted toward larger volumes 16 wk after large MI. RV systolic pressure increased gradually over time; however, the gain in RV weight was always in excess of RV systolic pressure. The ratios of skeletal to cardiac α-actin and β-MHC to α-MHC were increased after MI in both ventricles in a similar fashion. Because RV wall stress was not increased after infarction, mechanical factors may not conclusively explain hypertrophy, which maintained balanced loading conditions for the RV even after large LV infarction. RV remodeling might be triggered by changes of LV hemodynamics, but there may be influences of other factors such as humoral activation as well. The purpose of the present study was therefore to test the hypothesis that RV changes after LV MI are not solely due to RV volume overload caused by LV backward failure. In addition, the value of cine-MRI for assessment of the RV was tested for the rat MI model. Furthermore, passive pressure-volume curves, which are an established technique for the LV, were acquired for the RV.

METHODS

Animals and experimental MI. Adult male Wistar rats were used, which weighed 269 ± 3 g at the beginning of the study. Coronary artery ligation was performed as described previously under ventilation and ether anesthesia (7, 10, 22). The left anterior descending branch was ligated between the pulmonary outflow tract and the left atrium. A total of 134 rats were subjected to coronary ligation; 19 rats were sham operated. The mortality of this procedure was 50%. All procedures were approved by the institutional animal research committee.

MRI. MRI was performed 2 and 8 wk after MI on a 7-T Biospec (Bruker) under inhalation anesthesia applied by nose cone (1.5 vol% isoflurane supplemented by 0.5 l/min oxygen). An ECG-triggered fast-gradient echo sequence (FLASH) (8) was used with the following parameters: flip angle 30°, echo time 1.1 ms, repetition time 3.2 ms, and 12 frames/heart cycle. Eighteen to twenty-two contiguous ventricular short-axis slices of 1 mm thickness with no interslice gap were acquired to cover the entire range of the ventricles. With a field of view of 50 mm and an image matrix of 128 × 128, the in-plane resolution was 390 μm. Data analysis was performed with an operator-interactive threshold technique by one trained observer as described previously (18). In all slices, myocardial and ventricular volumes were determined from end-diastolic and end-systolic images by multiplication of compartment area and slice thickness (1 mm). Total volumes were calculated as the sum of all slice volumes. LV mass was calculated as LV end-diastolic myocardial volume multiplied by the myocardial-specific gravity (1.05 g/cm³). Stroke volume (SV) and ejection fraction (EF) were calculated with the end-diastolic (EDV) and end-systolic (ESV)
volumes (SV = EDV – ESV; EF = SV/EDV). For cardiac output, SV was multiplied by heart rate (HR). For calculation of time-volume curves to characterize filling dynamics, all 12 time frames of a single midventricular slice were used for segmentation of RV and LV slice volume.

RV mass was not determined because the spatial resolution was deemed insufficient for reliable segmentation of the thin RV wall. However, RV wall thickness was measured in a midventricular slice and used for estimation of hypertrophy. Wall thickness was measured in three segments of the RV wall, and mean wall thickness was measured from end-diastolic and end-systolic frames and used for calculation of wall thickening.

MI size was determined for every slice as the myocardial portion of the LV with significant thinning and akinesia or dyskinesia during systole (18). Relative MI size was calculated by taking the sum of the endocardial and epicardial circumferences of end-systolic frames occupied by the MI and dividing by the sum of the total endocardial and epicardial circumferences (18).

