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ORIGINAL ARTICLES

Ventricular Function

In Vivo Assessment of Cardiac Remodeling After Myocardial Infarction in Rats by Cine-Magnetic Resonance Imaging

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ABSTRACT

The rat infarct model offers important parallels to the process of remodeling after myocardial infarction (MI) in humans. The aim of this study was to test the feasibility of cine fast low-angle shot (FLASH) magnetic resonance imaging (MRI) for assessment of the infarcted and noninfarcted rat heart and to compare the results with established methods. In group A, MRI was done 8–16 weeks after MI on a 7-T scanner using an electrocardiogram-triggered cine-FLASH sequence. We determined left ventricular (LV) volumes and mass, wall thickness, MI size, cardiac output, and ejection fraction. Afterward, MI size was histologically determined. In group B, after MRI eight controls and eight rats 16 weeks after MI underwent conventional hemodynamic measurements for determination of cardiac output, LV volumes, and ejection fraction by electromagnetic flowmeter and pressure-volume curves. LV wet weight was determined. In group A, MRI-acquired MI size (18.5 ± 2%) was smaller than histology (22.8 ± 2.5%, $p < 0.05$) with close correlation ($r = 0.97$). In group B, agreement in LV mass was found between MRI and wet weight (controls, 537.6 ± 19.6 vs. 540.3 ± 18.4 mg; MI, 865.1 ± 39.2 vs. 865.1 ± 41.3 mg; for the difference p = ns, $r = 0.97$, $p < 0.05$) and in the MRI and flowmeter measurements (cardiac output, controls 73.1 ± 2.9 vs. 75.2 ± 2.6 ml/min; MI 82.4 ± 5.2 vs. 81.9 ± 3.7 ml/min; for the difference p = ns, $r = 0.80$, $p < 0.05$). End-diastolic volume by MRI differed from pressure-volume curves with good correlation (controls, 343.9 ± 8.4 vs. 262.7 ± 12.8 μl; MI, 737.0 ± 70.5 vs. 671.1 ± 64.1 μl; $p < 0.05$ each, $r = 0.96$, $p < 0.05$). Cine-FLASH-MRI is a valuable diagnostic tool applicable to the rat model of MI. Being noninvasive and exact, it offers new insights in the remodeling process after MI because serial measurements are possible.

KEY WORDS: *Infarct size; Hypertrophy; MRI; Myocardial infarction; Pressure-volume curves; Rat; Remodeling; Ventricular function.*

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INTRODUCTION

Time course and morphologic and functional features of left ventricular (LV) remodeling have been studied both in animal models (1,2) and in humans (3,4). Myocardial infarction (MI) with consecutive LV dilation in rats has proved to predict conditions in humans (5,6). The existing parallels make it a valuable model for the search of new therapies for postinfarction heart failure. In this model, hemodynamic studies are performed at the end, LV volume is determined by pressure-volume curves (PVCs) of the arrested heart, and infarct size is measured postmortem by planimetry of histologic slices (5–7). Cine-magnetic resonance imaging (MRI) is highly accurate (8,9) and noninvasive and so can complete the existing diagnostic features. MRI is the well-established gold standard method for in vivo quantification of cardiac LV volumes and mass in humans (10–12). It provides high temporal and spatial resolution and offers the ability of serial measurements for follow-up of structural and functional changes in the intact heart of small laboratory animals (13–17). Measurement of LV mass by MRI has been validated in healthy rats and in rats with aortic stenosis and regurgitation (13) but not in rats with MI.

Zierhut et al. (14) and Rehwald et al. (17) describe major problems with electrocardiogram (ECG)-triggering in rats with MI and thus with quantification of LV mass. Zierhut et al. tested a spin echo method not involving cine-techniques for the measurement of infarct size. A correlation with histologic MI size of $r = 0.73$ was found (14). Accuracy of MRI seemed to be too low for serial investigations of remodeling. Furthermore, to our knowledge MRI volumetry in these small-sized animals has not been validated. Thus, the purpose of our study was to test the feasibility of cine fast low-angle shot (FLASH) MRI for evaluation of changes of LV geometry and function in rats with myocardial infarction. We compared MRI-acquired parameters (LV mass, maximal circumference and diameter of the left ventricle, end-diastolic and stroke volume, cardiac output, ejection fraction) to parameters acquired by established invasive or postmortem methods. Furthermore, we tested the value of cine-MRI for determination of MI size in this model.

