Serial echocardiographic assessment of left ventricular dimensions and function after myocardial infarction in mice

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Abstract

Objective: To test the usage of serial echocardiography in mice with induced myocardial infarct (MI) and to characterize the mouse model of MI. Methods: C57 mice underwent open-chest surgery to induce left coronary artery occlusion or sham-operation (SH). Echocardiography was performed before and at 1, 2.5, 6 and 9 weeks after surgery. Left ventricular end diastolic and end systolic dimensions (LVEDd, LVESd) and fractional shortening (FS) were measured. Haemodynamics was determined at week 9 by LV catheterization and hearts were examined morphologically. Results: Post-infarct mortality was 46% (10 / 22), of which, 70% died of acute heart failure or LV rupture within the first week. LV dimensions and FS remained stable in SH group (n = 10) during the study period. In surviving MI mice (n = 12), there was modest LV dilatation and fall in FS at week 1. Compared with week 0 values, there were progressive increase in LVEDd (+50\%+66\%) and LVESd (+124\%+171\%), and decline in FS (−53\%−73\%) during the 2.5−9 week period. Infarcted mice also had lower LV systolic pressure (LVSP), dP/dt and dP/dt (all P < 0.01 vs. SH group). Infarct size, LVSP and dP/dt significantly correlated with FS and LV dimensions (r = 0.61−0.80, all P < 0.01). Conclusions: LV remodeling and dysfunction in mice with MI are time-dependent processes and early remodeling seems associated with high risk of rupture and acute pump failure. Our findings provide a baseline description of this murine model and confirm echocardiography as a reliable means to serially assess changes of cardiac structure and function after MI. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Heart failure; Infarction; Remodeling; Ultrasound; Ventricular function

1. Introduction

Myocardial infarction (MI) remains the leading cause of cardiac death in Western countries. The development of heart failure after MI is closely related to alterations in left ventricular (LV) structure. Numerous clinical and experimental studies have shown that ventricular dilatation impairs chamber performance and bears important prognostic implications [1−4]. The change in geometry after transmural MI is a progressive process, now referred as post-infarct remodeling. However, under clinical settings, the natural process of post-infarct LV remodeling is difficult to define due to medications and various complications.

Animal models of MI have been widely used in different species, such as the dog, pig, rabbit and rat [5−8]. Recently, gene-targeted mouse models have been extensively used in research on cardiovascular diseases [9−12], providing powerful tools for a better understanding of underlying molecular mechanisms of heart failure. This calls for establishing and characterizing murine heart failure models.

The changes in LV structure and function after experimental MI can be assessed using various techniques. Some approaches, however, are terminal procedures providing information only at a single time point. Ventriculography and magnetic resonance imaging are not readily used in animal experiments due to lack of facilities or economic considerations. Transthoracic echocardiography provides an excellent and non-invasive method for longitudinally...
monitoring the changes of LV geometry and function in vivo. With the availability of high-frequency ultrasound transducers, this technique has been increasingly used in various animal studies, including mice, with the reliability and repeatability of this techniques being proven [13–15]. Although some investigators assessed LV structure and function after experimental MI in mice with this technique [16], there has been no study on serial examination of post-infarct LV remodeling and function in mouse MI model.

This study was designed to characterize the time course of LV remodeling and functional changes after MI in the mouse using echocardiography. Further, we also tested the reliability of echocardiography by correlating echo parameters with other functional and morphometric measures.

2. Methods

2.1. Animals and microsurgery

C57BL mice, aged 6–8 months, body weight ranging 23–34 g, were used. Mice were housed in a facility with a 12/12 light and dark cycle, and free access to water and Norco mouse pellets. Animals were randomly divided into MI groups (n=22, male/female 6/16) and sham-operation (SH) control groups (n=10, M/F 4/6).

