Mouse model of post-infarct ventricular rupture: time course, strain- and gender-dependency, tensile strength, and histopathology

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Abstract

Objective: Recent studies on mice with surgically induced acute myocardial infarction (AMI) have documented the frequent occurrence of ventricular rupture, an event not previously reported in other laboratory species. We have examined the natural history, histopathology and myocardial mechanical strength in mice with AMI.

Methods: AMI was induced by coronary artery occlusion and animals were monitored for fatal events. Gross and histological examinations were undertaken.

Results: Rupture occurred in the left ventricular free wall at 2–6 days after AMI. Incidence of rupture in male mice varied among three strains studied (3% for FVB/N, 27% for C57B/6j, and 59% for 129sv, \( P < 0.05 \)) and was lower in female than male mice (23% vs. 59%, \( P < 0.05 \)). Histologically, ruptured hearts had rapid-occurring and severe infarct expansion, multifocal intramural hemorrhage and leucocyte infiltration at the border zone and infarcted zone. In vitro, infarcted left ventricles demonstrated a 50–60% reduction in muscle tensile strength. This reduction preceded the onset of rupture and was related to the time-window of rupture and to infarct size.

Conclusion: LV wall rupture in the mouse occurs within a narrow time-window after AMI and is strain- and gender-dependent. Infarct expansion, regional hemorrhage with formation of hematoma and leucocyte accumulation are important pathological changes leading to reduced myocardial tensile strength.

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Keywords: Myocardial infarction; Ventricular rupture; Animal model

1. Introduction

Cardiac rupture occurs in 1–6% of patients with acute myocardial infarction (AMI) and accounts for 10–20% of all in-hospital deaths due to AMI [1,2]. The survival is poor in rupture victims with an in-hospital mortality of 60–90% [3,4]. Autopsy studies detected ruptures in 31–65% of patients who died of AMI [5–9]. Following the introduction of thrombolytic therapy, there has been a significant increase in the percentage of autopsy-proven rupture [6,7,10,11], indicating the lack of effective preventive intervention.

Morphologically rupture can be classified into three types. Type-I/II (early) ruptures result from a narrow slit or regional erosion of infarcted wall and usually occur within 48 h. Type-III (late) rupture is characterized by regional thinning and bulging of the ventricular wall, i.e. infarct expansion [5,10,12]. Thrombolytic therapy appears to reduce the prevalence of late but increase the risk for early rupture [7,11].

Rupture is believed to result from continuous stretch of infarcted and structurally weakened myocardium. Erosion
of necrotic tissues and intramural hemorrhage are also implicated in the pathogenesis of rupture [3,10]. Experimental research has shown that during AMI there is a rapid and substantial degradation of collagen subsequent to activation of matrix metalloproteinases (MMPs) [13]. With the loss of collagen struts to tether myocytes together, infarcted cardiomyocytes, under continuous stretch, undergo slippage and lengthening leading to infarct expansion and eventually rupture [14].

The absence of an animal model constitutes a major hurdle for research on the occurrence, mechanism and prevention of rupture. Species such as rats, rabbits, dogs, pigs and sheep are commonly used for research on AMI, but rupture after a transmural AMI has not previously been reported. Furthermore, previous studies on these species also showed lack of change, compared with control preparations, in the mechanical strength of acutely infarcted myocardium [15–19].

With the increasing use of the mouse in heart research, it has been realized that, like humans, mice with AMI develop ventricular rupture [20–23]. In this model, rupture develops within 3–6 days after AMI and the reported incidence is between 20% and 35% [21,23–25]. Research on genetically manipulated mice has documented the importance of MMP activation as a key factor for rupture [21,22,24]. These findings strongly indicate the usefulness of the murine rupture model. However, there has been lack of a detailed description on pathophysiological characteristics and rupture pathogenesis of this model. Also, it remains unclear whether the incidence of rupture varies among commonly used mouse strains. Thus, the aims of this study were to explore: (1) natural history and histopathology of rupture in this model, (2) potential strain- and gender-dependent differences, (3) changes in muscle tensile strength post-AMI, and (4) importance of infarct size (IS) in pathogenesis of rupture.

2. Methods

2.1. Animals and open-chest surgery

Three different strains of male and female mice were used at 3–4 months of age: FVB/N, C57B/6J and 129sv. Animals were housed in groups in an environment with 12/12 h day/night cycle and free access to water and food. All...
procedures used were approved by the local ethics committee in accordance with NIH guidelines for animal research.