METHODS

Experimental Protocol

Group A

Forty female Wistar rats (body weight, 260–280 g) were subjected to left coronary artery ligation as described previously by Pfeffer et al. (2). Mortality of this procedure was 35%. MR investigations were done 8, 12, or 16 weeks after MI ($n = 10$, 8, and 8, respectively). Postmortem MI size and LV diameter and circumference were measured as described below.

Group B

Eight healthy Wistar rats and eight rats 16 weeks after left coronary artery ligation (body weight 260–300 g) underwent first MRI and subsequently hemodynamic measurements for comparison of cardiac output and LV volumes. Finally, LV wet weight was determined and compared with LV mass acquired by MRI.

All procedures conformed with the *Guide for the Care and Use of Laboratory Animals* published by the U.S. National Institutes of Health (NIH Publication No. 85-23, revised 1996).

MRI Measurements and Data Analysis

In group A, MRI studies were performed under pentobarbital anesthesia (initial dose, 30 mg/kg IP). The animals were intubated and ventilated (small animal ventilator, Ugo Basile, Italy) and connected to a home-built ECG-trigger unit (18).

MRI experiments were performed on a 7.05-T BIOSPEC 70/21 scanner (Bruker, Germany). A home-built rat size whole body coil was used as transmitter and a surface coil as receiver (Fig. 1) (19). For imaging, we used an ECG-triggered fast gradient echo (FLASH) cine sequence (20). Flip angle was 30 to 40 degrees, echo time

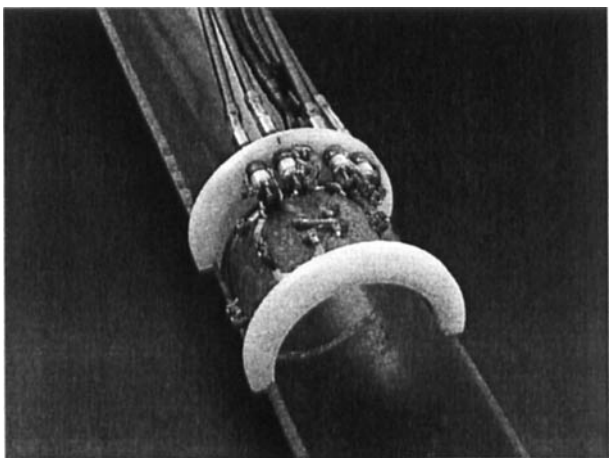

Figure 1. Quadrature surface receiver coil mounted on the animal holder.

was 1.1 msec, and repetition time was 3.2 msec; 12 frames per heart cycle were obtained. The total acquisition time for one cine sequence was 40 to 50 sec depending on heart rate (total acquisition time = 128 phase-encoding steps × 2 averaging steps × length of one heart cycle). The measurements were averaged four times to increase signal-to-noise ratio. Fifteen to 18 contiguous ventricular short-axis slices of 1-mm thickness were acquired to cover the entire heart. Total scan time was in the range of 15 min. With a field of view of 3 to 4 cm and an image matrix of 128 by 128, in-plane resolution was 230 to 310 μm.

Data analysis was done using an operator-interactive threshold technique (Fig. 2). Myocardial and ventricular slice 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 slices. LV mass was calculated as LV myocardial volume multiplied by the myocardial specific gravity (1.05 g/cm^3). MI size was determined for every slice as the myocardial portion with significant thinning and akinesia or dyskinesia during systole. MI size was calculated by dividing the sum of the endocardial and epicardial circumferences occupied by the infarct by the sum of the total epicardial and endocardial circumferences of the left ventricle. This method was adapted from the histologic determination of MI size first described by Pfeffer et al. (2). MI size was measured both from end-diastolic and end-systolic frames. Maximum diameter and circumference and myocardial thickness of the left ventricle were determined using a software tool developed in our department (International Data Language, Research Systems Inc., Boulder, CO). All measurements were performed by one observer.

