

Cardiac rupture complicating acute myocardial infarction: the clinical features from an observational study and animal experiment

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Abstract

Background.

Cardiac rupture (CR) is a fatal complication of ST-elevation myocardial infarction (STEMI) with its incidence markedly declined in the recent decades. However, clinical features of CR patients now and the effect of reperfusion therapy to CR remain unclear. We investigated the clinical features of CR in STEMI patients and the effect of reperfusion therapy to CR in mice.

Methods.

Two studies were conducted. In Study 1, Data of 1456 STEMI patients admitted to the First Hospital, Xi'an Jiaotong University during 2015.12.~2018.12. were analyzed. In Study 2, 83 male C57BL/6 mice were operated to MI, 39 mice were allocated for MI (group-1) and 21 mice for 1 h (group-2) and 23 mice for 4 h (group-3) ischemia followed by reperfusion. All operated mice were monitored up to day-10. Animals were inspected three times daily for the incidence of death and autopsy was done for all mice found died to determine the cause of death.

Results.

CR was diagnosed in 40 patients: free-wall rupture in 17, ventricular septal rupture in 20, and combined locations in 3 cases, present in 19 patients at admission and diagnosed in another 21 patients during 1 ~ 14 days post-STEMI, giving an in-hospital incidence of 1.4%. The mortality of CR patients was high during hospitalization accounting for 39% of total in-hospital death. By multivariate logistic regression analysis, older age, peak CK-MB and peak hs-CRP were independent predictors of CR post-STEMI. There were 17 deaths in group-1 during day 3–6 post MI. In the two IR groups, one mouse died of acute heart failure at day-5 post surgery and the rest of mice survived to the end of experiment without onset of rupture.

Conclusion.

CR remains as a major cause of in-hospital death in STEMI patients. CR Patients are characterized of being elderly, having larger infarct and more server inflammation. Reperfusion therapy can decrease CR incidence sharply.

Background

Cardiac rupture (CR) consists of free wall rupture (FWR) and ventricular septum rupture (VSR), and is a lethal mechanical complication of acute myocardial infarction (MI) ¹, the incidence of CR was between 7

to 20% in ST-elevation MI (STEMI) patients during 1970s to 1990s^{2, 3}, when CR was reported to occur either early after the onset of MI (type I or II, approximately 55%) or during the sub-acute phase accompanied with overt cardiac remodeling (type III, 45%)³. Factors including old age⁴, female gender⁵, and large infarct size² were found to be associated with the risk of CR. With the routine use of thrombolytic drugs and revascularization therapy including percutaneous coronary intervention (PCI), the incidence of CR has decreased to the current approximately 1%^{3, 6}, attributable to thrombolytic^{7, 8} and reperfusion therapies¹. Primary PCI (pPCI) as the standard treatment for MI has remarkably reduced the in-hospital mortality and improved the long-term outcomes.

Nevertheless, current literature indicates that CR remains as an emergency of modern cardiology contributing to the total in-hospital mortality in MI patients³. It is unclear on the clinical features of CR in the era of reperfusion therapy, a knowledge essential for the evaluation and timely intervention of CR events and preventive procedures. Accordingly, the aim of this study was to investigate the incidence, associated risk factors, timing of occurrence, and clinical outcomes of this complication in acute MI patients in the PCI era and influence of reperfusion in MI mice.

Methods

This study was done within both MI patients and animal experiments.

Patients

A retrospective medical record review study was conducted using the electronic patient record system of the First Affiliated Hospital of Xi'an Jiaotong University in Shaanxi province. We screened the records of patients who were admitted to the CCU of the study hospital during December 2015 and December 2018 and identified patients with STEMI. Exclusion criteria included patients with non-STEMI, unstable angina, or recent or remote MI. This protocol was approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (Shaanxi 710061, China) and was in accordance with the Helsinki Declaration's guidelines. Informed consent was obtained for all participants and families.

Animals

Male C57BL/6 mice which were introduced from Jackson Laboratory (USA) aged 12–15 weeks of age were used. Mice were anesthetized using the mixture of ketamine/xylazine/atropine (20/100/1.2 mg/kg, respectively) and put on a heated pad. As we previously described⁹, open-chest surgery was done to induce either permanent coronary artery occlusion (group-1) or ischemia-reperfusion (IR). In another two group of mice, coronary artery occlusion was induced for one hour (group-2) or four hours (group-3), followed by reperfusion. All operated mice were monitored up to day-10. Animals were inspected three times daily for the incidence of death and autopsy was done for all mice found died to determine the cause of death. Mice were housed in standard conditions with food and water provided ad libitum in a 12 h/12 h light/dark cycle. After this study, all mice were euthanized with pentobarbital overdose. These

procedures described were approved by a local animal ethics committee in compliance with the Australian Code for the Care and Use of Animals for Scientific Purposes (8th edition) and the ARRIVE guidelines.

Diagnosis of ST-elevation myocardial infarction

According to the AHA/ACCA¹⁰ and ESC¹¹ guidelines for STEMI patients, diagnosis of STEMI was based on the concurrence of chest pain or symptoms compatible with acute heart failure or unexplained syncope, ST-segment elevation ≥ 1 mm in 2 inferior or lateral leads or ≥ 2 mm in ≥ 2 precordial leads and elevation of cardiac biomarkers (CK-MB or troponin-T).