Mice were anaesthetized by intraperitoneal injection with a mixture of ketamine (8 mg/100 g), xylazine (2 mg/100 g), atropine (0.06 mg/100 g) and a pain reliever, temgesic (0.02 mg/100 g), and the chest was shaved. Animals were then intubated with a 20G intravenous catheter and ventilated with a mixture of O2 and room air, using a model 683 ventilator (Harvard Apparatus). The stroke volume was 0.5 ml and the respiratory rate was 85 breaths/min. Animals were placed in a supine position on a heating pad. After a left anterior thoracotomy, the heart was exposed and the location of the left coronary artery (LCA) on the surface of LV anterior wall was identified. A 7-0 silk suture (Ethicon) was placed around the LCA. After placing a 2-0 silk suture alongside the LCA (to prevent cutting of the vessel), the 7-0 suture was tightened. Occlusion of the LCA was confirmed by change in the color at the involved LV wall. Warmed saline was then injected into the chest cavity and lungs were expanded to displace air before the chest was closed. Sham-operated mice underwent similar surgery without occlusion of the LCA. The surgical procedure was performed with the aid of a microscope (Wild M3B, Heerbrugg, Switzerland) at ×6.4 or ×16 magnification. The technical details were described previously [17]. All procedures have been approved by the local animal experimentation committee in accordance with the Australia Code of Practice for the Care and Use of Animals for Scientific Purposes (6th edition, 1997).

2.2. Echocardiography

Transthoracic echocardiography was performed using a Sonos 5500 ultrasound machine (Hewlett Packard Co.) with a 12 MHz phased array transducer and a frame rate of 41/s. The transducer was covered with a surgical latex glove finger filled by ultrasound transmission gel to provide a standoff of 0.5–0.7 cm. The transducer was used at a depth setting of 2 cm to optimize resolution. Mice were anaesthetized with a half dose of the anesthetic mixture used for open-chest surgery to maintain light anesthesia and spontaneous breath. The chest was shaved. Mice were placed on a heating pad in a shallow left lateral position and a standard lead II electrocardiogram was recorded for heart rate (HR) measurement. After a 2-dimensional (2 D) image was obtained in parasternal short axis view at the level close to papillary muscles, a 2 D guided M-mode trace crossing the anterior and posterior wall of the LV was recorded at a sweep speed of 100 mm/s. Caution was given not to apply excessive pressure over the chest, which could cause bradycardia and deformation of the heart. The following parameters were measured digitally on the M-mode tracings and averaged from 3 cardiac cycles: LV internal end-systolic and end-diastolic diameters (LVEDd, LVEDd), external LV diastolic diameter (ExLVEDd), anterior and posterior wall thickness of systole and diastole (Awt th, Awd th, Pws th and Pwd th). The measurements were made using the leading edge method of the American Society of Echocardiography [18]. Particular attention was given to acquire the largest LVEDd from the 2 D image in infarcted mice to avoid underestimation of LV dilatation due to asymmetric alterations in the LV cavity. LV fractional shortening (FS) was calculated as 

\[ \text{FS} \% = \left[ \frac{\text{LVEDd} - \text{LVEDd}}{\text{LVEDd}} \right] \times 100 \]

LV mass was calculated following an uncorrected cube formula: 

\[ \text{LV mass} = \left( \text{LVEDd} + \text{Awt th} + \text{Pwd th} \right)^3 - \text{LVEDd}^3 \times 1.055, \text{ where 1.055 is the gravity of myocardium} \] [19,20].

2.3. Reproducibility

To determine intra-observer variability of M-mode measurement, another 7 normal C57BL mice were studied by one observer on two different occasions. For inter-observer variability, these mice were examined by two observers for all M-mode measurements.

2.4. Hemodynamic assessment

Animals were anaesthetized with pentobarbitone (8 mg/100 g) and atropine (0.06 mg/100 g). The right carotid artery was exposed. A micro-tipped transducer catheter (1.4F, Millar Instrument Inc.), connected to transducer control unit and a polygraph (Grass model 7), was placed into the artery and then advanced into the LV. The aortic blood pressure, LV systolic pressure (LVSP), LV end-
diastolic pressure (LVEDP) and the maximal rates of rise and fall in LV pressure (dP/dt\text{max}, dP/dt\text{min}) were recorded. The measurements were made from consecutive 8–10 beats and averaged. HR was derived from pulse signals.

