than DC-SIGN have been reported for identifying DC. DC-SIGN is a type II transmembrane protein that belongs to a family of calcium-dependent lectins diversely used by human APC, such as tissue-residing mDC, alveolar and lymph node macrophages, and endothelial cells from liver sinusoids,[33–36] and was identified as a novel DC-specific adhesion receptor on human DC that is essential in several key functions throughout the life cycle of DC.[33] Therefore, it was assumed that CD209 was appropriate for identifying mDC infiltrated in human infarcted myocardium. Finally, there is potential for reverse causation and/or confounding factors such as white blood cell count that could also affect inflammatory response including DC recruitment. In addition, patients with cardiac rupture may have had histologic changes due to greater wall tension, such as less collateralization. Since we could not conclude that there was a causal relationship among DC, reparative fibrosis, and cardiac rupture, further study is warranted.

In conclusion, we identified DC infiltration in human infarcted myocardium, and observed a strong association between the number of DC and impaired reparative fibrosis and the development of cardiac rupture, suggesting a protective role of DC during the post-MI healing process.

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Disclosures

None.

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Decreased Myocardial Dendritic Cells is Associated With Impaired Reparative Fibrosis and Development of Cardiac Rupture After Myocardial Infarction in Humans

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ORIGINAL RESEARCH

Trends in the Clinical and Pathological Characteristics of Cardiac Rupture in Patients With Acute Myocardial Infarction Over 35 Years

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***Background*—**There is little known about whether the clinical and pathological characteristics and incidence of cardiac rupture (CR) in patients with acute myocardial infarction (AMI) have changed over the years.

***Methods and Results*—**The incidence and clinical characteristics of CR were investigated in patients with AMI, who were divided into 3 cohorts: 1977–1989, 1990–2000, and 2001–2011. Of a total of 5699 patients, 144 were diagnosed with CR and 45 survived. Over the years, the incidence of CR decreased (1977–1989, 3.3%; 1990–2000, 2.8%; 2001–2011, 1.7%; P=0.002) in association with the widespread adoption of reperfusion therapy. The mortality rate of CR decreased (1977–1989, 90%; 1990–2000, 56%; 2001–2011, 50%; P=0.002) in association with an increase in the rate of emergent surgery. In multivariable analysis, first myocardial infarction, anterior infarct, female sex, hypertension, and age >70 years were significant risk factors for CR, whereas impact of hypertension on CR was weaker from 2001 to 2011. Primary percutaneous coronary intervention (PPCI) was a significant protective factor against CR. In 64 autopsy cases with CR, myocardial hemorrhage occurred more frequently in those who underwent PPCI or fibrinolysis than those who did not receive reperfusion therapy (no reperfusion therapy, 18.0%; fibrinolysis, 71.4%; PPCI, 83.3%; P=0.001).

***Conclusions*—**With the development of medical treatment, the incidence and mortality rate of CR have decreased. However, first myocardial infarction, anterior infarct, female sex, and old age remain important risk factors for CR. Adjunctive cardioprotection against reperfusion-induced myocardial hemorrhage is emerging in the current PPCI era. **(*J Am Heart Assoc.* 2014;3:e000984 doi: 10.1161/JAHA.114.000984)**

Key Words: Heart rupture • mortality • myocardial infarction • reperfusion

Cardiac rupture (CR), which can include free-wall rupture (FWR) or ventricular septal rupture (VSR), is a major lethal complication of acute myocardial infarction (AMI). Prior to the primary percutaneous coronary intervention (PPCI) era, the incidence of CR was 6%[1–4] and known risk factors include female sex, old age, first myocardial infarction (MI), anterior infarct, and hypertension.[2,5–7] Becker and colleagues identified 3 morphological types of FWR. Type 1 rupture is characterized as an abrupt, slit-like myocardial tear and corresponds to the acute phase of MI (<24 hours). In type 2 rupture, an area of myocardial erosion is evident, indicating a slowly progressive tear. Type 3 rupture has marked thinning of the myocardium and perforation in the central portion of aneurysm, which typically occurs during the late phase of MI (>7 days).[8] This pathological classification system can be also applied to VSR.