Diagnosis of cardiac rupture

Among STEMI patients, using CCU-equipped Phillips iE33 system, echocardiography was performed at day-1 after admission, as well as before hospital discharge or when the following conditions were observed during the infarct evolution: hypotension, syncope, chest pain, ECG changes, severe arrhythmias or conduction disturbances. Patients were placed on supine or on left recumbent position. 2-Dimensional echocardiograms were acquired using Phillips iE33 ultrasound system and S5-1 probe. Images were obtained in the standard parasternal long- and short-axes, apical and subcostal 4-chamber views. Color-Doppler echocardiography was used in conjunction with 2-dimensional echocardiography. All images were recorded on videotape and analyzed by at least two experienced echocardiography specialists. Diagnosis of CR was based on echocardiographic findings and clinical manifestation. FWR was diagnosed by the presence of echo-signal free space of the free wall myocardium or presence of pericardial effusion (Fig. 1A and 1B), Color Doppler detected blood flow shunt between the ventricle and the pericardium (Fig. 1B) when patients developed sudden onset of cardiogenic shock, conscious disturbance, and pulseless electric activity (electro-mechanic dissociation) after being in a stable condition¹². VSR was suggested by physical examination of strong cardiac murmur and diagnosed by echocardiography as presence of echo signal-free space of the ventricular septum (Fig. 1C and 1D) and Color Doppler detected blood flow signal across the ventricular septum (Fig. 1D)¹². Among MI mouse, CR diagnosis depends on autopsy. 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 death⁹.

Clinical measurements

Investigators and a trained interviewer collected all the clinical data. Potential predictive variables evaluated in this study included demographic characteristics (age and sex), classical cardiovascular risk factors (smoking, hypertension, diabetes mellitus and alcohol consumption), characteristics of MI (localization, culprit artery, numbers of diseased vessels) and Killip's classification. Smoking was defined as smoking cigarettes within 1 month of the index admission. Alcohol consumption was defined as drinking > 30 mL ethanol per day in men and > 15 mL ethanol per day in women. Hypertension was defined as a cuff blood pressure $\geq 140/90$ mmHg and/or the current use of antihypertensive medications. Diagnosis of diabetes was confirmed as plasma fasting glucose was ≥ 7.0 mM (or the 2-h

postprandial glucose was > 11.1 mM) and /or there was current use of anti-diabetic medication. Killip classification was assigned for the presence and severity of heart failure for STEMI patients according to AHA/ACCA¹⁰ and ESC guideline.¹¹ Infarct location was determined by electrocardiogram and echocardiography.. Selective coronary angiograms were obtained using the Judkins or Sones technique. The coronary arteries were analyzed by routine angiogram. On the basis of luminal stenosis $\geq 50\%$ as significant coronary stenosis, the number of coronary arteries with lesion was determined. Information also included socio-economic features of patients as resident of urban or countryside. Surrounding country-level regions, including counties and county-level cities, were then designated as rural area.

Laboratory parameters

For measurement of hemoglobin, blood cell counts or high-sensitivity C-reactive protein (hs-CRP), blood was collected via the median cubical vein using EDTA-containing tubes at admission and daily afterwards. Hemoglobin (HB), white blood cell (WBC) and neutrophils were measured with automated cell counters via standard techniques by HST201 (Sysmex, Japan). hs-CRP was measured by high-sensitivity particle-enhanced immunoturbidimetric method using BN II (Siemens, Germany). Blood was also drawn into sodium citrate-containing tubes, at admission and then daily after a 12-hour overnight fasting for measurements of fibrinogen, D-D dimer and fibrinogen degradation products (FDP), by using the latex agglutination test (Sysmex CA -7000, Sysmex, Japan). To detect the peak of creatine kinase-MB (CK-MB), blood was collected into tubes containing no anticoagulant at admission and then every 6 hours after symptom onset for 24 hours, CK-MB were tested by the spectrophotometric method using the Olympus AU640 Clinical Chemistry analyzer (Olympus Diagnostica, Hamburg, Germany).

Treatment and evaluation of patient outcomes

All patients were administered aspirin 300 mg and clopidogrel 600 mg or ticagrelor 180 mg, followed by aspirin 100 mg, clopidogrel 75 mg or ticagrelor 180 mg daily for at least 12 months. All patients received β -blockers, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and statins according to the AHA/ACCA¹⁰ and ESC STEMI guidelines¹¹, unless there were contraindications to these drugs. All patients were administered pPCI or delay PCI based on clinical manifestation according AHA/ACCA¹⁰ and ESC STEMI guidelines¹¹. All CR patients were suggested equally to reperfusion, intra-aortic balloon pumping (IABP), extracorporeal membrane oxygenation (ECMO), percutaneous closure or surgical repair, if patients had not contraindications. The primary outcome was mortality, defined as deaths of any cause in-hospital or within 60 days. In-hospital mortality was obtained from hospital medical records. Patients were also followed up for information of 60-day mortality by interview or telephone communication with these patients or their families.