Animals were anesthetized using a mixture of ketamine, xylazine and atropine (100, 20 and 1.2 mg/kg, respectively, i.p.) and put on a heated pad. The trachea was intubated via the oral cavity and animals received positive-pressure ventilation using a Harvard Ventilator (Model 683) with a tidal volume of 0.3 ml and a frequency of 120 breaths/min. Under a surgical microscope, a left thoracotomy was performed to expose the heart. The left coronary artery was identified and ligated with a 7–0 silk suture at a level about 1 mm below the edge of the left auricle, as described previously [21]. Sham-operation was also performed without ligating the coronary artery. Animals were administered with the analgesic carprofen (5 mg/kg, s.c.), diuretic furosemide (6 mg/kg, s.c.), and saline (0.5 ml, i.p.). Animals were inspected at least four times daily until death or killed at day 7.

2.2. Autopsy

Autopsy was performed on each animal found dead or killed after 7 days. The presence of a large amount of blood clot around the heart and in the chest cavity as well as a perforation of the infarcted wall indicated rupture death. Death was considered due to acute heart failure (HF) in mice with all of the following: presence of an infarct, pulmonary congestion (increased lung wet weight) and massive chest fluid accumulation, as described previously [20,21]. Sham-operation was performed without ligating the coronary artery. Animals were administered with the analgesic carprofen (5 mg/kg, s.c.), diuretic furosemide (6 mg/kg, s.c.), and saline (0.5 ml, i.p.). Animals were inspected at least four times daily until death or killed at day 7.

2.3. Measurement of tension-to-rupture (TTR)

To determine mechanical tensile strength of the ventricular myocardium, mice with AMI or sham-operation were killed at 24 h, 3 days or 7 days after surgery. Heart was removed and arrested in ice-cold saline. After trimming off atria and the right ventricle, the left ventricle (LV) was sectioned transversely into 4–5 rings of 1-mm thickness. The rings were immersed in saline at room temperature and then mounted on a stainless steel wire that was connected to a pre-calibrated force transducer, as illustrated in Fig. 1A. The tension required to rupture the ring (TTR, Fig. 1B) was determined using a data acquisition system (AD Instruments, Fig. 1C).

2.4. Pathological and histological analysis

Hearts were excised and fixed in 10% buffered formalin. Longitudinal or transverse paraffin sections were cut serially and stained with hematoxylin and eosin or Masson trichrome. Using a microscope, histological images were captured with a CCD video camera and analyzed, in a blinded fashion, using the Optimas 6.2 image analysis software (Media Cybernetics, Silver Spring, MD, USA). We analysed, either quantitatively or semi-quantitatively, three major histological changes: infarcted wall thinning, intramural hemorrhage, and accumulation of inflammatory cells in the infarcted area. Wall thinning was estimated using the ratio of the thinnest infarcted versus non-infarcted wall thickness. Regional hemorrhage and inflammatory cell accumulation were quantitated using a score system (0—not present, 1—mild, 2—moderate, 3—severe, and 4—very severe). Scores were given by two observers and averages were used after having inspected all sections from a heart.

2.5. Determination of infarct size (IS)

IS was determined using three different methods because infarcted hearts were used for different purposes (histology, TTR determination or gross images). For the hearts that were paraffin embedded and serially sectioned, the length of infarcted and non-infarcted segments of the LV was measured digitally using the Optimas 6.2 image analysis software, as described previously [20,21]. In some hearts, the atria and the right ventricle were trimmed off and the LV was cut into halves and pinned in such a way that the entire LV wall was flat. Photos were taken using a digital camera and the images were analysed using the Optimas 6.2 image analysis software to determine the surface areas of infarcted ventricular wall and the entire LV wall. For those hearts that were used for TTR measurement, following the analysis, LV strips were lined up and photographed. Using the Optimas 6.2 image analysis software, the length of infarcted segments and non-infarcted segments was measured for each individual strip. For all these measurements, IS was calculated as percentage of either the infarcted area or segment length divided by the entire LV area or the total length of LV segments.

2.6. Statistics

Data are presented either as percentage or means±SE. Categorical measurements (incidence, days, and histological scores) were analysed with Chi-square test, Fisher’s exact test or Kruskal-Wallis one-way ANOVA on rank. Normally distributed data was analysed by one- or two-way analysis of variance. P<0.05 was considered significant.