2.5. Morphological examination and infarct size measurement

After completion of functional measurement, the heart was excised. LV, right ventricle (RV) and atria were separated and weighed. Lung and liver weights were obtained and tibial length (TL) was measured. The LV was fixed in 10% PBS buffered formalin, embedded in paraffin and serially cut from the apex to the base. A transverse section (5 μm) was collected every 0.8 mm and 6–8 sections were obtained from each LV. Sections were stained (hematoxylin and eosin) and digitalized. The lengths of entire endocardial and epicardial circumference and portion of infarcted segment from both sides were measured using the Optimas 6.2 program. Percentages of infarcted LV of endocardial and epicardial circumferences were calculated and averaged from all sections to determine the infarct size (IS) [21]. The largest endocardial circumference from a single LV section was used as an index for the extent of LV dilatation.

2.6. Experiment protocol

After initial echocardiography, 22 mice were subjected to LCA ligation and 10 mice underwent sham operation. By 1, 2.5, 6 and 9 weeks after surgery, echocardiography was performed on all surviving animals. Within 3–5 days after the final echo test, catheterization was performed for LV functional measurement. Then organ weights were obtained and the hearts were fixed for histological analysis.

2.7. Statistical analysis

Values are shown as mean±SE, unless indicated. Student’s unpaired t-test was used to compare results between MI and SH groups with Bonferroni’s correction when applicable. Paired t-test was used for within group comparison. The least-squares method was used for linear regression and correlation between selected variables. P<0.05 was considered significant. Inter- and intra-observer differences were calculated as difference between two observations divided by the mean of the observations and expressed as percentages. Agreement between two measurements was determined according to the method of Bland and Altman [22], a coefficient of variability was calculated as mean±2SD of the differences between two measurements.

3. Results

3.1. Mortality

All mice survived surgery and the 10 sham-operated mice survived throughout the study. All 22 mice that underwent LCA ligation developed transmural MI and 10 (46%) died during the 9-week period. Of these, 4 died of LV rupture and 3 of acute heart failure, judged by postmortem findings (large infarct, cardiac dilatation, massive pleural effusion and severe lung congestion), all within the first week after MI. Of the remaining deaths, one occurred 33 days after surgery, another 2 mice were lost immediately before week 1 and week 6 of echocardiography due to critical heart failure and intolerance of the routine anesthesia. In those animals that died of heart failure (n=6), the extent of lung congestion, judged from the lung weight, was significantly greater than that in both SH mice and mice surviving with MI (306±44 vs. 148±5 and 158±8 mg, respectively, P<0.01). The average IS in these 10 hearts was 49.5±2.3% (ranged 34.9–57.5% of LV). The 4 mice that died of rupture had IS of 48.1±4.9%, which was similar to that of the 6 mice died of heart failure (50.6±2.2%).

In 7 mice that died within the first week, the infarcted wall (anterior) thickness, measured from LV sections, was reduced to 38±4.4% of that of non-infarcted wall (posterior).

3.2. Body weight, organ weights and infarct size

BW was similar in both groups before surgery, but was lower in MI group 9 weeks after surgery. There was no difference in the tibial length. Thus, the organ weights are presented as absolute values. The weights of whole heart, LV and atria in the MI group were significantly greater than in the SH group (all P<0.05, Table 1). Considering a substantial loss of myocardium in the infarcted segment, an increase in LV weight indicates hypertrophy of the non-infarcted myocardium. The lung weight was not different between MI and SH groups (Table 1). The liver weight in infarcted mice was lower than in sham-operated mice, probably indicating the cardiac functional disturbance. In the 12 surviving mice, IS was 37.4±3.2% (ranged 15.2–55.2%). Fig. 1 shows transverse LV sections from mice with MI.