Over the past several decades, the mortality rate for AMI has been decreasing with the development of reperfusion therapy and adjunctive pharmacological therapies.[9] Several studies have reported that early reperfusion therapy may also reduce the incidence of CR.[10–13] However, since the majority of these studies were performed over a relatively short time period, long-term trends in the incidence of CR remain unclear. In addition, changes in the management of AMI may have influenced the risk factors or pathological characteristics of CR. For example, while early fibrinolysis can restore epicardial blood flow, late fibrinolysis may promote

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hemorrhagic dissection into the necrotic myocardium and accelerate rupture.[14–16] It remains unknown whether this paradoxical phenomenon occurs in the current PPCI era. Therefore, the present study was designed (1) to analyze whether the incidence of CR and its risk factors in patients with AMI have changed over a 35-year period in association with advances in medical therapy, and (2) to analyze the association between pathological CR findings on autopsy and prior reperfusion therapy (no reperfusion, fibrinolysis, or PPCI).

Methods

Study Population

Beginning in September 1977, patients with AMI who were admitted to our institution were registered prospectively through the collection of information on clinical profiles and in-hospital outcomes, including the development of CR. By December 2011, a total of 5699 consecutive patients with AMI were hospitalized at our institution. The patients were divided into 3 cohorts: 1977–1989 (n=1742), 1990–2000 (n=1921), and 2001–2011 (n=2036). Diagnosis of AMI was based on elevation of cardiac enzymes (creatine kinase MB fraction >2 times the upper limit of the normal range, or total creatine phosphokinase >2 times the upper limit of the normal range) along with at least 1 of the following criteria: (1) symptoms consistent with cardiac ischemia, (2) development of pathologic Q waves on electrocardiography, or (3) ST-segment elevation or depression on electrocardiography.[17] This study was approved by the National Cerebral and Cardiovascular Center Institutional Review Board for Clinical Research.

Data Collection

The following information was obtained from the AMI registry or medical record: age, sex, presence of coronary risk factors (hypertension, diabetes or impaired glucose tolerance, dyslipidemia), history of previous MI, use of reperfusion therapy during the early phase of AMI, presence of CR, emergent surgery status, and in-hospital mortality. History of hypertension was defined as follows: from 1977 to 1999, systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥95 mm Hg, or antihypertensive therapy;[18] from 2000 to 2011, systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive therapy.[19] Diagnosis of diabetes or impaired glucose tolerance was based on the World Health Organization criteria.[20] Dyslipidemia was defined as total cholesterol >220 mg/dL or dyslipidemia therapy. PPCI was defined as percutaneous coronary intervention in the infarct-related artery within 12 hours of initial medical contact. Fibrinolysis was defined as intravenous or intracoronary administration of urokinase, prourokinase, or tissue plasminogen activator within 12 hours of initial medical contact. Rescue percutaneous coronary intervention was categorized as fibrinolysis.

Diagnosis of CR

Acute FWR was defined as an abrupt transmural rupture of the infarcted area, causing hemopericardium and death in <30 minutes. Subacute FWR was defined as a gradual or incomplete rupture of the infarcted area with slow or recurrent bleeding into the pericardial sac, causing progressive or recurrent cardiac tamponade.[21] VSR was diagnosed on the basis of abnormal shunting through the interventricular septum on color Doppler echocardiography or a significant increase in oxygen saturation in the right ventricle.[10]