**Hemodynamic measurements and pressure-volume curves.** For the RV, passive seven weeks after MI, rats were anesthetized with ether. Cannulas were inserted into the trachea for artificial ventilation, into the right carotid artery and jugular vein, and into a femoral vein. Pressures were measured through a short segment of fluid-filled polyethylene (PE)-50 tubing connected to a microtip manometer (Millar). The carotid cannula was advanced into the LV and then withdrawn to the aortic arch while pressures were recorded. The jugular vein cannula was advanced into the RV. LV and RV systolic (LVSP and RVSP) and end-diastolic pressures (LVEDP and RVEDP), the maximum rate of rise of LVSP and RVSP (LV dP/dt max and RV dP/dt max), mean arterial pressure (MAP), and HR were measured under light ether anesthesia and spontaneous respiration. Mean right atrial pressure (RAP) and HR were measured under light ether anesthesia and spontaneous respiration. Mean right atrial pressure (RAP) was measured after the right jugular vein catheter was withdrawn to the right atrium. A flow probe (2.5 or 3.0 mm; Statham) was placed around the ascending aorta for measurement of aortic blood flow, which was taken as the cardiac index (CI) (22). Systemic vascular resistance index was calculated as (MAP – RAP)/CI and was expressed as millimeters of mercury per milliliter per minute per kilogram of body weight. Thereafter, warmed (39–40°C) Tyrode solution was infused into a femoral vein at a rate of 40 ml·kg⁻¹·min⁻¹ for 45 s (22). Maximum cardiac performance was defined as peak values of cardiac output and SV during Tyrode infusion. Ten to fifteen minutes after the volume load, the arterial catheter was advanced into the LV. A second volume loading was applied to determine the peak LVEDP and RVEDP. Passive pressure-volume curves of the LV were obtained as previously described (6). The heart was arrested by potassium chloride, and a double-lumen catheter (PE-50 inside PE-200) was inserted into the LV via the ascending aorta. The atrioventricular groove was ligated, and isotonic saline was infused at a rate of 0.76 ml/min via one lumen while intraventricular pressure was recorded through the other with an open catheter in the LV. Two pressure-volume curves were recorded for both ventricles.

**PCR.** Total RNA was isolated from surviving LV myocardium (septum) and the RV free wall of rats with large MI with TRIzol reagent (Invitrogen). After reverse transcription (SuperScript II, Invitrogen), α- and β-myosin heavy chain (MHC) iso-mRNAs and skeletal cardiac α-actin iso-mRNAs were amplified by PCR as previously described (13) with digoxigenin-labeled forward primers. After digestion with the restriction enzyme Tru9I for MHC and SacI for α-actin (Roche), fragments of the PCR amplification product were separated on 8% and 6% polyacrylamide gels, respectively (lengths: 309 bp for α-MHC and 259 bp for β-MHC; 202 bp for skeletal and 161 bp for cardiac α-actin). DNA fragments were transferred onto a nylon membrane positively charged (Roche) and exposed to film suitable for detection of chemiluminescence (Kodak BioMax Light). The resultant bands on the autoradiograms were then quantified with NIH Image (version 1.61, National Institutes of Health, Bethesda, MD), and results were expressed as ratios of β- to α-MHC mRNA and skeletal cardiac α-actin mRNA.

**Infarct size.** Histological measurement of MI size was performed as previously described in the hemodynamic groups (22, 31). The hearts were fixed in formalin, embedded in paraffin, sliced in serial sections from apex to base, mounted, and stained with Sirius red. Infarct size was determined by planimetric measurement with a digital image system (Mocha computer digitizing program) and calculated by dividing the sum of endocardial and epicardial circumferences occupied by the infarct by the sum of the total endocardial and epicardial circumferences.

**Data analysis.** Results are expressed as means ± SD unless otherwise indicated. Infarcts were classified as small (<35%) and large (>35%). In a previous serial MR study, 35% has been shown to be the cutoff value between large MI progressing into heart failure and small MI without progressive dilatation (19). Total pulmonary vascular resistance (PVR) was calculated as RVSP divided by CI. Pre-capillary PVR was defined by (RVSP – LVEDP) divided by CI, because pulmonary arterial pressure was not measured. An estimate of RV end-diastolic wall stress was calculated from hemodynamic data as (RVEDP × RV operating volume)/RV weight and from MRI data as RVEDV/RV end-diastolic wall thickness. An estimate of RV systolic wall stress was calculated as RVSP/RV weight.

Statistical comparisons among various groups over time were evaluated by ANOVA, followed by Duncan test to isolate significance of differences between individual means. P < 0.05 was considered to indicate statistical significance.

**RESULTS**

**Animal numbers, infarct size, body weights, and ventricular weights.** Histological infarct size was similar 4, 8, and 16 wk after MI, and therefore comparisons between time points are feasible. The RV weight-to-body weight ratio (RV/BW) was unchanged in rats with small MI but significantly increased in rats with large MI over time (Table 1).