Statistical analyses

Analyses were performed using SPSS version 13.0. Normally distributed values are presented as mean \pm SD, and differences between groups were determined using ANOVA followed by Student's t-test. Variables with a skewed normal distribution are presented as medians (interquartile range), and between-group differences for these variables were determined using Rank-Sum test. Categorical variables are presented

as percentages, and the differences between groups were tested using Chi-square test. The logistic model was used to evaluate the associations between cardiac rupture and variables. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Survival estimates were generated using Kaplan-Meier method. Significance was defined at the 5% level using a two-tailed test.

Results

Incidence and time-course of cardiac rupture

During December 2015 to December 2018, a total of 5844 consecutive patients were admitted to the CCU. Of them, 2568 patients were excluded according to the exclusion criteria and the remaining 1456 patients with confirmed STEMI diagnosis were included in this retrospective study. There were 40 patients diagnosed CR, VSR occurred in 20 cases, FWR in 17 cases and combined location in 3 cases. 19 patients had CR before arriving the hospital with estimated symptom-to-CR interval of 4 hours to 15 days. CR occurred within hospital in 21 patients giving the in-hospital incidence of CR 1.4% (21/1456). In 9 patients CR developed post-pPCI, and 2 case received thrombolytic therapy. As shown in Fig. 2, 18 patients (45%) developed CR within 24 h after chest pain symptoms onset. And 16 patients (40%) occurred CR during 2–6 days after symptoms onset, and another CR occurred in another 4 (10%) patients during 7–15 days after STEMI.

Characteristics of cardiac rupture

Because the data of MI patients among 2018 was not complete, we analyzed the data of the patients between 12. 2015 to 12. 2018. Relevant patient baseline characteristics are summarized in Table 1. 56% of CR patients admitted to hospital within 12 hours whilst 12% of CR patients arrived to hospital during 12–24 hours after the onset of symptom, and the ratio of patients who arrived to hospital within 12 hours after symptom was higher in CR patients than CR-free patients (Table 1).

Table 1
Baseline clinical characteristics in 910 STEMI patients with and without cardiac rupture.

	Non-rupture (n = 885)	Rupture (n = 25)	P value
Age (year)	58.5 ± 11.7	70.3 ± 9.1	< 0.001
Male gender (%)	731 (82.6%)	14 (56.0%)	0.002
Socio-economic feature (rural area)	446(50.4%)	18(72.0)	0.041
Symptom-to-admission interval			0.017
<12 hours	324(36.6%)	14(56.0%)	
12 – 24 hours	41(4.6%)	3(12.0%)	
>24 hours	520(58.8%)	8(32.0%)	
Previous history			
Diabetes	127 (14.4%)	6 (24%)	0.145
Hypertension	380 (42.9%)	17 (68.0%)	0.014
Alcohol consumption	266 (30.1%)	0 (0%)	< 0.001
smoking	587 (66.3)	9 (36.0)	0.002
MI	53 (6.0%)	0 (0%)	0.392
Angina pectoris	237 (27.0%)	4 (16.0%)	0.145
Coronary surgery	24 (2.7%)	1 (4%)	0.506
Physical examination at admission			
Admission SBP (mmHg)	122 ± 20	120 ± 25	0.578
Admission DBP (mmHg)	77 ± 13	75 ± 17	0.638
Admission heart rate (bpm)	76 ± 14	89 ± 20	< 0.001
Killip class			0.371
I	552 (62.4%)	8 (72.7%)	
II	260 (29.4%)	1 (9.1%)	
III	43 (4.9%)	1 (9.1%)	

Data are mean (SD) or n (%) unless otherwise stated. SBP: systolic blood pressure, DBP: diastolic blood pressure, MI: myocardial infarction. Killip class for CR patients was obtained prior to onset of rupture (n = 11 in rupture group). Among all STEMI patients, 773 patients underwent coronary angiography.

	Non-rupture (n = 885)	Rupture (n = 25)	P value
IV	30 (3.4%)	1 (9.1%)	
MI localization			
anterior	359 (40.6%)	6 (24%)	0.143
inferior	389 (44%)	17 (68%)	0.093
Infarct-related coronary artery			0.328
Left anterior descending artery	429(56.6%)	11(73.3%)	
Left circumflex artery	58(7.7%)	2(13.3%)	
Right coronary artery	266(35.1%)	2(13.3%)	
Left main trunk	5(0.7%)	0(0.0%)	
Number of stenosed vessel			0.754
1	202(26.6%)	3(20.0%)	
2	269(35.5%)	5(33.3%)	
3	287(37.9%)	7 (46.7%)	
Data are mean (SD) or n (%) unless otherwise stated. SBP: systolic blood pressure, DBP: diastolic blood pressure, MI: myocardial infarction. Killip class for CR patients was obtained prior to onset of rupture (n = 11 in rupture group). Among all STEMI patients, 773 patients underwent coronary angiography.			

Patients with CR were older, more likely to be female and had hypertension history. CR groups also had lower incidence of previous MI and previous PCI. The incidence of diabetes mellitus or angina prior to the current MI was comparable between the two groups.

Clinical biochemical or angiographic findings

Patients with CR exhibited higher counts of WBC and neutrophils at admission, and higher peak levels of CK-MB and hs-CRP, and higher levels of D-D dimer and FDP (Fig. 3). There was a significant and positive correlation between peak CK-MB and peak hs-CRP ($r = 0.1991$, $P < 0.001$, $n = 896$). Of 25 CR patients, 15 cases (60%) underwent coronary angiography. There was no significant difference in patients without or with CR in characteristics of coronary lesion (Table 1).