Autopsy Study

Of a total of 551 consecutive autopsy cases with AMI, 64 had CR. We examined all 64 autopsy cases of CR with photomacrographs or heart specimens on autopsy. After fixation with 10% buffered formalin, specimens were sliced serially and transversely at 8-mm intervals from apex to the base. Each coronary artery was cut transversely from the ostium to the periphery at 3- to 4-mm intervals. The degree of luminal narrowing was recorded as a percentage of the vessel diameter. Patency of an infarct-related artery was defined as the absence of total occlusion. Myocardial hemorrhage in an infarcted area was defined as grossly recognizable hemorrhage in the infarcted myocardium on macroscopic examination. The Becker classification was determined based on macroscopic findings of the heart. Representative CR autopsy cases of each Becker type are shown in Figure 1.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and compared using the χ^2 test. Continuous variables are presented as means±SD or medians (interquartile range). Differences between baseline characteristics of participants in the 3 cohorts defined by date of hospital admission (1977–1989, 1990–2000, and 2001–2011) were analyzed using the Cochrane–Armitage test for trend for proportions and the Jonckheere–Terpstra test for continuous measures. Non-normally distributed continuous variables were compared using the Kruskal–Wallis test. Normally distributed continuous variables were compared using ANOVA. For all tests, $P<0.05$ was considered statistically