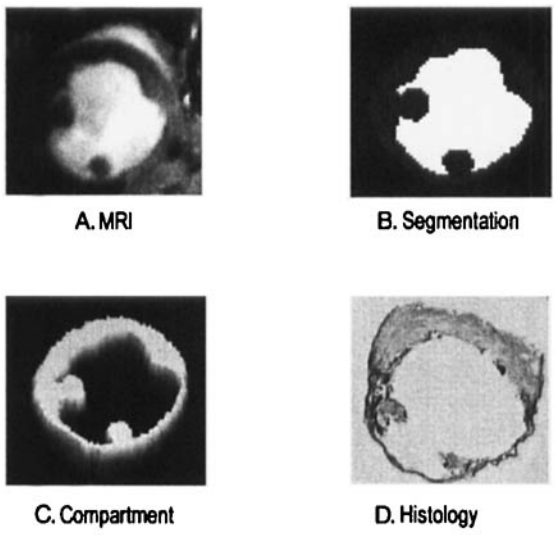

Figure 2. (A) MR image of a short-axis view at midventricular level 16 weeks after anterolateral MI. (B) Result of segmentation process. (C) Three-dimensional image of resulting compartment. (D) Image of corresponding histologic slice (right ventricle removed).

Postmortem Measurements

After MRI measurements, rats from group A were killed. The hearts were excised and fixed in distended form in 3.4% buffered formalin for 48 hr. Further, both atria and the right ventricular free wall were removed. The maximal diameter and circumference of the left ventricle were measured (2). Measurement of infarct size from postmortem hearts was done as described in detail by Pfeffer et al. (2). Briefly, the left ventricles were dehydrated in alcohol, cleared in xylene, and embedded in paraffin. Transverse serial sections of 20-μm thickness were obtained in 1-mm intervals from base to apex. The sections were mounted and stained with picric red staining collagen-rich scar tissue. The slices were scanned by a Sony video scanner, and infarct size was determined planimetrically similar to the MRI measurements (Scan Pro, Jandel Software). MI size was calculated by dividing the sum of the endocardial and epicardial circumferences occupied by the infarct by the sum of the total epicardial and endocardial circumferences of the left ventricle (2). Only transmural collagenous scar tissue was considered as infarcted region (Fig. 2).

Validation of Cardiac Output and LV Volumes

In group B, eight healthy animals and eight rats with MI were used for comparison of cardiac output, LV volumes, and mass. First, we did the MRI measurements as described for group A under inhalation anesthesia applied by nose cone (isoflurane 1.5 vol% supplemented by 0.5 ml oxygen/min). Afterward, hemodynamic measurements were done on these animals under isoflurane ventilation. During intermittent positive pressure ventilation (respiration rate 90 per minute, tidal volume 10 ml/kg) and after midsternal thoracotomy, a calibrated electromagnetic flowmeter (Statham, Oxnard, CA) was placed around the ascending aorta to measure the mean aortic blood flow. Cardiac output was obtained at about the same heart rate as the MRI measurements were done. Stroke volume (SV) was calculated from cardiac output (CO) and heart rate (HR) (SV = CO ÷ HR) as previously

described by Pfeffer and Frohlich (21). In one animal with infarction, flow measurements could not be completed due to cardiac arrest during surgical procedures.

For determination of LV end-diastolic operating volume, LV end-diastolic pressure measured in vivo is needed as well as the passive PVC obtained shortly after arrest of the heart. Systolic ventricular and aortic pressure and end-diastolic ventricular pressure were measured via the right carotid artery. The passive PVC of the left ventricle was obtained as described previously by Fletcher et al. (22). After arresting the heart with an intravenous potassium chloride injection, a double-lumen catheter was inserted into the left ventricle via the ascending aorta. Isotonic saline was infused at a rate of 0.76 ml/min via one lumen, whereas the intraventricular pressure was taken via the other. End-diastolic volume was defined as the volume at the in vivo acquired LV end-diastolic pressure. Ejection fraction (EF) was calculated using stroke volume (SV) and operating LV end-diastolic volume (EDV) (EF = SV ÷ EDV). Finally, the LV wet weight was determined.