Risk factor of CR

By multi-variables logistic regression models, age, female, peak CK-MB, peak hs-CRP and rural area were independent factors entered the regression model with OR between 2.49 to 12 (Fig. 4).

Therapy and prognosis of patients with CR

Of 885 CR-free STEMI patients, 293 patients underwent pPCI (32.2%) and 480 patient received delay PCI (54.2%). Among patients with CR, 10 cases underwent pPCI and 5 patients underwent delay PCI, with the rest 10 patients (40%) did not receive PCI, a percentage higher than other STEMI patients without CR (n = 112, 12.7%). Regarding the medications used, the proportions of the use of aspirin ($P = 0.027$), P2Y12 inhibitor ($P < 0.001$), statin ($P < 0.001$), β -blocker and ACEI/ARB ($P = 0.027$) were significantly lower in the patients with CR (Table 2). Except for medications and PCI, CR-related treatment was also applied to our patients including IABP (n = 10), ECMO (n = 2), open-chest surgery for VSR (n = 2), or device closure therapy for VSR (n = 2).

Table 2
Treatment characteristic in STEMI patients with or without cardiac rupture

	Non-rupture (n = 885)	Rupture (n = 25)	P value
Drugs			
Aspirin	858 (97.0%)	22 (88%)	0.006
P2Y12 inhibitor	850 (96.0%)	19 (76%)	< 0.001
ACEI/ARB	793 (89.6%)	12 (48%)	< 0.001
β -blocker	794 (89.7%)	14 (56%)	< 0.001
Statins	823 (93.0%)	12 (48%)	< 0.001
PCI type			< 0.001
primary PCI	283 (32.0%)	10 (40%)	
Delay PCI	475 (53.7%)	5 (20%)	
Non-PCI	127 (14.3%)	10 (40%)	
Data are n (%). ACEI/ARB: angiotensin converting enzyme inhibitors or angiotensin receptor blockers; PCI: percutaneous coronary intervention.			

Among 910 patients, a total of 41 patients died in-hospital and 54 patients died within 60 days. Of 25 CR patients, 16 patients (64%) died in hospital and 18 (72%) died within 60 days, contributing to 39% (16/41) in-hospital deaths and 33.3% (18/54) 60-day deaths. Other causes of in-hospital death were heart failure (10, 24.4%), arrhythmia (9, 22.0%) or cardiogenic shock (6, 14.6%). Similarly, non-CR reasons for 60-day deaths consisted of heart failure (17, 31.5%), arrhythmia (12, 22.2%) or cardiogenic shock (7, 13.0%). The post-STEMI survival was much lower in CR patients compared with CR-free patients (Fig. 5A). By survival analysis, open-chest surgery, hemodynamics support or device closure therapy may be associated with

improved prognosis (Fig. 5B). The death rate was higher in patients with FWR was than these with VSR (Fig. 5C).

CR time-course and influence of reperfusion in mice

A total of 83 mice were operated with 39 mice were allocated for group-1 and another 44 mice for IR, of which 21 mice for group-2 and 23 mice for group-3 ischemia followed by reperfusion. There were 7 mice died within 24 h after surgery due to surgical related reasons (bleeding, poor recovery from the procedure, $n = 5$) or acute heart failure ($n = 2$). The rest mice ($n = 36$, $n = 19$ and $n = 21$ mice for group-1, -2 and -3, respectively) were included in observation of incidence of rupture up to day-9 after surgery. At the end, all mice were euthanized and presence of cardiac infarct was confirmed by autopsy.

There were 17 deaths in group-1 occurring during day 3–6 post MI (Fig. 6). Autopsy indicated all deaths due to LV free wall rupture with large amount of blood clot in the chest cage, albeit presence of acute heart failure was identified in 3 mice (i.e. pulmonary congestion, chest pleural effusion). In the two IR groups, one mouse died of acute heart failure at day 5 post surgery (Group-3) and the rest of mice survived to the end of experiment without onset of rupture ($P < 0.001$ for either of group-2/3 vs group-1).

Discussion

This retrospective study leads to the following main findings. First, the current in-hospital CR incidence is 1.4% in STEMI patients but the real incidence is much higher considering the pre-hospitalization onset of CR since a high proportion of CR occurred within day-1 after STEMI. Second, the in-hospital and 60-day mortality of CR patients remains very high. Third, open-chest surgery, life support or device closure therapy are superior to medications to improve the prognosis of CR patients. Forth, the risk of CR is higher if STEMI patients are elderly, with large infarct size and high levels of inflammatory parameters. Finally, reperfusion post coronary artery occlusion completely eliminated onset of rupture in mice.