3.3. Echocardiographic measurement

The results of serial echocardiographic measurements immediately before and up to 9 weeks after surgery are shown in Fig. 2. All the parameters were similar between the two groups immediately before surgery and remained unchanged in the sham-operated group throughout the study period. In MI group, LV dimensions (LVEDd,
Table 1

<table>
<thead>
<tr>
<th>Body and organ weights</th>
<th>BW₀</th>
<th>BW₉</th>
<th>TL</th>
<th>HW</th>
<th>LV</th>
<th>RV</th>
<th>Atria</th>
<th>Lung</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>SH (n=10)</td>
<td>27.3</td>
<td>27.9</td>
<td>18</td>
<td>120</td>
<td>88</td>
<td>21</td>
<td>10</td>
<td>148</td>
<td>1245</td>
</tr>
<tr>
<td>MI (n=12)</td>
<td>26.8</td>
<td>25.6</td>
<td>17.7</td>
<td>138</td>
<td>102</td>
<td>23</td>
<td>13</td>
<td>115</td>
<td>1057</td>
</tr>
</tbody>
</table>

*BW₀, body weight at week 0 before surgery; BW₉, body weight at week 9 after surgery; HW, heart weight; LV, left ventricle; RV, right ventricle; TL, tibial length; SH, sham-operation; MI, myocardial infarction.

LVESd, ExLVDd) were increased (all P<0.05 vs. week 0 by paired t-test, Fig. 2A,B,C), and FS tended to be lower (P=0.06 vs. week 0) at week 1, although these parameters were not significantly different from SH group. Significant enlargement of LV dimension was noted at 2.5 weeks after MI compared with SH group. This was associated with substantial reduction in FS. During 2.5~6 weeks after MI, LV dimensions and FS changed little. By week 9 after surgery, however, the LV dilated further compared with the values at week 6 (P<0.05) with a further decrease in FS (P<0.05, Fig. 2D). Heart rates were not significantly different between SH and MI groups over the study period (Fig. 2F).

Prior to surgery (week 0), the thickness of ventricular walls was similar between SH and MI mice at diastole (anterior: 0.67±0.04 vs. 0.64±0.04 mm, posterior: 0.71±0.04 vs. 0.76±0.03 mm), and systole (anterior: 1.07±0.05 vs. 1.16±0.05 mm, posterior: 1.15±0.06 vs. 1.13±0.04 mm). The wall thickness remained unchanged in SH group throughout the study (data not shown). In MI group, there was no significant change in the thickness of non-infarcted (posterior) wall versus week 0 (data not shown). Compared with week 0 values, anterior wall thickness at systole (Awd th) was unchanged at week 1, but reduced by 36% at week 2.5, and by 50% at week 9 (P<0.05 vs. week 0 within MI group and P<0.01 vs. SH group at week 2.5 to week 9, Fig. 2). A significant reduction in Awd th was detected only at week 9 (~28%, P<0.05 vs. week 0 within MI group and P<0.05 vs. SH group at week 9).

Fig. 3 displays a serial M-mode echocardiograms from a representative mouse with large MI.

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**Fig. 1. Top:** Left ventricular sections from infarcted mice died of heart failure (A) or cardiac rupture (B) within the first week after surgery; **Bottom:** LV sections (C–E) from an infarcted mouse survived the entire study period. The infarct size was 57% (A), 47% (B) and 41% (C–E), respectively, calculated following the method described in the method section. Infarcted segments were indicated with lines. Bar=5 mm.
LV mass calculated from echo measurements was between 68±5 to 82±7 mg in SH mice during the study period (P=NS). During week 1–9 period, LV mass derived from echocardiography increased progressively from week 0 values (66±5 mg) by 130–192% (P<0.01 vs. SH group).