3. Results

A total of 356 mice were operated and 27 mice (8%) died within 24 h due to surgical reasons. Thirty-eight (16 sham-operated and 22 with AMI) surviving mice were killed during days 1–4 for TTR determination. Others were monitored for survival till day 7. All mice assigned to AMI groups had transmural infarct at LV free wall and the apex. IS ranged from 10% to 62%. Autopsy findings
indicated that all deaths were due to either rupture or heart failure (HF, Table 1). Only one mouse that died of rupture had concomitant HF.

### 3.1. Appearance of rupture

The site of rupture was identifiable microscopically in the majority of cases and was located either at the central or border zones of an infarct. The size of rupture varied from a fine perforation to a 2–3 mm slit (Fig. 2A). Ruptured LV always displayed regional dilatation and thinning of the infarcted wall (Fig. 2B,C). The lung/body weight ratio (mg/g) was comparable between ruptured and sham-operated mice (5.6±1.0 vs. 5.7±0.7 mg/g, P=NS), whilst mice that died of acute HF had a 2.4-fold increase in this ratio (14.0±3.6 mg/g, P<0.001 vs. sham-operated group), indicating pulmonary congestion.

### 3.2. Timing, incidence and between-strain difference of rupture

After surgery, animals were inspected at least four times daily. In fact, we inspected animals so frequent that we often witnessed sudden deaths due to rupture. The last inspection of animals was around 19:00 and the earliest was at 08:00. Those mice that died between these times were regarded as having had nighttime events. For all strains, mice were found to rupture during a time-window of days 2–6 after AMI.

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>FVB/N Male</th>
<th>FVB/N Female</th>
<th>C57B/6J Male</th>
<th>C57B/6J Female</th>
<th>129sv Male</th>
<th>129sv Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. operated</td>
<td>35</td>
<td>24</td>
<td>57</td>
<td>54</td>
<td>76</td>
<td>39</td>
</tr>
<tr>
<td>Surgery survivor</td>
<td>33, 94%</td>
<td>22, 92%</td>
<td>51, 89%</td>
<td>49, 91%</td>
<td>71, 93%</td>
<td>35, 90%</td>
</tr>
<tr>
<td>No. with IS &lt;30%</td>
<td>6</td>
<td>4</td>
<td>12</td>
<td>8</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>No. with IS&gt;30%</td>
<td>27</td>
<td>18</td>
<td>39</td>
<td>41</td>
<td>59</td>
<td>31</td>
</tr>
<tr>
<td>HF deaths</td>
<td>15, 45%†</td>
<td>15, 68%†</td>
<td>11, 22%</td>
<td>6, 12%</td>
<td>3, 4%†</td>
<td>3, 9%</td>
</tr>
<tr>
<td>Rupture death</td>
<td>1, 3%†</td>
<td>0, 0%</td>
<td>14, 27%</td>
<td>5, 10%</td>
<td>42, 59%†</td>
<td>8, 23%*</td>
</tr>
<tr>
<td>Total death</td>
<td>16, 48%</td>
<td>15, 68%†</td>
<td>25, 49%</td>
<td>11, 22%*</td>
<td>45, 63%</td>
<td>11, 31%*</td>
</tr>
</tbody>
</table>

All mice included had autopsy-confirmed transmural infarct. The differences between strains in the incidence of rupture or HF were highly significant.

* P<0.05 vs. respective male group.
† P<0.05 vs. respective group of C57B/6J.
As shown in Table 1, FVB/N mice had the lowest incidence of rupture but experienced a very high incidence of acute HF deaths mostly occurring within the first 3 days. In contrast, 129sv male mice had 4% incidence of acute HF death but 59% of incidence of rupture. C57B/6J mice had equal prevalence of rupture and HF deaths (Table 1).

Significant difference between C57B/6J and 129sv strains was evident in the timing of ruptures (Fig. 3). Whilst about 63% of ruptures occurred during days 2–3 (early rupture) after AMI in 129sv mice, C57B/6J mice displayed clear peak timing at day 4 and 84% of ruptures occurred during days 4–6 (delayed rupture, \( P<0.001 \) vs. 129sv).

Overall, rupture events were evenly distributed during night and day.

