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Risk of cardiac rupture after acute myocardial infarction is related to a risk of hemorrhage

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Abstract: Although cardiac rupture (CR) is a fatal mechanical complication of acute myocardial infarction (AMI), to date no predictive model for CR has been described. CR has common pathological characteristics with major bleeding. We aimed to investigate the relationship between the risk factors of major bleeding and CR. A total of 10 202 consecutive AMI patients were recruited, and mechanical complications occurred in 72 patients. AMI patients without CR were chosen as control group. Clinical characteristics including bleeding-related factors were compared between the groups. The incidences of free wall rupture (FWR), ventricular septal rupture (VSR), and papillary muscle rupture (PMR) were 0.39%, 0.21%, and 0.09%, respectively, and the hospital mortalities were 92.5%, 45.5%, and 10.0%, respectively. Female proportion and average age were significantly higher in the groups of FWR and VSR than in the control group (P<0.01); higher white blood cell count and lower hemoglobin were found in all CR groups (P<0.01). Compared to the control group, patients with CR were more likely to receive an administration of thrombolysis [26.39% vs. 13.19%, P<0.05], and were less likely to be treated with primary percutaneous coronary intervention (PCI) [41.67% vs. 81.60%, P<0.05]. The major bleeding scores (integer scores) of FWR, VSR, and PMR were (17.70±7.24), (21.91±8.33), and (18.60±7.88), respectively, and were significantly higher than that of the control group (11.72±7.71) (P<0.05). A regression analysis identified age, increased heart rate, anemia, higher white blood cell count, and thrombolysis as independent risk factors of CR, most of which were major bleeding-related factors. The patients with CR have a significantly higher risk of hemorrhage compared to the group without CR. Risk of CR after AMI is related to the risk of hemorrhage.

Key words: Acute myocardial infarction (AMI), Risk factor, Hemorrhage
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1 Introduction

Cardiac rupture (CR) after acute myocardial infarction (AMI) especially for ST-elevation myocardial infarction (STEMI) includes free-wall rupture (FWR), ventricular septal rupture (VSR), and papillary muscle rupture (PMR). With the development of emergency percutaneous coronary intervention (PCI), the incidence of CR has progressively declined since the 1980s (Figueras *et al.*, 2008); however, CR still constituted a common cause of in-hospital death in STEMI accounting for up to 20% of in-hospital mortality (Markowicz-Pawlus *et al.*, 2007; French *et al.*, 2010). In fact, FWR is associated with a high mortality from electromechanical dissociation (EMD) or pericardial tamponade, and is often unresponsive to resuscitative maneuvers; VSR and PMR patients often progress to refractory heart failure. Therefore, the prognosis of CR is very poor. The prevention of mechanical complications should be emphasized. The determination of CR risk factors plays an important role in the prevention of CR. Independent risk factors associated with CR reported before are female gender, advanced age, low body mass index (BMI), high heart rate, ST-segment elevation, and thrombolysis, most

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of which could also increase the risk of major bleeding (Yip *et al.*, 2003; Bueno *et al.*, 2005; Okino *et al.*, 2005; Markowicz-Pawlus *et al.*, 2007; López-Sendón *et al.*, 2010; Qian *et al.*, 2011). CR itself has the common pathological characteristics of hemorrhagic disease. Myocardial hemorrhage makes the myocardium susceptible to rupture (Sane *et al.*, 2009). There is a lack of systemic research on the correlation between hemorrhage risk factors and CR. The objective of this study was to investigate the relationship between risk factors of major bleeding and CR.