3.4. Reproducibility of echocardiographic measurements

Table 2 summarizes inter- and intra-observer variabilities of measurements of LV dimensions and wall thickness. The variability of inter- and intra-observation was small for LV dimensions but relatively greater for measures of wall thickness. The absolute differences between two determinations and the coefficients of variability in both inter- and intra-observer were small for both LV dimensions and wall thickness. The variation of intra-observer was smaller than that of inter-observer. All data from M-mode tracing were within the 95% confidence interval. No systematic error was presented between inter- and intra-observations (all P>0.05 by paired t-test). These results indicate that this technique is reliable and reproducible.

3.5. Haemodynamics

Functional evaluation was performed on 21 mice at 9 weeks following surgery. The interval between last echocardiographic test (week 9) and catheter examination was...
Table 2

<table>
<thead>
<tr>
<th></th>
<th>Inter-observer</th>
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<th>Intra-observer</th>
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<tbody>
<tr>
<td></td>
<td>Error% Coefficient (mm)</td>
<td>Error% Coefficient (mm)</td>
<td></td>
<td></td>
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<tr>
<td>LVEDd</td>
<td>8±5.6</td>
<td>0.1±0.74</td>
<td>7.3±7.1</td>
<td>−0.04±0.82</td>
</tr>
<tr>
<td>LVESd</td>
<td>7.5±4.5</td>
<td>0.1±0.38</td>
<td>12.2±10.2</td>
<td>−0.08±0.74</td>
</tr>
<tr>
<td>Aws th</td>
<td>17.6±14.9</td>
<td>0.1±0.46</td>
<td>17±8.3</td>
<td>0.06±0.21</td>
</tr>
<tr>
<td>Awd th</td>
<td>16.7±18.5</td>
<td>0.1±0.22</td>
<td>12.8±16.7</td>
<td>0±0.28</td>
</tr>
<tr>
<td>Pws th</td>
<td>9.1±9.1</td>
<td>0.06±0.28</td>
<td>21.4±10.9</td>
<td>0.05±0.5</td>
</tr>
<tr>
<td>Pwd th</td>
<td>18.5±14.4</td>
<td>0±0.32</td>
<td>8.8±11.1</td>
<td>−0.02±0.2</td>
</tr>
<tr>
<td>ExL VDd</td>
<td>3.7±2.9</td>
<td>−0.12±0.46</td>
<td>5.9±4.4</td>
<td>−0.06±0.74</td>
</tr>
</tbody>
</table>

Values are mean±SD for percentage error and mean±2SD for coefficient of variability. LVEDd, left ventricular end diastolic diameter; LVESd, LV end systolic diameter; Aws th, anterior wall systolic thickness; Awd th, anterior wall diastolic thickness; Pws th, posterior wall systolic thickness; Pwd th, posterior wall diastolic thickness; ExL VDd, external LV diastolic diameter.

3–5 days. One infarcted mouse was lost due to failure in catheterization. The hemodynamic data are summarized in Table 3. HR was similar in the two groups. Mice with MI had lower arterial blood pressure, LVSP, dP/dt max, dP/dt min and elevated LVEDP (all P<0.05).

3.6. Correlations of echocardiographic, hemodynamic parameters and infarct size

FS correlated well with ExL VDd at all time points when data from infarcted and control mice were combined (n=119, r=−0.725, P<0.001), implying that the extent of LV dilatation is associated with deterioration of ventricular pumping. For the echo parameters obtained at week 9, linear regression plots (Fig. 4) show that FS significantly correlated with measures of LV contractility, such as LVSP (r=0.614), dP/dt max (r=0.729) and dP/dt min (r=0.80, all P<0.01), indicating that FS reliably reflects the ventricular contractile status. IS significantly correlated with FS (r=−0.706, P<0.01), LVESd (r=0.684, P<0.01) and the largest endocardial circumference (r=0.642, P<0.05) (Fig. 4), but not with LVEDd (r=0.426), ExL VDd (r=0.242), dP/dt max (r=−0.530) and dP/dt min (r=−0.382, all P=NS).