The overall incidence of CR reported in the literature prior to the pPCI era was 10–20%², and the incidence of CR reported over the recent 10 years is around 1%^{1,13,14}. In the current study, the in-hospital incidence of CR was 1.4% in STEMI patients. Practically, the true incidence of CR is difficult to reach, as indicated by our study revealing that 19/40 patients developed CR at admission. Such a high proportion of patients with early onset of CR highlights that CR remains a major challenge to modern cardiology and forms one of main reasons of sudden cardiac death post-MI. A further hurdle added to this challenge is the current very low autopsy rate. In a recent study, Chen *et al*/ analyzed 11,234 STEMI patients from the 7 major hospitals in China and found that the incidence of CR was between 1–4% among these hospitals¹⁵. Early reperfusion therapy could be the major factor responsible for the decline in the incidence of CR¹. The results of mice experiment provides a strong experimental evidence for the overt reduction of rupture in the last few decades with the initially increasing and currently routine use of primary PCI. Although ACC/AHA¹⁰ and ESC¹¹ guidelines recommend reperfusion therapy within the first 12 hours after symptom onset in all STEMI patients, some STEMI patients could not receive reperfusion therapy due to

various reasons including delay admission. Unfortunately, study has revealed that the proportion of patients in China who did not receive pPCI has not significantly improved over the last decade¹⁵. Low proportion of reperfusion therapy is likely one of the reasons for the onset of CR in-hospitalization.

Clinical reports prior to the reperfusion therapy era described the frequency of CR as two peaks: within 24 hours and during 6–14 days after STEMI with nearly even proportion^{2,16}. In our population study, whilst the early peak of CR remains, the late peak of CR seems blunted. Based on the Becker classification of CR¹⁷, early CR is mainly type-I or type-II, whereas late rupture were type-III associated with significant wall thinning and ventricular remodeling. The clinicopathological features of early and late rupture are different¹⁸. Early phase rupture is characterized by an abrupt slit-like tear in the infarcted myocardium, while late phase rupture exhibits infarct expansion and wall thinning¹⁸.

While some studies indicated that reperfusion therapy could only decrease the incidence of late rupture while showing limited benefit on the early CR^{16,19}, it is generally agreed that early reperfusion is able to reduce the rupture incidence²⁰. Although in this population study, 9 patients had early CR after pPCI, we cannot ignore the influence of reperfusion therapy. In the mice experiment, reperfusion therapy can decrease the CR incidence apparently. Whilst the mechanism for such an evident protection remains to be illustrated, considering that infarct size might be reduced by reperfusion after 1 h ischemia in mice study⁹, but not if ischemia last for 4 hours, it is clear that the protection associated with reperfusion not only to cardiomyocytes, but also to non-cardiomyocyte matrix tissues within the ischemic zone, is important. It remains to be tested whether mice with MI might develop CR under simulated hemodynamic, physical or psychological stressors.

Our study showed that the mortality of CR remained to be very high (64% within hospital and 72% within 60 days) relative to the earlier reports showing 100% mortality for FWR² and approximately 90% for VSR without treatment²¹, albeit the mortality of patients underwent surgery for correction of VSR varied between 20–60%^{12,22}. Management of CR patients is complex and might require a variety of therapeutic approaches, including pharmacologic (include ACEI, β -blocker, intravenous nitrates, and hydralazine) and device-based therapies to achieve afterload reduction and hemodynamic stabilization. Whilst medical therapy and non-pharmacologic methods may only stabilize CR patients, the treatment of choice is closure of rupture site by surgical and catheter-based means^{23,24}. The outcome of operated CR patients is closely related to their hemodynamic state prior to the surgery. Emergency surgery for CR has been limited in our hospital due to the fact that patients with CR are often in extremis prior the surgery and many died suddenly. On the other hand, currently the percutaneous devices to primarily close VSR are only applicable to selected cases with simple defects (e.g. VSR less than 15 mm in diameter) with the optimal time approximately 3 weeks following MI. In our cohort, only 2 out of 25 CR patients were suitable for percutaneous closure at 3 weeks after rupture occurred and they both survived over 60 days. Unfortunately, we experienced a high percentage of CR patients who refused further treatment because of reasons including critical conditions or high expenses.

In the current study, we revealed several independent risk factors of CR including female gender, old age, lower MI or angina history or higher heart rate, findings similar to earlier reports^{2, 5, 25, 26}. Our study also added mechanistic insight by showing that both infarct size and the extent of inflammation are underlying factors for the onset of CR. The enzymatic index of infarct size, peak CK-MB²⁷, was one of the independent risk factors of CR in patients with STEMI. However, caution is required since many patients died before they arrived hospital with their infarct size was difficult to assess due to lack of serial measure of CM-MB and hence such relationship between infarct size and the risk of early onset of CR remains elusive. CRP is a non-specific and commonly used biomarker for inflammatory response. Hepatic production of CRP is increased upon stimulation by various cytokines derived from innate immune response evoked by myocardial ischemia and infarction²⁸. We also observed a significant correlation between peak levels of CK-MB and CRP, implying a causative relation of the scale of infarct mass and subsequent inflammatory response. Indeed, others have also reported association of CRP levels and indexed infarct size^{29, 30}. Previous studies have shown that higher levels of CRP are associated with adverse prognosis in MI patients³¹ including CR. Further support of inflammatory mechanism comes from our finding of higher inflammatory cell counts in CR relative to non-CR patients.

We found that the majority of CR patients (68%) arrived hospital within 24 hours after symptom onset, a proportion higher than that of non-CR STEMI patients, albeit by logistic regression analysis excluded the time from symptom onset to hospital as an independent risk factor. The likely reason for the early admission of CR versus non-CR patients is due to the severity of symptom per se in patients with CR forcing them to seek medical assistance. Meanwhile, the rural location of residence of patients is an independent risk factor of CR. The possible explanation is that excessive time was required to arrive central hospitals to those patients who live in remote regions, and that common knowledge of MI was insufficient to those patients. Relevant to this is the limited availability of PCI especially pPCI in rural hospitals.