### 3.3. Gender differences

Whilst rupture occurred in both male and female mice of C57B/6J and 129sv strains (Table 1), the incidence was 2–3 fold higher in males than females (27% vs. 10% for C57B/6J, \( P=0.052 \), and 59% vs. 23% for 129sv, \( P<0.02 \), Table 1). Furthermore, unlike males that showed a peak number of rupture events at day 4 (C57B/6J) or predominantly during days 2–3 (129sv), female mice of both strains did not show

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**Fig. 3.** Timing of ruptures in male and female mice of C57B/6J and 129sv strains. Note that whilst male mice showed a clear peak onset time (day 4 for C57B/6J and day 3 for 129sv), female mice displayed more evenly and slightly delayed occurrence of rupture. \( P=0.177 \) for C57B/6J and \( P<0.02 \) for 129sv for the timing of rupture between genders. Comparison of C57B/6J and 129sv mice also revealed significant difference in the time course of rupture events with earlier onset for 129sv than C56B/6J mice (\( P<0.05 \) by Rank-sum test).

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**Fig. 4.** Histological features of infarcted and ruptured LV of 129sv male mice (H.E. staining). Microscopic view of LV myocardium from a sham-operated mouse (A) or a mouse that died of rupture (B) showing coagulative necrosis that occupies a large fraction of infarcted zone. Tissue sections showing intramural hemorrhage of the infarcted ventricular wall (arrows). Hemorrhage often occurred at multiple foci (C–E, arrows) and tended to merge together to form a hematoma (F, arrow). Panels (G) and (H) show a dissecting hematoma within the infarcted wall consisting of erythrocytes, high density of white blood cell (arrow) and white thrombi (*). (I) High density leucocyte accumulation at the border zone (arrow).
particular peak timing and appeared to have a delayed onset of rupture (Fig. 3).

3.4. Tension-to-rupture (TTR)

We determined TTR from LV rings. The common tear position in infarcted rings was at the border zone (Fig. 1B). Of 95 infarcted ventricular rings that were photographed after completion of TTR measurement, rupture occurred at border zone in 65% and at central zone in the remaining 35% rings. In LV rings from infarcted hearts that did not themselves contain an infarcted segment, the TTR was comparable to that of rings prepared from sham-operated mice (126±7 vs. 119±7 mN, P=NS). A significant fall in TTR by 50–60% was observed in LVs of 129sv and C57B/6J mice at a time when the onset of rupture is most frequent (Fig. 1D). Importantly, in both C57B/6J and 129sv mice, reduction in TTR was detectable as early as 24 h after AMI, a time that preceded the onset of rupture (Fig. 1D). TTR of infarcted LV rings from 129sv male mice returned to normal by day 7 (Fig. 1D).

3.5. Relation to infarct size (IS)

In this model, incidence of rupture was related to IS. Analysis of data from male mice of both C57B/6J and 129sv strains revealed an absence or very low incidence of rupture in mice with small IS (<30% of LV, 0% for C57B/6J, n=12; 8% for 129sv, n=12). While C57B/6J mice with moderate IS (30–45%) tended to have a higher incidence of rupture than mice with IS greater than 45% (46% vs. 20%, n=24 and 15 respectively, P=0.171), the incidence was comparable in 129sv mice with moderate and large IS (72% vs. 65%, n=36 and 23, respectively).

Changes in TTR were also related to IS. In the LV rings (all had transmural infarcts) prepared from hearts of 129sv male mice at day 3 after AMI, the rings from hearts with IS<30% had a greater TTR than that from hearts with IS of 30–45% (72±6 vs. 53±3 mN, P<0.01) or >45% (47±3 mN, P<0.01 vs. small IS group, 10–15 rings in each group). Similar difference was also observed in C57B/6J mice from LV rings at day 4 with IS<30% versus IS>30% (87±11 vs. 55±7 mN, P<0.05, each group had 15 rings).