**MRI.** With cine-FLASH MRI, RV volumes were determined in serial measurements. LV infarct size was 36% at 2 and 8 wk after MI as measured by MRI. In a previous study (18), we found the following relation between MRI and histological determination of MI
Table 1. Infarct size, RV weight, and hemodynamics

<table>
<thead>
<tr>
<th>MI %</th>
<th>BM</th>
<th>RVBW, g/kg</th>
<th>LVEDP, mmHg</th>
<th>RAP, mmHg</th>
<th>RVSP, mmHg</th>
<th>RV dP/dt max, mmHg·s⁻¹·10³</th>
<th>RVEDP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (n = 10)</td>
<td>4 wk (n = 13)</td>
<td>8 wk (n = 9)</td>
<td>16 wk (n = 9)</td>
<td>4 wk (n = 8)</td>
<td>8 wk (n = 8)</td>
<td>16 wk (n = 8)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27 ± 7</td>
<td>30 ± 6</td>
<td>30 ± 9</td>
<td>41 ± 8</td>
<td>45 ± 5</td>
<td>44 ± 8</td>
<td></td>
</tr>
<tr>
<td>3.9 ± 3.1</td>
<td>4.0 ± 2.5</td>
<td>3.9 ± 1.5</td>
<td>3.0 ± 2.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35 ± 6.3</td>
<td>36 ± 7</td>
<td>32 ± 6</td>
<td>32 ± 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.9 ± 1.2</td>
<td>3.1 ± 1.1</td>
<td>1.8 ± 0.6</td>
<td>2.0 ± 0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.51 ± 0.06</td>
<td>0.54 ± 0.1</td>
<td>0.57 ± 0.24</td>
<td>0.48 ± 0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. MI, myocardial infarction; BW, body weight; LVEDP, left ventricular (LV) end-diastolic pressure; RAP, right atrial pressure; RVSP, right ventricular (RV) systolic pressure; dP/dt max, maximum rate of systolic pressure increase; RVEDP, RV end-diastolic pressure.

- MI < 36% as found in the MI group yields a theoretical histological MI size of 40% and is therefore in the range of large infarcts seen in the hemodynamic group.

Typical MR images are shown in Fig. 1. To cover the entire RV, three to five additional short-axis slices in the superior direction had to be acquired because the roof of the RV is shifted cranially compared with the LV (Fig. 1). To prove that the quality of RV MRI is sufficient for volumetry, LV (LCO) and RV output (RCO) were compared. LCO was not significantly different from RCO (LCO: 118.5 ± 35.3 ml/min, RCO: 127.9 ± 35.7 ml/min; 8 wk after surgery, n = 21) with significant correlation (LCO = 27.6 ± 0.71RCO; R² = 0.52, P < 0.05).

As shown in Fig. 2, LVEDV and RVEDV increased from 2 to 8 wk after myocardial infarction. The increase of RVEDV between 2 and 8 wk was significantly higher in the MI group [ sham: +68.3 ± 39.1 µl (n = 9), MI: +175.9 ± 65.2 µl (n = 12), P < 0.05] and correlated to infarct size (r = 0.72, P = 0.004). RV end-diastolic wall thickness was significantly increased only in the MI group (Table 2). Compared with sham-operated rats, RV EF was lower at 2 wk (Table 2). At 2 wk after MI, RCO was lower than in sham rats but returned to normal 8 wk after MI. RV wall thickening was impaired 8 wk after MI.

In rats with large infarction, maximal RV and LV volumes did not occur at the same time point of the cardiac cycle. Maximal LV and RV slice volumes were found to be one to two image frames apart from each other (example shown in Fig. 3). These frames were recalculated into time (individual sampling time for cardiac cycle divided by number of frames), and the result was a mean delay of peak RV filling of 11 ± 14 ms at 2 wk and 16 ± 17.5 ms at 8 wk after MI. In infarcted rats this delay was found to be correlated to infarct size at 2 and 8 wk (2 wk: r = 0.54; 8 wk: r = 0.66; both P < 0.05) and inversely correlated to RV EF at 8 wk only (r = −0.54; P < 0.05, both n = 12). Despite the desynchronization of RV and LV diastolic filling, end systole was always coincident. In sham-operated rats no RV delay was observed (example shown in Fig. 3).