In Vitro PVC Measurements

To compare postmortem PVCs for absolute quantification of LV volumes with beating hearts, a separate set of experiments in isolated rat hearts was performed. The rats were anesthetized by an intraperitoneal injection of pentobarbital sodium (35 mg/kg). After rapid excision of the heart, the aorta was dissected free and mounted onto a cannula attached to a perfusion apparatus as previously described (23). Retrograde perfusion of the heart was started in the Langendorff mode with oxygenated Krebs-Henseleit buffer at 37°C with constant coronary perfusion pressure set to 100 mm Hg. LV pressure was measured by a latex balloon inside the left ventricle while the intraventricular balloon was inflated stepwise by 0.05 ml (23). In vitro PVC was obtained in six isolated beating (LV end-diastolic pressure) or potassium chloride-arrested hearts. Arrested hearts were studied with coronary perfusion pressure at either zero or 100 mm Hg ($n = 6$ each). The results were compared with additional in situ-obtained PVCs after KCl cardiac arrest. KCl was administered through the vein as usual ($n = 6$) or through the aorta ($n = 6$) as in the isolated hearts.

Statistical Data Analysis

If not indicated otherwise, all data are means ± SEM. For statistical analysis, a statistic software package (Statview, Macintosh, SAS Institute Inc., Cary, NC) was used. We did Student's t-test for paired group comparison. $p < 0.05$ was considered statistically significant. For evaluation of agreement between the studied methods, Bland-Altman-Analysis was performed (24). Correlation between groups was tested by regression analysis.

RESULTS

Comparison of Methods

Group A

Mean diastolic MRI-determined MI size was 0.9% smaller than systolic MI size (18.0 ± 2.1% vs. 17.1 ± 2.3%). This difference was not significant, and correlation was high ($r = 0.99$, $p < 0.001$). When compared with the infarct size determined histologically (22.8 ± 2.5%), in vivo measured MI size was significantly smaller (18.0 ± 2.1%, $p < 0.001$). Correlation of MRI- and postmortem-determined MI size was close ($r = 0.97$, $p < 0.001$) (Fig. 3). When this comparison was split for the different time points (8, 12, and 16 weeks after MI), similar results were obtained ($r = 0.98$, $r = 0.96$, and $r = 0.98$, respectively; $p < 0.05$ all).

Compared with the in vivo MRI data, the maximum LV circumference in the formalin-fixed hearts was 5.25 mm (13.3%) smaller and the diameter 1.27 mm (10.2%) (mean difference). These findings were significant ($p < 0.001$ both).

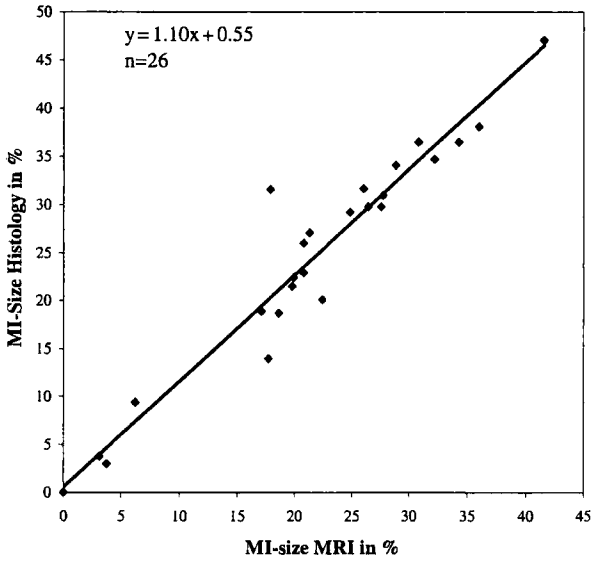

Figure 3. Regression analysis of MRI-acquired and histologically measured MI size (group A).

Table 1

Comparison of MRI and Conventional Measurements

	MRI		Conventional Method		
	MI	Control	MI	Control	*r*
MI size (%)	18.5 ± 2		22.8 ± 2.5*		0.97
LV mass (mg)	865.1 ± 39.2	537.6 ± 19.6	865.1 ± 41.3	540.3 ± 18.4	0.97
EDV (μl)	737.0 ± 70.5	343.9 ± 8.4	671.1 ± 64.1*	262.7 ± 12.8*	0.96
SV (μl)	259.1 ± 10.4	224.4 ± 7.8	245.8 ± 13.5	221.2 ± 9.2	0.70
CO (ml/min)	82.4 ± 5.2	73.1 ± 2.9	81.9 ± 3.7	75.2 ± 2.6	0.80
EF (%)	36.7 ± 2.4	65.3 ± 1.6	41.9 ± 3.8*	84.4 ± 2.3*	0.97

MI size obtained from group A; other values from group B. Values are means ± SEM. *r*, correlation coefficient of methods (MI plus control).