2 Materials and methods

2.1 Study population

We analyzed a total of 10 202 consecutive AMI patients at Chinese People's Liberation Army General Hospital (Beijing, China) from January 2000 to January 2012. A total of 72 consecutive patients with CR after AMI (40 with FWR, 22 with VSR, and 10 with PMR) were enrolled in our study. Most CR occurred in STEMI patients. The clinical diagnosis of AMI was based on the concurrence of at least two of the three following features: chest pain, elevated myocardial enzymes [creatine kinase (CK), CK muscle-brain fraction (CK-MB), troponin T], and acute electrocardiographic changes. Diagnosis of STEMI was based on the concurrence of chest pain or symptoms compatible with acute or subacute heart failure or unexplained syncope and ST-segment elevation ≥1 mm in two inferior leads or ≥2 mm in two precordial leads. The diagnosis of FWR was based on strict necropsy or clinical manifestations and results of examination: echocardiography and diagnostic pericardiocentesis. Echocardiography showed massive pericardial effusion and diagnostic pericardiocentesis was performed immediately; routine testing of bloody pericardial effusion supported the diagnosis of FWR; VSR was established by surgery or echocardiography; PMR was confirmed by operation or echocardiography. We performed matched pair case-control study with the ratio of 1:4, and 288 patients without CR were chosen to match the 72 patients with CR, serving as the control group. Matching factors included clinical classification of acute myocardial infarction [STEMI or non-STEMI (NSTEMI)], the year of hospital admission, and whether there was occurrence of cardiogenic shock upon admission. The AMI patients received aspirin, clopidogrel, or ticlopidine, statin, subcutaneous low-molecular-weight heparin (LMWH), β-blockers, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), unless there were contraindications to these drugs. Tirofiban was given to those patients who had medium- or high-risk of coronary thrombus during or after PCI (intravenous bolus 10 μg/kg followed by intravenous infusion of 0.15 μg/kg/min) (van de Werf *et al.*, 2008; Kushner *et al.*, 2009). The bleeding-related factors analyzed in our study included: female gender, age, baseline heart rate, initial hemoglobin, initial serum creatinine, white blood cell count, LMWH plus glycoprotein (GP) IIb/IIIa antagonists, baseline systolic blood pressure, and peripheral vascular disease. We provided a comparative analysis between CR and non-CR patients by bleeding-related risk factors, laboratory test results, concomitant diseases, and the treatment. All AMI patients in our study had been scored by integer score and CRUSADE score. The integer score, which was based on six baseline measurements plus anticoagulation therapy, could identify the patients at increased risk of major bleeding (Mehran *et al.*, 2010). The CRUSADE bleeding score, which was based on eight baseline predictors, quantifies risk for in-hospital major bleeding (Subherwal *et al.*, 2009). Both the risk models have predictive values for in-hospital major bleeding. Undue effort often promotes the occurrences of CR, so early off-bed movement, repeated coughing, vomiting, and forced defecation were considered undue exercises for patients in the acute phase of AMI, and were recorded.

2.2 Statistical analysis

Descriptive statistics were expressed as mean± standard deviation (SD). Variables following a non-normal distribution were expressed as median (interquartile range). The means of normally distributed variables were compared by using the Student's *t*-test. For comparison of the distribution of risk factors between groups, χ^2 analysis was used. The Mann-Whitney *U* test was used for those with non-normal distribution. Independent CR risk factors were calculated using multivariable logistic regression models (enter method). Statistical analysis was performed using SPSS Version 19.0 (SPSS Inc., USA). Statistical significance was set at $P<0.05$.

3 Results

3.1 Incidence of CR

In the 10202 consecutive patients with AMI, FWR occurred in 40 patients (0.39%), VSR occurred in 22 patients (0.21%), and PMR occurred in 10 patients (0.09%). There were 359 patients died during the acute phase of AMI with a total early mortality of 3.52%. Of all dead patients, 203 patients with pump failure died, accounting for 56.54% of the in-hospital mortality; 48 patients with CR died, accounting for 13.37% of the in-hospital mortality. CR was the second cause of early mortality after hospitalization in our study. Most mechanical complications occurred in STEMI patients. All patients with FWR or VSR, and eight of those with PMR presented ST-segment elevation, whereas the remaining two patients with PMR presented ST-segment depression, and 94.44% of CR patients developed new Q waves. FWR was a complication with high mortality, and the in-hospital mortality of FWR group was up to 92.5%, while the in-hospital mortalities of VSR and PMR were 45.5% and 10.0%, respectively.

3.2 Clinical features in the patients with CR

Patients who developed mechanical complications had several differences in clinical manifestations compared to patients who did not. The clinical features are shown in Table 1. FWR and VSR occurred significantly more frequently in elderly and female patients ($P<0.01$). Histories of diabetes mellitus, hypercholesterolemia, and smoking were comparable in patients between CR and non-CR groups. Hypertension was more often present in the FWR group than in the control group, so was the peripheral vascular disease ($P<0.05$). The baseline heart rates were significantly higher in FWR, VSR, and PMR groups than in the control group ($P<0.05$). The initial hemoglobin levels of FWR, VSR, and PMR groups were all significantly lower than that of the control