MRI parameters of LV remodeling consisting of LV dilatation and hypertrophy are displayed in Table 2.

Hemodynamic measurements. LVSP and MAP tended to decrease after MI (data not shown). LVEDV substantially increased in rats with large MI. RAP tended to increase in rats with MI. In rats with large MI, RVSP increased at 16 wk and RV dP/dt max increased at 4 wk after operation but remained unchanged in other groups. RVEDV also did not change in MI rats (Table 1). Peak LVSP during volume loading increased in rats with large MI 8 and 16 wk after operation (not shown), whereas peak RVEDV remained unchanged (Table 3).

RV passive pressure-volume curves of rats with small MI remained unchanged. A rightward shift toward larger volumes occurred in rats with large MI at 16 wk (Fig. 4). Total PVR was increased in rats with large MI 16 wk after operation, but precapillary PVR did not change after MI (Table 3). RV volume-to-mass ratio was normal in rats with small MI (not shown) and shifted to the right 4 wk after large MI but was back to normal 8 wk after MI (Fig. 5). RV operating volume increased by trend after large MI. RV end-diastolic wall stress remained unchanged after MI (Table 3). RV systolic pressure-to-weight ratio was decreased in rats with large MI 16 wk after operation (Table 3).

LV passive pressure-volume curves showed a rightward shift toward larger volumes in proportion to MI size and time after MI (not shown). These data were in good accordance with LV dilatation detected by MRI (Fig. 2). In contrast to RV volume-to-mass ratio, LV volume-to-mass ratio was shifted toward larger volumes in proportion to MI size and over time after MI.

Hypertrophic markers. The ratio of β-MHC to α-MHC was significantly higher in rats 12 wk after large MI in the RV as well as in the LV (sham LV: 0.28 ± 0.02, MI LV: 1.13 ± 0.26, sham RV: 0.17 ± 0.16, MI RV: 1.43 ± 0.34, P < 0.001 MI vs. respective sham-operated rat). The ratio of skeletal to cardiac α-actin was changed in a similar fashion by myocardial infarction (sham LV: 0.12 ± 0.02, MI LV: 0.41 ± 0.22, sham RV: 0.24 ± 0.05, MI RV: 0.58 ± 0.12, P < 0.001 MI vs. respective sham-operated rat). There were no
significantly differences between the RV and the LV in either ratios. RV β-MHC/α-MHC correlated to RV/BW ($r = 0.96$, $P = 0.0002$) and RV skeletal/cardiac α-actin correlated to RV/BW ($r = 0.85$, $P < 0.005$).

**DISCUSSION**

In this study, the time course of changes in RV morphology, function, and hemodynamics after LV MI have been followed for the first time. Even in rats after large MI, hypertrophy and dilatation remained balanced, with no increase in wall stress or chronic decline of RV function. RV volume overload was also not detected. RV diastolic peak filling was found to be delayed. RV MR volumetry in the rat model of MI and application of pressure-volume curves for assessment of RV remodeling proved feasible.

*Validity of RV MRI.* MRI, the gold standard for RV volumetry in humans (3, 21, 29), was used for the first time to assess RV changes in a LV infarct rat model. In this study, RV data were measured from LV short-axis slices, because a study by Jauhiainen et al. (12) showed no advantage of different slice angulations in human cardiac casts for RV volumetry. As shown in RESULTS, RCO correlates reasonably with LCO. This may serve as evidence that the quality of RV MRI is sufficient for reliable volumetry in this model. A higher correlation of RCO to LCO might be achieved in an experimental setting with more scattering of cardiac output values, for instance, in a study using rats of different ages.