* $p < 0.05$ vs. MRI of the same group.

LV, left ventricular; EDV, end-diastolic volume; SV, stroke volume; CO, cardiac output; EF, ejection fraction.

Group B

Mean MI size of infarcted animals in group B was 30.2 ± 3.1% by MRI. There was no significant difference between MRI-determined LV mass and the actual postmortem LV weight in healthy and infarcted animals (Table 1) with good correlation in the regression analysis ($r = 0.97$, $p < 0.001$, slope 1.03, offset 10.5 mg). Comparison of LV mass in the end-systolic and end-diastolic frame of the MRI scans also revealed no significant difference (p = ns) and high correlation ($r = 0.96$, $p < 0.001$).

Good agreement was found for cardiac output and stroke volume acquired by different methods (see Bland-Altman plot, Fig. 4 and Table 1). End-diastolic volume by MRI was significantly higher than postmortem determined end-diastolic LV operating volume in controls and in infarcted animals (Table 1). This difference was bigger in healthy (23.4%) than in infarcted animals (9%). Because of the difference in end-diastolic volume, ejection fraction was lower in the MRI measurements than the calculated ejection fraction (Table 1).

Comparison of In Situ and In Vitro PVCs

The PVCs of isolated beating hearts and of in situ arrested hearts are shown in Fig. 5A. In vitro PVCs obtained from arrested hearts were significantly shifted to the left compared with those of beating hearts. The volume of in situ arrested hearts was smaller than that of in vitro beating hearts (not significant). The change of coronary perfusion pressure from 100 to 0 mm Hg in arrested hearts did not lead to a shift of PVCs (data not shown).

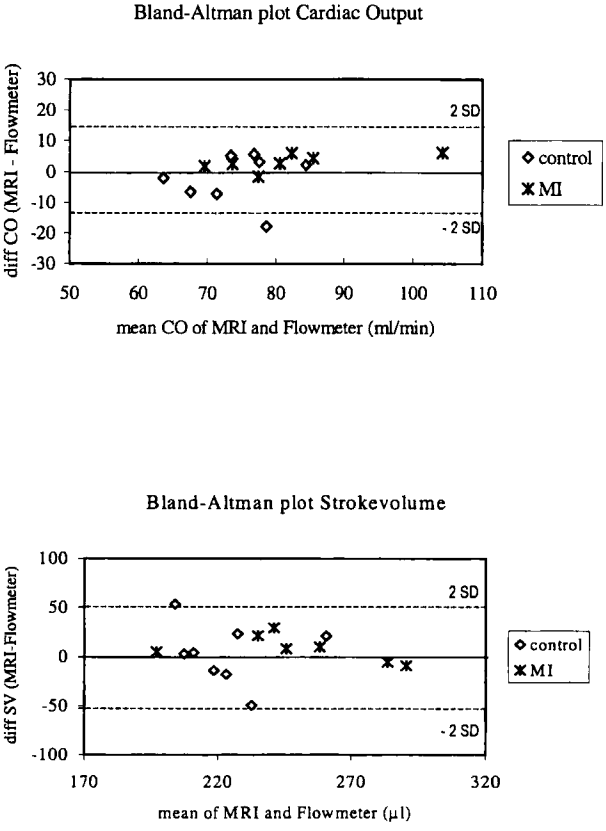

Figure 4. Bland-Altman plot for comparison of cardiac output (CO; top) and stroke volume (SV; bottom) of healthy and infarcted animals acquired by MRI and conventional hemodynamic measurements. *y* Axis is the difference (diff) of one parameter acquired by both methods from the same animal, *x* axis is the mean of the same parameter acquired by both methods, and SD is standard deviation of differences (group B).