Table 1 Comparison of clinical features by mechanical complication type

Clinical feature	Control (n=288)	FWR (n=40)	VSR (n=22)	PMR (n=10)
Female gender	60 (20.83%)	15 (37.50%)*	12 (54.54%)*	3 (30.00%)
Age (year)	60.99±13.18	67.28±9.48*	66.50±10.21*	66.00±9.19
BMI (kg/m^2)	25.11±3.60	24.08±3.15	24.59±2.03	23.32±2.12
History of hypertension	144 (50.00%)	27 (67.5%)*	12 (54.54%)	7 (70.00%)
History of diabetes mellitus	70 (24.31%)	9 (22.50%)	8 (36.36%)	2 (20.00%)
History of hypercholesterolemia	54 (18.75%)	10 (25.00%)	12 (54.54%)*	1 (10.00%)
History of smoking	149 (51.74%)	12 (30.00%)*	10 (45.45%)	4 (40.00%)
Peripheral vascular disease	29 (10.07%)	14 (35.00%)*	6 (27.27%)*	1 (10.00%)
Myocardial infarction in the past	62 (21.53%)	7 (17.50%)	6 (27.27%)	2 (20.00%)
Baseline heart rate (beat/min)	79.73±15.21	87.75±19.55*	89.59±21.91*	95.50±28.42*
Baseline systolic blood pressure (mmHg)	121.58±19.66	117.65±22.44	116.86±23.97	122.10±23.19
Baseline diastolic blood pressure (mmHg)	71.00±12.55	71.78±15.90	70.82±20.50	76.00±12.28
Anterior myocardial infarction	153 (53.12%)	29 (72.50%)	21 (95.45%)	7 (70.00%)
Initial LDL-C (mmol/L)	2.48±0.94	2.98±0.81*	2.65±0.61	2.81±0.89
Serum creatinine (μmol/L)	77.55 (64.65–93.75)	90.30 (72.77–124.75)	121.50 (84.95–154.75)	109.40 (83.30–140.50)
Initial hemoglobin (g/dl)	131.22±17.31	122.32±17.53*	117.73±19.21*	111.20±14.88*
HCT (%)	0.404±0.052	0.388±0.051	0.353±0.053*	0.336±0.037*
White blood cell ($\times10^9$/L)	9.39±2.96	10.88±3.11*	11.03±3.97*	11.96±4.15*
Ejection fraction (%)	50.64±8.42	47.42±8.38	41.50±9.27	45.30±13.99
Integer score	11.72±7.71	17.70±7.24*	21.91±8.33*	18.60±7.88*
Crusade score	21.61±13.74	33.70±15.05*	45.36±16.11*	39.50±13.38*
In-hospital mortality	9 (3.12%)	37 (92.50%)*	10 (45.50%)*	1 (10.00%)*

* Different from the non-CR (control) group at $P<0.05$. FWR: free-wall rupture; VSR: ventricular septal rupture; PMR: papillary muscle rupture; BMI: body mass index; LDL-C: low density lipoprotein cholesterol; HCT: hematocrit. Values are expressed as mean±SD or number (percent) or median (interquartile range)

group (P<0.01), while the white blood cell counts were significantly higher in FWR, VSR, and PMR groups than that of the control group (P<0.01). The integer-based bleeding risk scores of FWR group (17.70±7.24), VSR group (21.91±8.33), and PMR group (18.60±7.88) were significantly higher than that of the control group (11.72±7.71); similarly, the CRUSADE scores of FWR group (33.70±15.05), VSR group (45.36±16.11), and PMR group (39.50±13.38) were significantly higher than that of the control group (21.61±13.74, P<0.05). Very high integer scores (>20) occurred in 15 patients with FWR (37.5%), 12 patients with VSR (54.5%), and 7 patients with PMR (70.0%). The results are shown in Fig. 1. The actual major bleeding rate (according to the thrombolysis in myocardial infarction (TIMI) bleeding classification) of CR group was 8.33% (6/72), which is higher than that of the control group (1.73%, 5/288, P<0.05); therefore, the CR group had a tendency of major bleeding.

3.3 Treatment in the patients with CR

The relationship between CR and treatment is presented in Table 2. Thrombolysis was performed in 19 patients with rupture (26.39%) [12 (30.0%) of 40 with FWR, 4 (18.19%) of 22 with VSR, 3 (30.0%) of 10 with PMR] and in 38 patients without rupture (13.19%); the rate of thrombolysis was thus significantly higher in the CR group than in the non-CR group (P<0.05). While primary PCI was performed only in 30 patients with rupture (41.67%) [12 (30.0%) of 40 with FWR, 12 (54.54%) of 22 with VSR, 6 (60.0%) of 10 with PMR] and in 235 patients without rupture (81.60%). The rate of primary PCI was significantly lower in the CR group than in the non-CR group (P<0.05). Thrombolysis was associated with higher rates of CR by univariate analysis (P<0.05). There was no difference in treatment with heparin plus GPIIb/IIIa antagonists between the groups.