*RV remodeling.* The present study documents a remarkable ability of the RV to compensate for increased afterload due to LV infarction and dysfunction. RV weight was increased in rats with large MI compared with sham-operated rats and rats with small MI after 8 wk, as was RV wall thickness shown by MRI. These observations are in good accordance with previous studies in this model (7, 10, 22, 32). Consistent with the increase of RV mass, increased ratios of β-MHC to α-MHC and skeletal to cardiac α-actin were found. Although the initial injury by ischemia was imposed on...
Table 2. LV and RV morphology and performance in MRI

<table>
<thead>
<tr>
<th></th>
<th>Sham (n = 9)</th>
<th>MI (n = 12)</th>
<th></th>
<th>Sham (n = 9)</th>
<th>MI (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ML, %</td>
<td>0</td>
<td>0</td>
<td>2 wk</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>369 ± 50</td>
<td>0</td>
<td>36 ± 14</td>
<td>317 ± 35†</td>
<td>314 ± 52</td>
</tr>
<tr>
<td>LV mass, mg</td>
<td>636.6 ± 104.7</td>
<td>755.7 ± 97.2*</td>
<td>698.0 ± 92.8</td>
<td>884.1 ± 136.1†</td>
<td></td>
</tr>
<tr>
<td>LV EF, %</td>
<td>72.5 ± 4</td>
<td>70.8 ± 4.8</td>
<td>39.9 ± 10.5†</td>
<td>34.6 ± 15.3†</td>
<td></td>
</tr>
<tr>
<td>RV EF, %</td>
<td>76.3 ± 6.9</td>
<td>70.7 ± 3.5*</td>
<td>62.3 ± 11.4†</td>
<td>61.6 ± 14.5</td>
<td></td>
</tr>
<tr>
<td>RV CI, ml·min⁻¹·kg⁻¹</td>
<td>344.7 ± 66.9</td>
<td>298.0 ± 45.3</td>
<td>283.5 ± 89</td>
<td>224.5 ± 187.4†</td>
<td></td>
</tr>
<tr>
<td>RV SV, µl</td>
<td>108.5 ± 35.4</td>
<td>153.6 ± 33*</td>
<td>181.4 ± 76.2†</td>
<td>255.2 ± 115.7†</td>
<td></td>
</tr>
<tr>
<td>RV EDV/WT, mm</td>
<td>349.9 ± 75.3</td>
<td>373 ± 67.8</td>
<td>295.1 ± 80</td>
<td>397.2 ± 96.3*</td>
<td></td>
</tr>
<tr>
<td>RV ESV, µl</td>
<td>108.5 ± 35.4</td>
<td>153.6 ± 33*</td>
<td>289.2 ± 75.3*</td>
<td>275.1 ± 103.2</td>
<td></td>
</tr>
<tr>
<td>RV SWT, %</td>
<td>92.4 ± 71.1</td>
<td>70.8 ± 41.1</td>
<td>82.1 ± 30.8</td>
<td>39.4 ± 22.2†‡</td>
<td></td>
</tr>
<tr>
<td>RV end-diastolic WT, mm</td>
<td>0.7 ± 0.3</td>
<td>1.0 ± 0.3</td>
<td>0.8 ± 0.1</td>
<td>1.1 ± 0.35*</td>
<td></td>
</tr>
<tr>
<td>RV EDV/WT, µl/mm</td>
<td>670.5 ± 211.3</td>
<td>545.9 ± 145.4</td>
<td>607.1 ± 127.3</td>
<td>659.3 ± 293.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; CI, cardiac output/body weight; SWT, wall thickening; WT, wall thickness. *P < 0.05 vs. 2 wk, †P < 0.05 vs. sham.

the LV, the changes of hypertrophic markers occurred equally in both ventricles.

Dilatation of the RV was detected by a shift of pressure-volume curves toward larger volumes. This dilatation was confirmed by serial MRI. In contrast to LV remodeling (19), RV dilatation seen in rats with large MI did not result in increased wall stress. The increase in RV weight over time was greater than the increase in volume. For the LV, a progressive increase in volume-to-mass ratio was seen, which stabilized between 8 and 16 wk after MI as previously reported for rats with this MI size (19). For the RV, this ratio instead decreased over time. At in vivo RVEDP ("operating volume"), it was in a normal range for all groups of MI rats at all times (Fig. 4). From MRI data, an estimation of RV wall stress was calculated by the quotient RVEDV/RV wall thickness, which was not significantly different from that in sham-operated rats and did not change from 2 to 8 wk (Table 2). These data suggest that diastolic wall stress was not increased and RV volume overload did not occur. This observation is in accordance with previous reports on regional biochemical changes in the heart after MI (1, 11, 15). Total creatine kinase was reduced in the surviving myocardium of the rat LV 8 wk after MI but normal in RV myocardium (15). It has been suggested that decreased creatine kinase activity indicates pump failure (11). Calcium uptake was reduced in the LV 4 and 8 wk after MI but increased in the RV (1). In contrast, reprogramming of the isoenzyme pattern of creatine kinase and myosin and reexpression of atrial natriuretic peptide occurred homogeneously in both ventricles (15, 17).