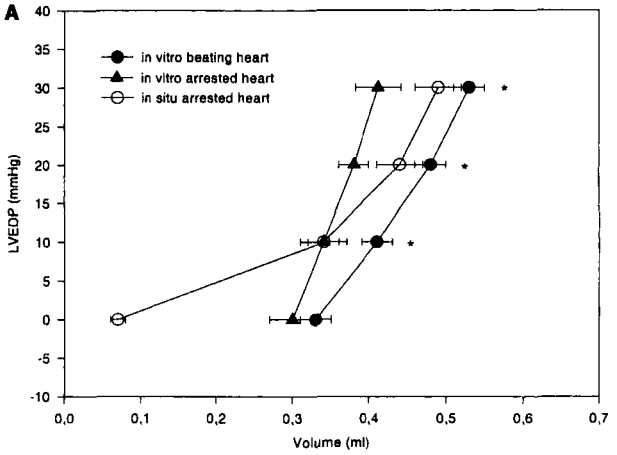

Figure 5. (A) Comparison of in situ and in vitro pressure-volume curves of arrested hearts to the isolated beating heart (n = 6 each). Perfusion pressure of isolated hearts was 100 mm Hg. Arrest by potassium chloride leads to a shift toward smaller volumes. (B) Comparison of way of delivery of potassium chloride (n = 6 each). Perfusion pressure of isolated hearts was 100 mm Hg. Arterial injection leads to more pronounced shift toward smaller volumes. LVEDP, left ventricular end-diastolic pressure.

Remodeling Post-MI MRI Parameters

There were no significant differences in MI size for rats studied at 8, 12, and 16 weeks (24.0 ± 3.1%, 24.0 ± 3.0%, and 23.6 ± 2.2%, respectively), allowing us to compare the different time points of group A. By a previous definition, MI sizes from 5% to 30% are considered small (2). There was a significant increase in LV mass from 8 to 16 weeks after MI (524.1 ± 27.6 mg vs. 641.7 ± 42.9 mg; $p = 0.02$) (Table 2). This hypertrophy affected myocardial wall thickness, showing a significant increase in wall thickness in the surviving myocardium of the lateral wall from 8 to 16 weeks measured in end-diastole (1.46 ± 0.17 vs. 2.03 ± 0.26 mm; $p < 0.05$) (Table 2). There was no significant LV dilation or impairment of LV function from 8 to 16 weeks after MI (Table 2).

DISCUSSION

A major result of this study was that cardiac volumetry by MRI and by the established invasive or postmortem methods of this small-sized and pathophysiologically important heart failure model are in good agreement. Differences in volumetry between PVCs and MRI have been addressed in an extra set of experiments using isolated beating hearts. Another major finding was the shift of PVCs toward smaller volumes when hearts were arrested. Therefore, end-diastolic volume obtained from arrested hearts is considerably smaller than in vivo. In addition, we present a highly exact noninvasive method for determination of infarct size in this model, giving us the chance of serial investigations of "late" cardiac remodeling.

Comparison of Cine-MRI to Other Methods

MI Size

In the rat model of MI, cine-FLASH-MRI allows in vivo quantification of MI size without contrast media, when scar formation is completed. MI size determined by MRI was at diastole 0.9% smaller than at systole. Being a relative parameter, this phenomenon can be explained by shortening of the surviving myocardium in systole. The circumferential length of the infarct scar does not shorten; hence, infarct size increases.

The significant difference between MRI- and histologically determined MI size may be explained as follows. Thinning and lost function identify MI and hence determine MI size in the MRI method. Lost function may be due to necrosis and consecutive scar formation, stunning, or hibernation (25,26). Therefore, overestimation of MI size in MRI seems to be more likely than underestimation.

Determination of the infarcted region in histologic slices is precise, because the collagen-rich infarct scar is dyed red and surviving myocardium yellow. However, MI size is a relative quantity, and shrinkage of tissue

Table 2

Morphology and Function of the Left Ventricle at 8, 12, and 16 Weeks After MI (Group A)