A significant body of knowledge has been generated by preclinical studies on the mechanism and therapeutic intervention of CR. With the demonstration of the mouse as the only laboratory species that develop CR post transmural MI like human patients³², numerous studies have been conducted in mice^{9, 33}. Mechanistically, rupture event occurred in mice within a single onset peak timing (days 4–5) and there was no early onset of rupture within the first 48 hrs. This differs from human patients with MI showing that significant percentage of CR occurred within the first 24 hours and that following reperfusion and other therapies, the previously reported second peak of CR events was largely diminished CR in the mouse model typically occurs during 3–5 days after STEMI exhibiting wall thinning and dilatation by histopathology³², simulating the human type-III rupture. In the mouse model of MI, the infarct size and scale of inflammatory response are pivotal determinants of CR, observations in keeping with the findings from the present study^{9, 34}. Furthermore, mice with an old age had a higher risk of CR than young counterparts and that such difference was associated with more severe cardiac inflammation³⁵. Regional inflammation results in accumulation of proteinases, particularly matrix metalloproteinase-9, responsible for the breakdown of existing collagen networks leading to reduced tensile strength of the infarcted

wall³⁶⁻³⁸. Therapeutically, studies on mice have revealed successful inhibition of CR by anti-inflammatory therapies³⁹, reperfusion or use of some currently routine medications like anti-platelet drugs, ARB or ACEI³³. Collectively, our findings on patients with CR are supported in part by studies in the mouse model of CR regarding significance of infarct size, age³⁵, inflammation^{37,39} and histopathology of type-III CR^{9,32}. Unlike human patients, CR in the mouse never occurs in the first day after MI and such species difference is interesting albeit unknown in the mechanism. Further research is required to illustrate the mechanism of early CR and test therapeutic interventions.

Our study has a few limitations that are worth to be discussed. This was a retrospective observational study consisting data from a single center, and hence had a limited number of CR cases. Some of laboratory or angiographic data were unable to obtain in those patients who had CR at admission. Furthermore, the diagnosis of CR was based on echocardiographic images and clinical characteristics, but without pathologic (autopsy) validation.

Conclusion

CR remains as a major cause of death in patients with MI and that the clinical features of CR patients such as risk factors, time-course, clinical presentation and mortality remain largely the same relative to the pre-PCI era. And what's more, reperfusion therapy can decrease CR incidence sharply.

Abbreviations

CR: Cardiac rupture, FWR: free wall rupture, VSR: ventricular septum rupture, MI: myocardial infarction, STEMI; ST-elevation myocardial infarction, PCI: percutaneous coronary intervention, pPCI: Primary PCI, IR: ischemia-reperfusion, hs-CRP: high-sensitivity C-reactive protein, HB: Hemoglobin, WBC: white blood cell, FDP: fibrinogen degradation products, CK-MB: creatine kinase-MB, ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, IABP: intra-aortic balloon pumping, ECMO: extracorporeal membrane oxygenation, OR: Odds ratios, CI: confidence intervals.

Declarations

Ethics approval and consent to participate

The protocol about patients was approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (Shaanxi 710061, China) and was in accordance with the Helsinki Declaration's guidelines. Informed consent was obtained for all participants and families. The mice were introduced from Jackson Laboratory (USA) and informed consent was obtained from this laboratory. These procedures about animal experiments were approved by a local animal ethics committee in compliance with the Australian Code for the Care and Use of Animals for Scientific Purposes (8th edition) and the ARRIVE guidelines.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare no competing interests.

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Authors' contributions

QL, LB and XD designed the study, QL, JH, PL, YW and ZY collected the data, QL and XD analyzed and interpreted the data, QL and XD prepared and revised the manuscript. All authors read and approved the final manuscript.

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Figures

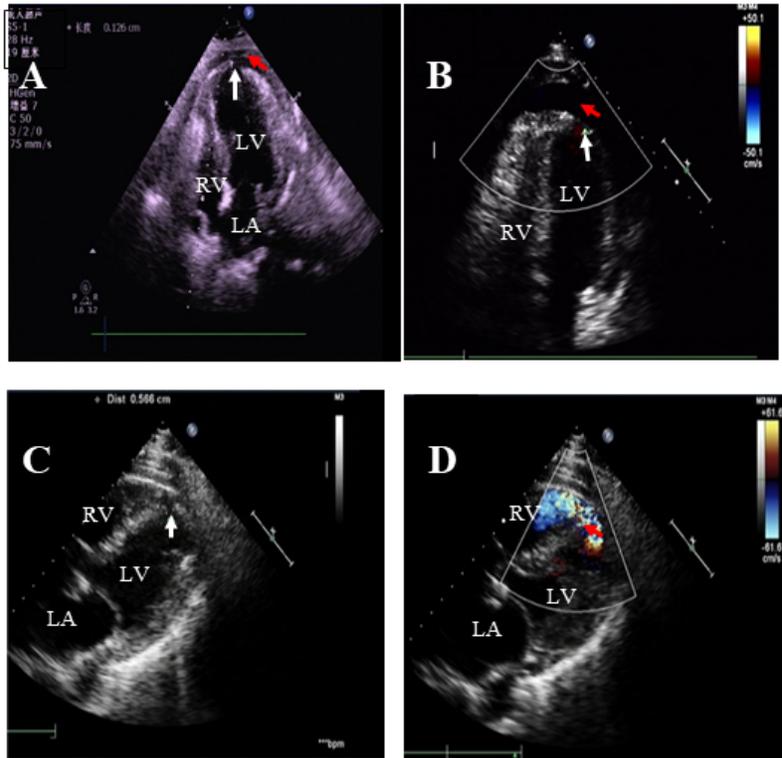


Figure.1
 Representative transthoracic echocardiographic image of patients with CR.