Because RV systolic volume, which is sensitive to pulmonary arterial pressure, was not measured in the hemodynamic group, assumptions about systolic wall stress remain uncertain (14). RVSP was increased in rats with large MI 16 wk after operation. Nevertheless, markedly increased RV weight maintained RVSP-to-weight ratio in the range of that in sham-operated animals. In addition, at the time when RV hypertrophy developed, 4 and 8 wk after MI, RVSP was not elevated. Despite hypertrophy, RV chamber stiffness constants also remained within a normal range after MI (data not shown), most likely because changes of mass were in proportion to changes of volume. Accordingly, RV function was depressed 2 wk after MI (decreased RCO in MRI) but later returned to adequate levels as suggested by the normal RVSP, RVEDP, and RV dP/
RV REMODELING AFTER MYOCARDIAL INFARCTION

Table 3. Peak cardiac performance, total and precapillary PVR, operating volume/ventricular weight ratios, and RV end-diastolic wall stress

<table>
<thead>
<tr>
<th></th>
<th>Sham (n = 10)</th>
<th>Small Infarction (&lt;35%)</th>
<th>Large Infarction (≥35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 wk (n = 13)</td>
<td>8 wk (n = 9)</td>
<td>16 wk (n = 9)</td>
</tr>
<tr>
<td>RVSP\textsubscript{max}, mmHg</td>
<td>37 ± 6.3</td>
<td>32 ± 14</td>
<td>34 ± 3</td>
</tr>
<tr>
<td>RV dP/dt\textsubscript{max}, mmHg/s \times 10^3</td>
<td>2.6 ± 0.63</td>
<td>2.3 ± 1.4</td>
<td>2.0 ± 0.6</td>
</tr>
<tr>
<td>RV dP/dt\textsubscript{max}, mmHg</td>
<td>10.1 ± 3.1</td>
<td>9.1 ± 3.9</td>
<td>12.1 ± 3.3</td>
</tr>
<tr>
<td>Total PVR, mmHg/ml\textsuperscript{-1-min\textsuperscript{-1}-kg\textsuperscript{-1}}</td>
<td>0.19 ± 0.03</td>
<td>0.20 ± 0.07</td>
<td>0.26 ± 0.06</td>
</tr>
<tr>
<td>Precapillary PVR, mmHg/ml\textsuperscript{-1-min\textsuperscript{-1}-kg\textsuperscript{-1}}</td>
<td>0.15 ± 0.03</td>
<td>0.16 ± 0.03</td>
<td>0.19 ± 0.06</td>
</tr>
<tr>
<td>LV vol/LV weight, ml/g</td>
<td>0.31 ± 0.12</td>
<td>0.50 ± 0.21</td>
<td>0.60 ± 0.18</td>
</tr>
<tr>
<td>RV vol/RV weight, ml/g</td>
<td>1.33 ± 0.69</td>
<td>1.55 ± 0.61</td>
<td>1.73 ± 0.72</td>
</tr>
<tr>
<td>RV end-diastolic wall stress, mmHg/ml-mg\textsuperscript{-1}</td>
<td>6.17 ± 9.34</td>
<td>6.77 ± 5.37</td>
<td>7.09 ± 5.1</td>
</tr>
<tr>
<td>RVSP/RV weight, mmHg/g</td>
<td>184 ± 41</td>
<td>186 ± 43</td>
<td>149 ± 39</td>
</tr>
</tbody>
</table>

Values are means ± SD. RVSP\textsubscript{max}, RVSP corresponding to peak stroke volume index (SVI); RV dP/dt\textsubscript{max}, RV dP/dt corresponding to peak SVI; PVR, pulmonary vascular resistance; LV vol, LV operating volume; RV vol, RV operating volume; *P < 0.05 vs. sham; †P < 0.05 vs. small MI (4 wks); ‡P < 0.05 vs. sham-operated rats. 