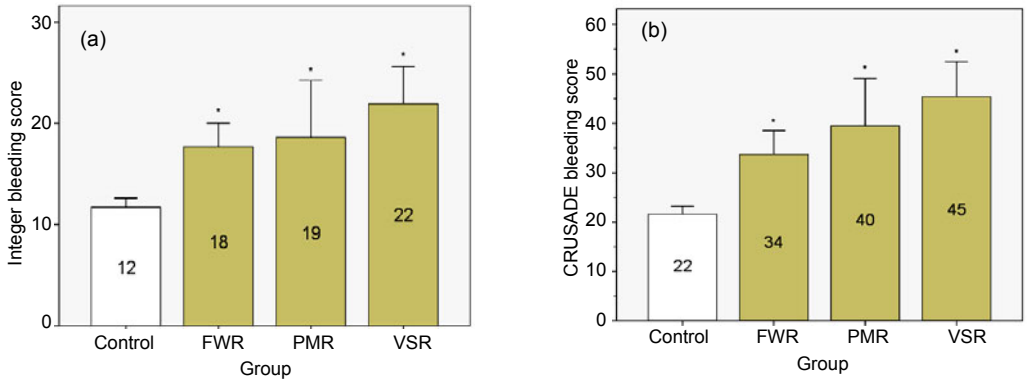

Fig. 1 Integer bleeding scores (a) and CRUSADE bleeding scores (b) of control, FWR, PMR, and VSR patients

* P<0.05 vs. control group. FWR: free-wall rupture; PMR: papillary muscle rupture; VSR: ventricular septal rupture. Data are expressed as meas±SD

Table 2 Comparison of in-hospital treatments

Group	Statin	β-blocker	ACEI/ ARB	Aspirin+ clopidogrel or ticlopidine	Low-molecular-weight heparin	GPIIb/IIIa inhibitor plus heparin	Primary PCI	Thrombolysis	Mechanical ventilation	Surgery
Control	288 (100%)	228 (79.17%)	208 (72.22%)	287 (99.65%)	271 (94.10%)	66 (22.92%)	235 (81.60%)	38 (13.19%)	14 (4.86%)	0 (0%)
FWR	40 (100%)	19 (47.50%)*	10 (25.00%)*	37 (92.5%)*	34 (85.00%)*	11 (27.50%)	12 (30.00%)*	12 (30.00%)*	2 (5.00%)	3 (7.50%)
VSR	22 (100%)	19 (86.36%)	15 (68.18%)	21 (95.45%)	20 (90.91%)	1 (4.54%)	12 (54.54%)*	4 (18.18%)	9 (40.90%)*	10 (45.45%)
PMR	10 (100%)	9 (90.00%)	7 (70.00%)	10 (100%)	10 (100%)	5 (50.00%)	6 (60.00%)	3 (30.00%)	0 (0%)	4 (40.00%)

* P<0.05 vs. control group. FWR: free-wall rupture; VSR: ventricular septal rupture; PMR: papillary muscle rupture; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; PCI: percutaneous coronary intervention. Data are expressed as n (%)

3.4 Risk factors of CR after AMI

Undue physical effort was documented in 18 patients with rupture (25.00%) [12 with FWR (30.0%), 6 with VSR (27.2%)], and in 25 control patients (8.68%, $P<0.01$). Abnormal activities before CR included early off-bed movement (8.33%, 6/72), persistent coughing or vomiting (6.94%, 5/72), and forced defecation (9.72%, 7/72). Coronary angiographic data showed the culprit artery mainly was the left anterior descending artery in both the FWR (7/12, 58.33%) group and the VSR group (7/12, 58.33%), while it was the left circumflex artery in the PMR group (4/6, 66.67%). Multivariable analysis identified independent predictors of CR: (1) age per extra 10 years [odds ratio (OR): 1.384, 95% confidence interval (CI): 1.076–1.780, $P<0.01$], (2) heart rate per extra 20 beats/min (OR: 1.453, 95% CI: 1.069–1.975, $P<0.05$), (3) initial hemoglobin level (OR: 0.973, 95% CI: 0.957–0.990, $P<0.01$), (4) count of white blood cell (OR: 1.133, 95% CI: 1.034–1.242, $P<0.01$), (5) thrombolysis (OR: 3.620, 95% CI: 1.762–7.436, $P<0.01$), which is shown in Table 3. There was a close correlation between bleeding-related risk factors and CR.