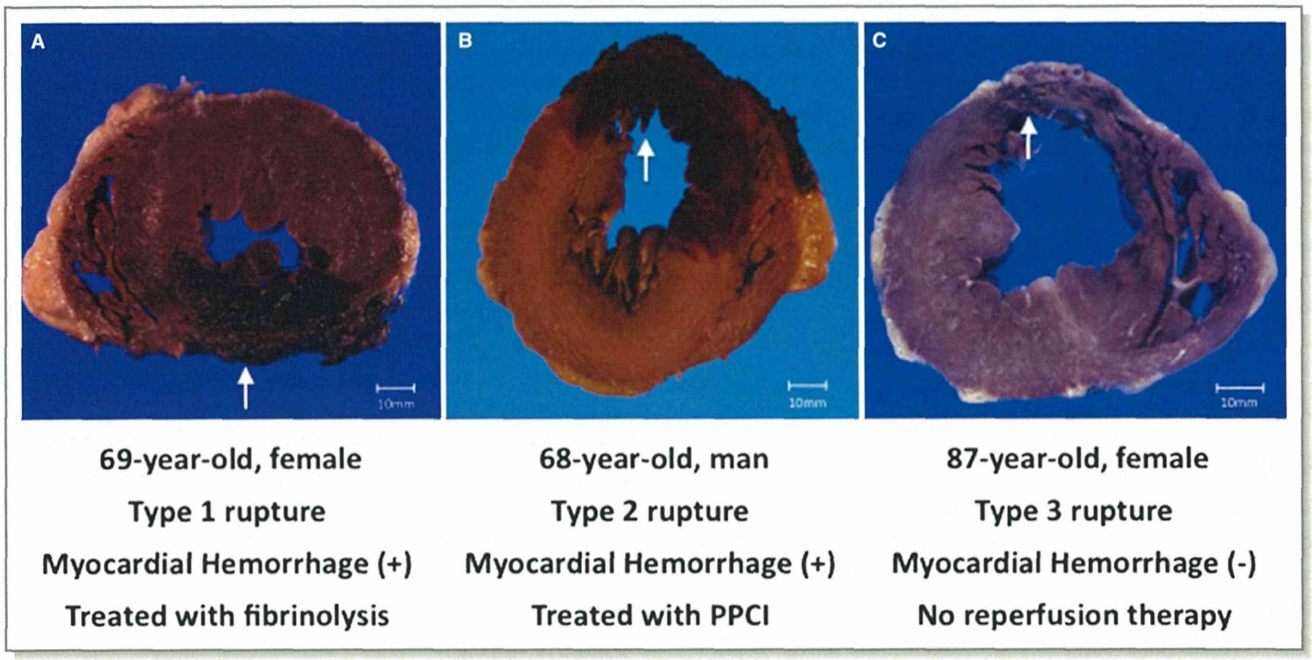

Figure 1. Representative autopsy cases of CR. A, A 69-year-old woman with inferior acute myocardial infarction (AMI) and Becker type 1 rupture. She underwent fibrinolysis 4 hours after the onset of AMI, and developed cardiac rupture (CR) 8 hours after the onset of AMI. Arrow indicates the inferior free-wall rupture with massive myocardial hemorrhage. There is no wall thinning in the infarcted area. B, A 68-year-old man with anterior AMI and Becker type 2 rupture. He underwent primary percutaneous coronary intervention (PPCI) 5 hours after the onset of AMI, and developed CR 11 hours after the onset of AMI. Arrow indicates the anterior free-wall rupture with massive myocardial hemorrhage and erosion. Myocardial erosion at the site of rupture can be observed. C, An 87-year-old woman with anterior AMI and Becker type 3 rupture; reperfusion therapy was not performed. She developed CR 12 days after the onset of AMI. Arrow indicates the anterior free-wall rupture with marked thinning of the infarcted myocardium.

significant. To identify risk factors for CR, univariable and multivariable Poisson regression models were constructed using the following variables: female sex, first MI, age >70 years, anterior infarct, hypertension, fibrinolysis, and PPCI. Stepwise selection with a *P*-value of 0.1 for backward elimination was used to select the best predictive model. To assess the interaction effects of change in risk factors and different time periods, we included the product of time period and risk variables in multivariable models. All analyses were performed using the statistical software JMP 10.0.2 (SAS Institute Cary, NC, USA) and STATA, version 13 (STATA Corp LP, College Station, TX).

Results

Trends in the Clinical Characteristics of AMI Patients Over a 35-Year Period

The characteristics of the patients in the 3 cohorts are shown in Table 1. Between 1977 and 2011, the mean age of patients with AMI increased from 63 to 68 years, the percentage of female patients increased from 20.2 to 27.4%, and prevalence of hypertension increased from 31.6 to 69.1% ($P<0.001$, respectively). Importantly, the use of reperfusion therapy significantly increased over time, from 2.5 to 70.7% ($P<0.001$). In particular, the use of PPCI dramatically increased from 0.2% in 1977–1989 to 66.6% in 2001–2011 ($P<0.001$) (Figure 2).

Changes in the Incidence of CR Over Time

CR developed in 144 of 5699 patients, including 95 with FWR (n=60; acute, n=35; subacute, n=26) and 63 with VSR. FWR and VSR occurred together in 14 patients. The overall incidence of CR was 2.5%. The diagnosis of FWR was confirmed in 86 patients: 44 at autopsy, 33 during surgery, and 9 with pericardiocentesis. In the remaining 9 patients, the diagnosis of FWR was based on cardiac arrest or hypotension with echocardiographic evidence of cardiac tamponade. Diagnosis of VSR was confirmed in 57 patients: 28 during surgery and 29 at autopsy. In the remaining 6 patients, the diagnosis of VSR was made using right heart catheterization or Doppler echocardiography.

Over time, the incidence of CR progressively decreased (3.3%, 2.8%, and 1.7%, respectively, for the 3 time periods studied; $P=0.002$) with increased use of PPCI (0.2%, 28.0%,

Table 1. Characteristics of Patients With AMI (Total n=5699)

	1977–1989 (n=1742)	1990–2000 (n=1921)	2001–2011 (n=2036)	*P* for Trend
Age*, y	63.0±10.9	65.5±11.2	68.1±12.1	<0.001
Female, n (%)	352 (20.2)	426 (22.2)	557 (27.4)	<0.001
Hypertension, n (%)	550 (31.6)	1007 (52.4)	1406 (69.1)	<0.001
Diabetes or IGT, n (%)	327 (18.8)	679 (35.4)	1113 (54.7)	<0.001
Dyslipidemia, n (%)	111 (6.4)	706 (36.8)	1151 (56.5)	<0.001
Previous MI, n (%)	372 (21.4)	503 (26.2)	345 (17.0)	<0.001
Infarct location, n (%)				
Anterior	774 (44.4)	866 (45.1)	857 (42.1)	0.069
Inferior	512 (29.4)	610 (31.8)	782 (38.4)	<0.001
Lateral	146 (8.4)	266 (13.9)	277 (13.6)	<0.001
Other	310 (17.8)	179 (9.3)	120 (5.9)	<0.001

AMI indicates acute myocardial infarction; IGT, impaired glucose tolerance; MI, myocardial infarction.
*Mean±SD data, Jonckheere–Terpstra test for trend.