3.6. Histological findings

Fig. 4A shows the appearance of normal LV myocardium. The infarcted region was largely occupied by coagulative necrotic myocardium (Fig. 4B). The most striking finding was intramural hemorrhage that was observed in all ruptured mouse hearts irrespective of the time when rupture developed (Figs. 4C–G and 5A). This was consistent with autopsy findings of visible subepicardial hemorrhage (Fig. 2A). Hemorrhage existed at any layer within the infarcted wall and appeared either as multifocal sites (Fig. 4C,D) or as a sizeable haematoma (Fig. 4E,F). Hematoma consisted of white thrombi, erythrocytes and white blood cells (Fig. 4H). Intramural hematoma of ruptured hearts was not common at day 2 but increased to 60–70% during days 3–5 (P<0.05), followed by a sharp drop at day 6 (Fig. 5B). The histological score indicated that hemorrhage reached a severe level by days 4–5 (score: 3.0±0.30 for day 4 and 2.9±0.26 for day 5, Fig. 5B) and then declined rapidly, in parallel with the incidence of hematoma. There was widespread neutrophil accumulation around infarcted myocardium (Fig. 4G–I) and the degree was increasing during days 2–7 after AMI with the averaged score increased from under 2 at day 2 to over 3.5 at days 6–7 (Fig. 5B). Accumulation of inflammatory cells became more prominent around border zones and hemorrhagic areas than that at central zones. Histological score system of 0–4 was applied, representing not present, mild, moderate, severe and very severe, respectively. Results from 129sv female mouse hearts (n=7, 3 died of rupture and 4 killed at day 4 after AMI) were also included and *P<0.05 vs. day 4 male group.
cells appears to be most prominent around either the border zone or an intramural hematoma compared with that at central infarcted zone.

The thickness ratio of infarcted/non-infarcted LV walls was reduced to $0.21 \pm 0.01$ at day 2 ($n=15$). No further reduction in this ratio was observed subsequently ($0.25 \pm 0.01$, $0.26 \pm 0.01$, $0.25 \pm 0.03$ and $0.20 \pm 0.02$ for days 3, 4, 5 and 6, respectively, $7–26$ group).

To further elucidate the gender difference in rupture risk, histological parameters were compared between male and female 129sv mice. All hearts in the male group ($n=10$) had rupture. As female mice had a lower incidence of rupture, female group consisted of three hearts with rupture at day 4 and four hearts from mice that were killed at day 4 for tissues acquisition. Histological analysis showed that, compared with males ($n=10$), infarcted hearts from female mice tended to have a less severe intramural hemorrhage (score: $2.1 \pm 0.26$ vs. $3.0 \pm 0.3$, $P=0.088$, Fig. 5) and absence of hematoma ($P<0.05$ vs. $60\%$ in males, Fig. 5). Further, female hearts had significantly less severe inflammatory cell accumulation in the infarcted area, especially at the border zone and at hemorrhagic sites (both $P<0.05$, Fig. 5). The ratio of wall thickness was not significantly different between females and males ($0.28 \pm 0.03$ vs. $0.26 \pm 0.02$).

4. Discussion

The present study has revealed several key features of the mouse rupture model, the only one available and now increasingly used [21–26]. First, onset of rupture requires a critical extent of infarct and occurs within a narrow time-window. Second, there are strain- and gender-dependent differences in the risk and timing of rupture. Third, tensile strength of the infarcted myocardium was reduced during the critical days where rupture was most prevalent. Finally, incidence of hemorrhage within the infarcted ventricular wall of ruptured hearts was very high. Overall, the murine rupture model described here simulates clinical situation in a number of ways, including time-course, requirement for transmural AMI, presence of infarct expansion, absence of concomitant HF, and histopathology (Table 2).

This is the first report showing strain-dependent difference in the incidence of rupture. The incidence and timing of rupture observed in C57B/6J mice were comparable to those reported by other groups [22–26]. Rupture was rare in FVB/N but common in 129sv mice. In this study, FVB/N mice had a poor tolerance to AMI and a high percentage of such mice died of acute HF within 48 h after AMI prior to the time-window of rupture. In contrast, 129sv mice with AMI rarely died of acute HF and thus the majority of such mice survived through to the time-window for rupture. Such difference might be attributable to the different functional tolerance to AMI. While the reason for the strain-related difference remains unclear based on the present study, our findings may be useful in selection of mouse strains for research on myocardial infarction focusing either on HF, ventricular remodeling or rupture.

A higher incidence of rupture was observed in male than in female mice, the finding in keeping with the recent report by Cavasin et al. [23]. Our study revealed that infarcted hearts from female mice had less severe intramural hemorrhage and inflammatory cell accumulation compared with male counterparts. These findings highlight the significance of the histological changes in the pathogenesis of rupture. In the clinical setting, risk for rupture is reported to be higher in women than men [1,6]. Compared with male counterparts, female patients who developed rupture usually were older, had higher prevalence of diabetes, hypertension and were more likely to have the first onset of AMI [1,3,6,9]. These confounding factors might all contribute to the risk of rupture. Thus, it is important to study male and female mice at an advanced age.