Table 3 Predictors of CR in the multivariate analysis

Risk factor	*P*	OR	95% CI
Female gender	0.077	1.073	0.992–1.160
Age per extra 10 years	0.011	1.384	1.076–1.780
Heart rate per extra 20 beats/min	0.017	1.453	1.069–1.975
Hemoglobin level	0.002	0.973	0.957–0.990
White blood cell count	0.008	1.133	1.034–1.242
Thrombolysis	0.001	3.620	1.762–7.436

OR: odds ratio; CI: confidence interval

4 Discussion

CR is a complication of myocardial infarction with an exceedingly high mortality rate (French *et al.*, 2010). The incidence of mechanical complication after AMI is 0.4% to 0.9% (Okino *et al.*, 2005; Pedrazzini *et al.*, 2008; French *et al.*, 2010; López-Sendón *et al.*, 2010). In our study, the mechanical complication rate was 0.70%. Despite improvements in STEMI and NSTEMI treatment, the incidence of CR remains significant. Our study showed that CR was the second cause of death in patients with AMI, while pump failure was the first cause of death in patients with AMI. The prevention of mechanical complications should be emphasized in the coronary care unit (CCU). It is important to develop an early practical risk score to evaluate the risk of CR in AMI patients.

Our study showed patients with mechanical complication had high risk scores of major bleeding. There is a close correlation between major bleeding risk factors and CR. In other words, hemorrhagic risk is strongly linked with subsequent CR in patients with AMI. CR has common pathological characteristics similar to major bleeding: transmural infarct is associated with focal hemorrhage, neutrophilic infiltration, and lysis of myofibrils. Unusual hemorrhagic infiltration was found in the necrotic areas with presence of leukocytes, which can explain why white blood cell counts were higher in the CR group than in the non-CR group in our study (Fang *et al.*, 2007; 2008). Severe post-infarction pericardial effusion increases mortality of AMI and some of which are related to myocardial hemorrhage and CR (Kameda *et al.*, 2006; Figueras *et al.*, 2010).

It is important to prevent CR in the course of AMI treatment. In our study, thrombolytic use was more prevalent in CR group. Thrombolysis was associated with incidence of CR, even when successfully reperfused. Several reports have demonstrated that thrombolysis was an independent risk factor of CR (Altunkeser *et al.*, 2002; Bueno *et al.*, 2005; Okino *et al.*, 2005; Dhand *et al.*, 2010). Thrombolysis could also induce myocardial hemorrhage, and the rescue PCI patients have significantly higher mortality compared with those treated by primary PCI (Gao R.L. *et al.*, 2010). Optimal primary PCI therapy could reduce cardiac infarct size, which correlates with the CR (Gao X.M. *et al.*, 2010). In our study, primary PCI could decrease the incidence of CR. The progressive decline in the incidence of CR over a 30-year period was associated with progressive implementation of medical intervention including more generous use of primary PCI (Figueras *et al.*, 2008). Such knowledge will aid to facilitate personalized decision-making for patients at high risk of CR. We could evaluate the risk of CR after AMI according to the integer or CRUSADE score, since there is a definite correlation between CR and high bleeding risk score. To minimize

the incidence of CR, we should avoid the triggers of mechanical complication for patients with high CR risk, such as prolonging the bed time, avoidance of strenuous activities, acesodyne, sedation, laxative, prevention of severe coughing, and vomiting. Early use of β-blockers and ACEIs or ARB could also help to prevent CR (Figueras *et al.*, 2008; Pedrazzini *et al.*, 2008). Current therapy of CR consists mainly of surgery with high mortality (Sakaguchi *et al.*, 2008; Haddadin *et al.*, 2009).

The limitations of this study are: this was a retrospective, single-center study which covered a period of 12 years, during which interventional techniques and medical treatments have changed tremendously. This study included some cases diagnosed on clinical manifestations rather than strict necropsy. It was likely that some of undue effort was unreported or over-reported, and we admitted that recall bias did exist in the undue effort statistics. Therefore, the lack of more accurate information about undue activity in both the control and CR groups was a drawback of the study.

5 Conclusions

CR is associated with high in-hospital mortality. The patients with CR have significantly higher risk of hemorrhage compared to the group without CR. Furthermore, some of the hemorrhage related factors such as age, increased heart rate, anemia, high white blood cell count, and thrombolysis are also independent risk factors of CR.

Compliance with ethics guidelines

Geng QIAN, Hong-bin LIU, Jin-wen WANG, Chen WU, and Yun-dai CHEN declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for which identifying information is included in this article.

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