	Weeks Post-MI		
	8	12	16
MI size (%)	24.0 ± 3.1	23.0 ± 3.4	23.6 ± 2.2
Body weight (g)	298 ± 10	313 ± 22	305 ± 20
LV mass (mg)	524.1 ± 27.6	539.2 ± 34.3	641.7 ± 42.9*
Wall thickness lateral wall (mm)	1.46 ± 0.17	1.63 ± 0.3	2.03 ± 0.26*
Wall thickness of infarct scar (mm)	0.99 ± 0.13	0.87 ± 0.16	0.93 ± 0.24
Cardiac output (ml/min)	45.5 ± 6.3	36.1 ± 2.3	43.4 ± 4.1
Stroke volume (µl)	139.4 ± 19.7	115.3 ± 7.3	118.2 ± 14.5
Heart rate	329 ± 17	313 ± 22	367 ± 19
End-diastolic volume (µl)	526.0 ± 84.2	493.8 ± 68.0	444.4 ± 66.8
End-systolic volume (µl)	386.4 ± 74.6	378.5 ± 68.2	326.1 ± 53.4
Ejection fraction (%)	28.3 ± 3.0	27.0 ± 4.2	27.4 ± 1.6

Values are means ± SE.
* $p < 0.05$ vs. 8 weeks.

caused by formalin must therefore be taken into account (27,28). This phenomenon may become obvious in the difference of MRI-determined maximal LV circumference and diameter and the postmortem measurements; we found a decrease of 13.3% and 10.2% in circumference and diameter after formalin fixation. In the intact noninfarcted myocardium there are more cells than within the scar; therefore, osmotic effects can cause more pronounced shrinkage in this part of the ventricular wall than in the MI scar. This inhomogeneity in shrinkage could lead to a shift of MI size toward larger values. However, both methods correlate well and can be used to select animals for infarct size.

Zierhut et al. (14) compared histologically determined relative MI size as infarcted surface area of the left ventricle to infarcted area measured by a spin echo sequence in rats with chronic MI and found a correlation coefficient of $r = 0.73$. In our study correlation was closer ($r = 0.97$), probably due to two reasons. Zierhut et al. determined infarct size by MRI 3 weeks after infarction and by histology 26 weeks after MI. Relative MI size might change in between due to either infarct expansion or unproportional lengthening of uninfarcted myocardium caused by ventricular dilation. Additionally, we found it helpful to watch the animated cine-frames as a movie while determining MI size, because absent wall motion is an important property of the infarcted region. This was not possible in the above-mentioned study because only one diastolic and one systolic image was obtained. The noninvasive MRI method can be used serially and could be applied for investigation of infarct expansion or impact of therapy on MI size in individual animals.

LV Mass

LV mass acquired by MRI was in good agreement with actual postmortem LV weight. Serial and noninvasive evaluation of hypertrophy of the left ventricle is therefore possible in the rat model of MI. In addition, measurement of myocardial wall thickness can be done for a better distinction of the modus of hypertrophy (concentric, eccentric, or asymmetric hypertrophy).

Cardiac Output and Stroke Volume

Whereas the MRI measurements are noninvasive, the measurements by flowmeter are done after midsternotomy. The surgical procedures lead to a stimulation of the sympathetic nervous system, resulting in a higher level of autonomic activation of the heart (29,30). Because of the open-chest procedure, animals had to be ventilated, whereas they were breathing spontaneously in the MRI measurements. Artificial ventilation does usually affect cardiac output. As Chihara et al. (31) showed in male wistar rats, a fall of cardiac output of 20.9% due to intermittent positive pressure ventilation was caused by an increased central venous pressure, leading to impaired systemic venous return. The raised central venous pressure was caused by positive intrathoracic pressure during inspiration. In our measurements of cardiac output by flowmeter, the thorax was open and so no positive intra-

thoracic pressure could develop to raise the central venous pressure. One can conclude that in the open-chest situation, influence of mechanical ventilation on cardiac output is minimal.

The concentration of isoflurane was adjusted to achieve the same depth of anesthesia that was controlled by heart rate (hemodynamic measurements, 342 ± 11; MRI, 326 ± 9; p = ns).

The question if temporal resolution (12 frames per heart cycle) is high enough to determine true end-systolic volume may be of concern. With a heart rate of 320 min^{-1}, time between two cine-frames is 15.6 msec (8.3% of the heart cycle). With our method it is possible to go up to 20 frames per cycle, but this did not seem to be necessary because stroke volume (stroke volume = end-diastolic volume–end-systolic volume) was in good agreement with the reference measurements.