Figure 1

Representative transthoracic echocardiographic images from patients with cardiac rupture. A. 2-D image revealed discontinuity of the left ventricular (LV) wall (white arrow) and pericardial effusion (red arrow). B. Color Doppler image demonstrated shunting of blood flow from the LV to the pericardium (white arrow) and presence of pericardial effusion (red arrow). C. ventricular septum discontinuity (white arrow) in 2-D and presence of pericardial effusion (red arrow). D. Color Doppler image demonstrated shunting of blood flow from the LV to the pericardium (white arrow) and presence of pericardial effusion (red arrow).

image. D. shunting of blood from the LV to the right ventricle (RV, red arrow) in Color Doppler image; LA= left atrium; RA= right atrium.

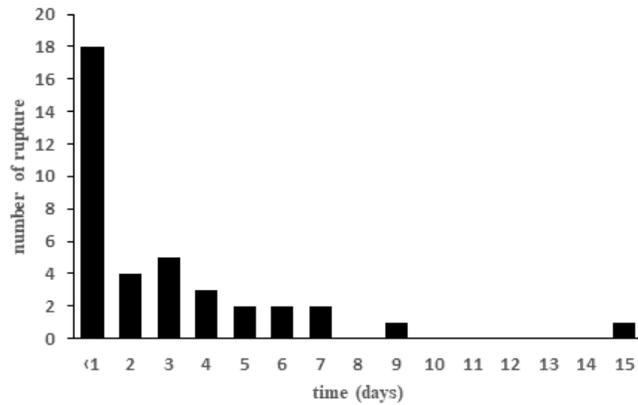


Figure 2.

The times (days) from symptom onset to cardiac rupture diagnosis

Figure 2

The times (days) from symptom onset to cardiac rupture diagnosis.

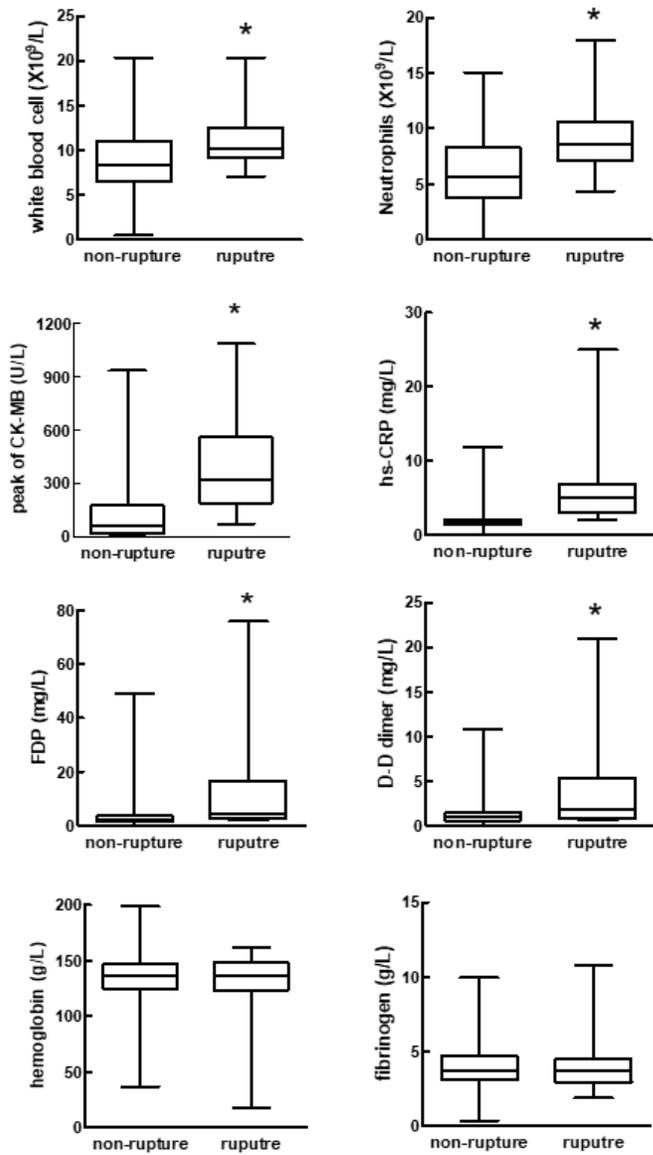


Figure 3.
Comparison of parameter between STEMI with or without rupture.

Figure 3

Comparison of laboratory parameter between STEMI with or without cardiac rupture. CK-MB: creatine kinase-MB, hs-CRP: high sensitive C-reactive protein, FDP: fibrinogen degradation product, WBC: white blood cell. *P<0.05 vs. STEMI without CR. Note: n=11 in rupture group for peak CK-MB and peak hs-CRP.