The correlation between LV mass by week 9 echocardiography and actual LV weight was significant in SH group (r=0.734, P<0.01), but not in MI group (r=−0.068, P>0.05).

4. Discussion

With the development of transgenic technology, gene-manipulated murine models have been commonly used in cardiovascular research. Therefore, characterizing murine models of cardiac disorders is both timely and important. By means of echocardiography, we studied the natural process of post-infarct LV remodeling in the mouse in vivo. The study time points were chosen for the purpose of monitoring the remodeling process occurring at early and late phases. Modest LV enlargement was detected at week 1 and progressive ventricular dilatation was noted between 2.5 and 9 weeks. This enlargement of LV chamber was associated with hemodynamic deterioration. We also demonstrated, for the first time in the mouse, that the echocardiographic parameters correlated well with LV contractile indices obtained by a catheter technique and with IS.

Post-infarct LV remodeling is a progressive process involving LV chamber dilatation, infarcted wall thinning and compensatory thickening in non-infarcted region [23]. The time-course of post-infarct LV dilatation can occur in acute, subacute and later phases [24]. Serial echocardiographic studies in patients have shown that LV dilatation can be observed from as early as 3 days and lasted 30 months after MI, and the dilatation involved both infarcted and non-infarcted regions [25,26]. In the early phase of MI, infarct expansion and regional dilatation contribute to the ventricular enlargement [27]. Histological studies have revealed that infarct expansion is due to slippage between

Table 3

<table>
<thead>
<tr>
<th></th>
<th>HR beats/min</th>
<th>MAP mm Hg</th>
<th>LVSP mm Hg</th>
<th>LVEDP mm Hg</th>
<th>dP/dt max mm Hg/s</th>
<th>dP/dt min mm Hg/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>SH (n=10)</td>
<td>344±25</td>
<td>76±3</td>
<td>101±3</td>
<td>3.8±0.5</td>
<td>4889±339</td>
<td>−4067±310</td>
</tr>
<tr>
<td>MI (n=11)</td>
<td>295±15</td>
<td>64±3 b</td>
<td>82±4 c</td>
<td>5.4±0.3 c</td>
<td>3455±209 c</td>
<td>−2236±219 c</td>
</tr>
</tbody>
</table>

a SH, sham-operation; MI, myocardial infarction; HR, heart rate; MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, LV end diastolic pressure.

b P<0.05 vs. SH.
c P<0.01 vs. SH.
muscle bundles, most frequently occurs in transmural infarction [28], and is associated with rupture of the infarcted wall [29,30]. In the present study, 18% of infarcted mice died of LV rupture. Cardiac rupture could be considered as an extreme form of infarct expansion in which the expanded zone is insufficient to maintain the integrity of the ventricular wall before the deposition of collagen and scar formation [30,31].

Interestingly, we found that in the mice surviving of rupture and acute heart failure, LV dimensions only modestly increased at week 1 after MI (vs. week 0 within group), and that there was no evidence for the thinning of the infarcted anterior wall. This was in contrast to the findings from the 7 mice that died within the first week. Examination of the LV sections from these mice showed that LV chamber significantly dilated and the wall thickness in infarcted segment reduced to 38% of non-infarcted segment. This ‘discrepancy’ suggests that the early remodeling is associated with risk of rupture and acute heart failure, whilst those animals without early events may survive but undergo remodeling during subacute and chronic phases. The lack of obvious LV remodeling at week 1 by echo in the mice also differs from a report in the rat MI model [13], in which a marked increase in LVEDd (vs. SH group) was observed one week after MI.