In conclusion, cardiac output and stroke volume quantitated by either method were in good agreement (Fig. 4). The advantage of the noninvasive MRI method is the possibility of serial measurements investigating worsening of the circulatory situation after MI or improvement of cardiac function caused by therapy.

End-Diastolic Volume and Ejection Fraction

The difference between the MRI-acquired end-diastolic volume and the ex vivo acquired end-diastolic LV operating volume could be caused by overestimation by MRI or underestimation by PVCs. In fact, the threshold technique used for MRI may lead to overestimation by partial volume effects. However, diastolic LV mass quantified using the same segmentation borderline or stroke volume and cardiac output calculated by using end-diastolic volume are in good agreement with the reference methods, making an overestimation of end-diastolic volume in MRI unlikely. To further analyze a potential underlying mechanism, we compared PVCs obtained by various techniques. LV PVC of the in situ arrested heart has been used to analyze remodeling after MI (22). There are, however, major differences to the normal in vivo situation. We therefore compared PVCs in isolated isovolumic beating hearts and hearts arrested by potassium chloride and perfused with constant pressure at 100 or 0 mm Hg. The beating hearts showed larger volumes than arrested hearts. These results are in line with the MRI findings, suggesting the myocardium in arrested hearts might be stiffer and therefore the LV volume smaller in postmortem experiments because active relaxation is absent. Our results also showed that LV volumes obtained from in vitro arrested hearts were smaller than that of in situ arrested hearts. The reason might be that the buffer containing high potassium chloride concentrations was perfused through the aorta, whereas potassium chloride was given intravenously in the in situ setting.

To confirm this, we studied the effects of potassium chloride given through a catheter into the left ventricle in situ and found the volumes obtained in that group were also smaller than that of hearts arrested via jugular vein (Fig. 5B). Relaxation of the myocardium and myocardial stiffness are energy dependent (32). The metabolic situation of the postmortem ventricle before the onset of rigor mortis might already be altered compared with in vivo conditions (33,34). This suggestion is supported by the measurements of in vitro PVC discussed above. One could speculate that the contribution of the infarct scar to the LV wall not being influenced by metabolic changes might be the cause for the smaller difference of end-diastolic volume in rats with MI. The difference between MRI-acquired and PVC-derived end-diastolic volume led to a difference in ejection fraction of 19.1% in controls and 5.2% in infarcted rats.

Remodeling Post-MI MRI Parameters

According to the established categories for MI sizes, rats in our study had small infarcts, just below the threshold to moderate MI size (2). In agreement with the data in the literature, cardiac function in infarcted animals was maintained on a normal level with no further significant changes, indicating good compensation of the loss of about a quarter of their LV myocardium (1,2). Mechanisms of this compensation include eccentric hypertrophy, leading to dilation of the left ventricle within 8 weeks after MI (1,2). Our study demonstrates that in rats with small MI, dilation is completed after 8 weeks and no further decline of ejection fraction occurs from 8 to 16 weeks. The statistically significant weight gain of the left ventricle 8 weeks after MI did only result in increased wall thickness but not in further cavity enlargement. In rats with small infarcts, Pfeffer et al. (1) showed a slight but not statistically significant increase of LV weight-to-body weight ratio from 19 days to 3 months after MI. Slight scar thinning (not significant) might have been caused by "late scar remodeling." This phenomenon needs to be addressed in a serial study with more measurement time points.

In conclusion, we could show that cine-MRI is a valuable diagnostic tool applicable to the rat model of myocardial infarction, which is in good agreement with existing analytical methods. It allows for reliable and reproducible assessment of cardiac morphology and function, including wall thickness and motion, making it the method of choice for volumetric quantification. Com-

pared with other noninvasive methods, such as M-mode echocardiography (35,36), MR volumetry works without geometric assumptions and therefore offers a higher degree of accuracy in measurements of cardiac output and LV volumes; this is especially of importance in hearts deformed by asymmetric dilation after MI. MRI can be applied to assess the effects of therapeutical or other agents on infarct size, cardiac geometry, and function with high precision. The noninvasive character of MRI allows serial investigations of individual animals. This might give major insights into the pathophysiologic changes during the remodeling process from early on after coronary artery ligation. Thus, MRI bears a great potential to substantially contribute to the understanding of the underlying pathomechanisms in the development of chronic heart failure.

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