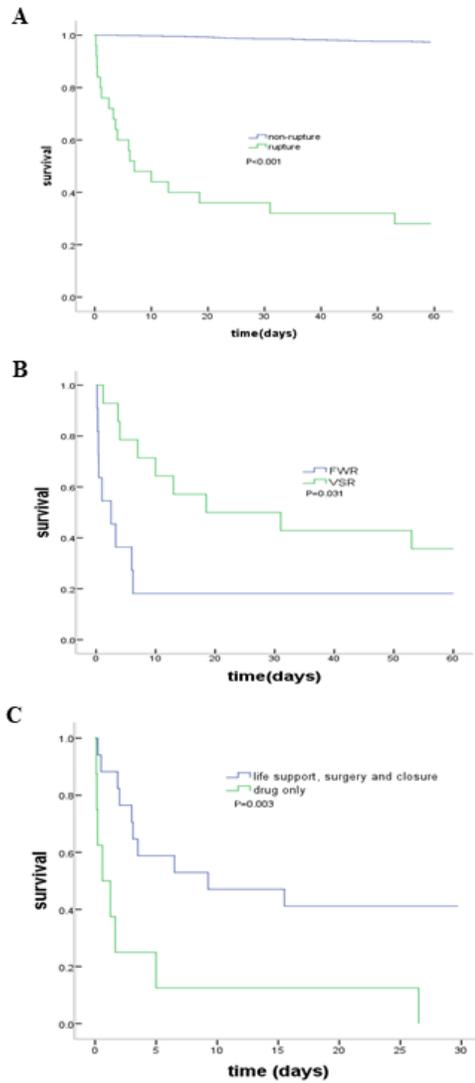


Figure 4.
The survival curves of patients with CR.

Figure 4

Multivariate logistic regression analysis of risk factors and the incidence of cardiac rupture. CK-MB: creatine kinase-MB; hs-CRP: high sensitive C-reactive protein.

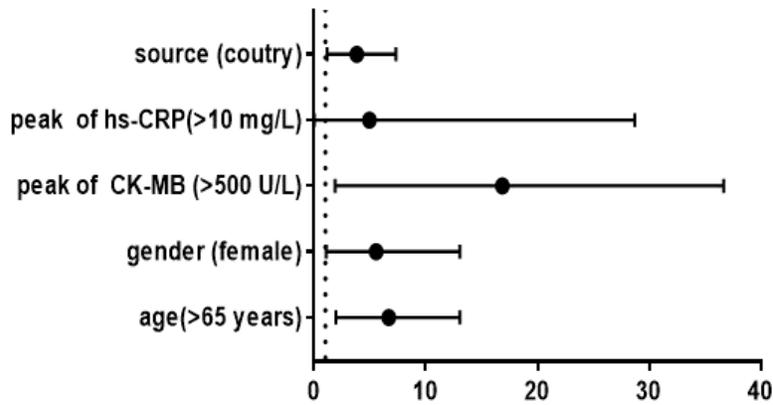


Figure 5.

Results of the multivariate logistic regression analysis of risk factors and the incidence of CR.

Figure 5

Survival curves of patients with cardiac rupture. A, compared between in STEMI patients with and without CR. B, compared between FWR group and VSR group. C, compared between drug treatment only and life support, surgery and closure in CR. FWR: free wall rupture, VSR: ventricular septum rupture.

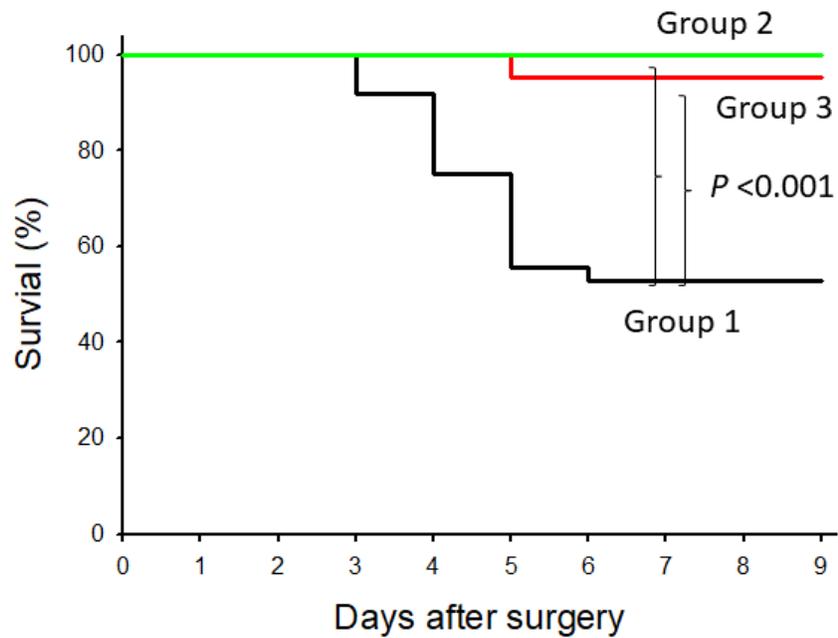


Figure 6.
Comparison of survival between 3 group mice .

Figure 6

Comparison of survival between 3 group mice . green line is group 2, red line is group 3, black line is group1.

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