A significant increase in LV dimensions was noted by 2.5 weeks after surgery. In MI group, LV dimensions maintained a relatively steady from 2.5 to 6 weeks. By week 9 after MI, LV cavity dilated further and the thickness of anterior wall in systole reduced by 50%. Recently, Patten et al. studied post-infarct remodeling in the mouse at a single time point of week 6 [16]. The changes in LV dimension and FS were similar to those we observed at week 6. During the 9-week study period, the thickening in LV posterior wall (non-infarcted region) could not be detected in MI group when compared within group (vs. week 0) or versus SH group. This might be explained as inadequate and eccentric hypertrophy to fully compensate for loss of myocardium or due partly to remodeling at non-infarcted segment. The progressive LV enlargement in the late post-infarct phase manifests as a global ventricular dilatation and involves both infarcted and non-infarcted segments [24].

With the progressive LV dilatation, LV function was markedly impaired in infarcted mice, evidenced by depression in arterial blood pressure, LVSP, dP/dt max, dP/dt min and FS, and elevation in LVEDP compared with sham-operated mice. We observed that FS started to decline at week 2.5 and reduced further by week 9. The fall in FS was parallel to the LV enlargement. Dilatation of LV reflects the increase in LV volume which can be considered as a compensatory mechanism to restore stroke volume at the early stage. However, LV dilatation occurred between 6 to 9 weeks may reflect the evolution into the stage of decompensatory dilatation without hemodynamic benefit. However, the obvious signs of ‘congestive’ heart failure.

Fig. 4. Top panel displays correlations between infarct size (IS) and fractional shortening (FS), left ventricular end systolic diameter (LVESd) measured by echocardiography at week 9 after surgery, and the largest endocardial circumference determined from left ventricular sections in infarcted mice. Bottom panel shows the correlations between FS and LV contractility, dP/dt max, dP/dt min, and left ventricular systolic pressure (LVSP), determined by catheter technique at week 9 after surgery.
were not observed in surviving mice with MI, based on non-significant changes in lung and RV weights. The LV dilatation with consequent increase in wall stress acts as the primary stimuli for ventricular remodeling and hypertrophy, and eventually lead to heart failure [32,33].

In this study, we measured external LV diastolic diameter and found that this index was useful, particularly in mice with MI. After experimental MI, the infarcted anterior wall was not always clearly imaged, due to wall thinning, akinesis and postoperative adhesion. Under this situation, ExLVDd can be used as an assessment on the extent of ventricular dilatation.

In sham-operated mice, LV weight and LV mass by echo correlated well with a 9% underestimation of LV mass by echocardiography. Previous studies have shown that echocardiography reliably estimates LV mass using an uncorrected cube formula in normal mice and mice with hypertrophy following aortic banding [19,34,35]. A discrepancy was noted between LV mass derived from echocardiographic technique and the actual weight in the mice with MI. LV mass by echocardiography increased approximately 2-fold over a 9-week period, and this could be taken as an indication for hypertrophy of noninfarcted myocardium. However, no correlation was found between LV mass by echocardiography and by weight, and echo-derived LV mass markedly overestimated the extent of hypertrophy, most likely due to non-uniform changes in LV geometry. Therefore, LV mass by echocardiography is not valid in the mouse MI model.

An important limitation in this study is the accuracy in the wall thickness measurement by echocardiography. The phased array 12 MHz transducer used gave the resolution of approximately 0.14 mm. Although satisfactory 2 D guided M-mode recording could be obtained in most mice with MI, infarcted anterior wall was not always readily identified. Thus, precise measurement of ventricular wall thickness and structure in the mouse heart remains to be resolved. With the recent development in echo technique [36], this limitation can be overcome. The number of MI mice in this study was relatively small. It certainly limits the power of showing relationship of IS and the extent of LV remodeling and dysfunction.

In conclusion, the present study in the mouse provides evidence that echocardiography is a reliable and noninvasive means to study the process of LV remodeling and dysfunction after MI. Post-infarct LV remodeling in mice is a time-dependent process and early remodeling seems associated with high risk of rupture and acute pump failure. These functional and morphometric findings give a baseline description on this murine model.

Acknowledgements

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