Although quantitative measurement remains to be generated, indirect clinical evidence suggests a reduced tensile strength of human myocardium with AMI [3,4]. Earlier experimental studies examined tensile strength of infarcted myocardium prepared from different species and reported no change after AMI [15–19]. In sharp contrast to these studies, we have shown, for the first time, a reduction in tensile strength of infarcted mouse myocardium. Importantly, reduced tensile strength precedes the timing of rupture and a greater than 50% reduction was observed at the peak time of rupture. This finding has both mechanistic

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### Table 2

<table>
<thead>
<tr>
<th>Human</th>
<th>Mouse</th>
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<tbody>
<tr>
<td>Incidence</td>
<td>1–6% [1,2]</td>
</tr>
<tr>
<td>Timing of rupture</td>
<td>≤2 days (early); 3–10 days (late) [5–7,10–12]</td>
</tr>
<tr>
<td>Position of rupture</td>
<td>Often at border zone [28]</td>
</tr>
<tr>
<td>Transmural infarct</td>
<td>Yes [10,12,30,34]</td>
</tr>
<tr>
<td>Infarct size</td>
<td>Early: usually small [10,12] Late: moderate to large [10,28]</td>
</tr>
<tr>
<td>Infarct expansion</td>
<td>Early rupture: not present [5,12] Late rupture: present [5,12]</td>
</tr>
<tr>
<td>Muscle mechanical strength</td>
<td>Unknown but likely to be reduced [3,4]</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Usually not present [5]</td>
</tr>
<tr>
<td>Leucocyte accumulation</td>
<td>Common [1,29–32]</td>
</tr>
<tr>
<td>Intramural hemorrhage</td>
<td>Present [3,10,31,34,35]</td>
</tr>
</tbody>
</table>
and practical implications. Fibrillar collagen forms a three-dimensional network providing tensile strength to the myocardium and preserving the alignment of adjoining myocytes. A low tensile strength is in keeping with the view that damage to the collagen network is a key mechanism of rupture and also in agreement with the reports that disruption of MMP genes reduces the incidence of rupture [22,26]. Practically, our finding suggests that TTR is a useful surrogate for rupture providing a quantitative measure of mechanical strength of the myocardium.

Our data revealed that rupture occurs both in the daytime and at night. The mouse is physically active during nighttime with significant elevation in blood pressures and heart rate [27]. Thus, lack of a nighttime-prevalence suggests that functional factors might not play an important role in this model.

There is limited clinical information regarding the relation of rupture and IS although it appears that early ruptures often occur in small to moderate sized infarcts but late ruptures are usually associated with a larger infarct [28]. Here we have provided experimental evidence showing that IS is related to the risk of rupture. First, irrespective of strain, rupture requires a critical extent of infarct. Second, TTR was significantly higher in hearts with a small than in those with large IS. Third, in C57B/6J mice, the incidence of rupture was 60% lower in mice with a large IS than that with a moderate IS. This could be explained by a more profound ventricular dysfunction associated with a large IS, rendering a substantially reduced force and systolic wall stress. In 129sv mice, however, due apparently to a good tolerance to AMI, prevalence of rupture was similar in mice with moderate and large IS.

This model had two common histological changes: inflammatory cell accumulation and intramural hemorrhage. Clinico-pathological studies reported that inflammatory cell accumulation was more common or more severe in ruptured than non-ruptured human hearts [1,29–32]. In the ruptured mouse hearts, intramural hemorrhage is so common and severe as to strongly imply its importance in rupture pathogenesis, though the exact mechanism for the severe local hemorrhage in this model is unclear. Thus, a higher rupture risk associated with thrombolytic therapy is likely due to an increase in local hemorrhage [33]. Different appearances of intramural hemorrhage, formation of hematoma and thrombi, seen in ruptured mouse hearts, imply that hemorrhage is a dynamic process. Regional bleeding also contributes to accumulation of white blood cells with enhanced MMP activity and consequent damage to the collagen network. Inflammatory cell accumulation in the infarcted myocardium is much more severe in the late-ruptured hearts than those of early-ruptures although the degree of infarct expansion was comparable. It is therefore possible that some differences exist in the pathogenesis of early and late ruptures in this model.

In conclusion, the mouse appears to be the only species that, like human, develops rupture after AMI. The features of ventricular rupture in the mouse, as described in this study in detail, would be helpful for further research using this model to elucidate the mechanisms, risk factors of rupture and to identify therapeutic approaches.

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