Fig. 4. RV passive pressure-volume curves in rats with large MI. Area between the 2 dotted lines represents the mean ± 2SE of sham-operated rats (n = 10). Vertical arrows indicate the baseline RV operating volumes (n = 8 for every time point). \(\dagger\)P < 0.05 vs. sham-operated rats.

Fig. 5. RV volume-to-RV weight ratio in rats with large MI (n = 8 for every time point). Area between the 2 dotted lines represents the mean ± 2SE of sham-operated rats. \(\dagger\)P < 0.05 vs. sham-operated rats (n = 10).

d\textsubscript{1max} at baseline and during volume loading and normal RCO and improved EF at 8 wk after MRI.

Total and precapillary pulmonary vascular resistance [RVSP/CI and (RVSP – LVEDP)/CI] were estimated with RVSP because mean pulmonary artery pressure was not available. The data suggest that an increase in precapillary PVR was small even in rats with large MI because RVSP increased by 5 mmHg versus sham-operated rats, whereas LVEDP increased by 10 mmHg. RVSP was significantly \((P = 0.00067)\) correlated with LVEDP \((r = 0.558)\) at 16 wk after MI. Thus increased load of the RV was primarily due to increased LVEDP rather than morphological or functional changes of the pulmonary vascular bed. This is somewhat in conflict with previous observations of more or less severe morphological changes of the pulmonary vasculature in rats with MI (5, 32). However, either those observations were made in the presence of excessively high LVEDP (32 ± 2 mmHg; Ref. 32), compared with a rather chronically compensated LV dysfunction with LVEDP of 14–21 mmHg in this study, or LVEDP was not measured (5).

LV remodeling. The ability of the RV to remain in a structural and functional compensated state was documented in the presence of severe LV remodeling and dysfunction. MI induced hypertrophy of surviving LV myocardium, as suggested by the increase of LV mass by 27% from 2 to 8 wk measured in MRI (Table 2). LV dysfunction was characterized by decreased CI and EF and increased LV filling pressure (LVEDP).
Delay of RV peak diastolic filling. The capability of high temporal and spatial resolution of MRI enabled the detection of a delay in RV filling in large MI. It has been found that there is RV and LV interaction (4, 27, 28) and that RV diastolic function is affected by LV failure (26, 30), but a delay of peak filling compared with LV peak filling has, to our knowledge, not been reported. Some temporal uncertainty is inherent in our method, because the cardiac cycle was sampled by only 12 frames and because of timing requirements that limit the acquisition period to being 5–10 ms shorter than the heart cycle. This led to delays of peak RV filling of one to two image frames, which were converted into an actual time delay with the individual interframe spacing of every MR measurement, which depends on HR. We ensured that this imaging period always contained both the end-systolic and end-diastolic phases. An additional problem is that the shape of the ECG signal is regularly distorted by the high magnetic fields and can therefore not serve as a landmark. This made further exact interindividual comparison of timing difficult. However, the described delay could clearly be identified. Because the delay is correlated to MI size, one could speculate that high LV filling pressures far exceeding RV diastolic pressures interfere with RV filling in rats with large MI. Maximal filling might only be achieved after LV isovolumetric contraction has started. Whether this phenomenon has a role in the impairment of RV function (as indicated by inverse correlation to RV EF) remains speculative. However, prolongation of diastole with constant HR results in shortening of systole.

In conclusion, the present study shows both LV and RV hypertrophy after MI. RV diastolic wall stress always remained normal. There was a correlation between RV weight and RVSP at 16 wk after MI. However, it is difficult to explain RV hypertrophy by pressure overload alone, because RVSP was normal during development of hypertrophy. The inconsistency between hypertrophy and relatively normal RV hemodynamics suggests that factor(s) independent of volume and pressure overload contribute to RV hypertrophy in this model, such as activated systemic and local renin-angiotensin system (16).

This work was supported by Deutsche Forschungsgemeinschaft, Sonderforschungsbereich “Pathophysiologie der Herzinsuffizienz” SFB 353/A8 and B1.

REFERENCES