66.6%, respectively; *P*<0.001) (Figure 2). The incidence of CR was significantly lower among patients who underwent PPCI (1.2%) compared to patients treated with fibrinolysis (2.9%) or those who did not undergo reperfusion therapy (3.3%) (*P*<0.001 for both PPCI versus fibrinolysis and PPCI versus no reperfusion therapy).

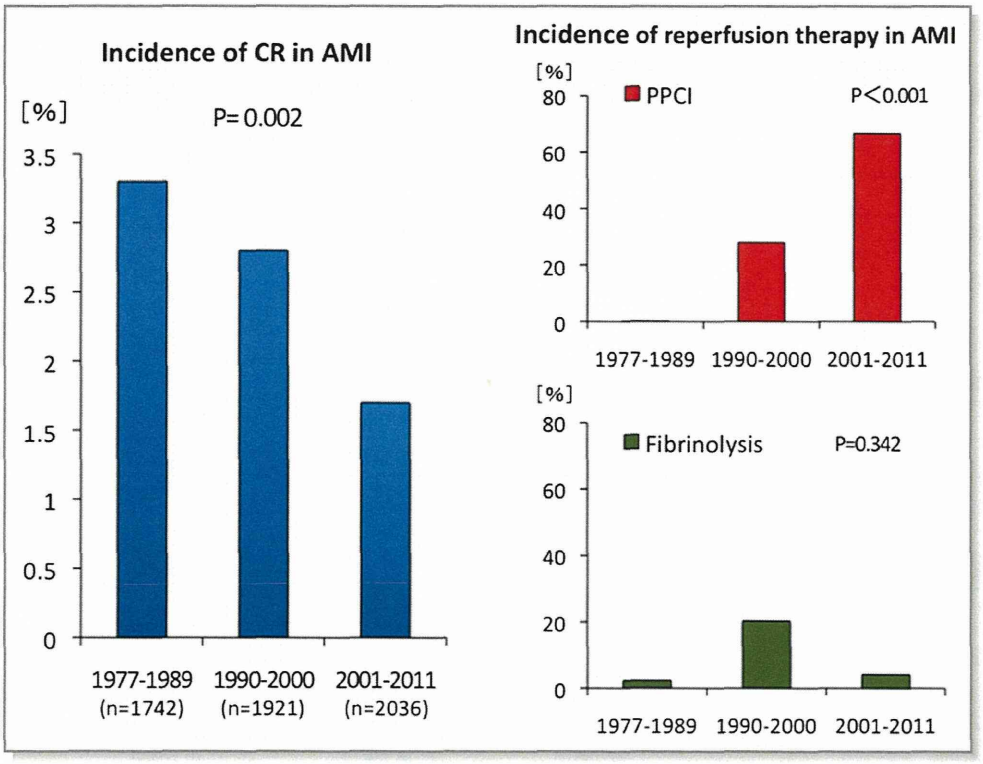

Figure 2. The incidence of cardiac rupture (CR) decreases in association with increased use of reperfusion therapy in patients with acute myocardial infarction (AMI). The left panel shows the incidence rate of CR in patients with AMI. The right-upper panel shows the incidence of primary percutaneous coronary intervention (PPCI) for AMI. The right-lower panel shows the incidence of fibrinolysis for AMI. A total of 5699 hospitalized AMI patients were divided into 3 cohorts: 1977–1989, 1990–2000, and 2001–2011.

Clinical Characteristics of Patients With CR and Changes in Risk Factors for CR

The clinical characteristics of patients with CR are shown in Table 2. Compared to all AMI patients, patients with CR were older and more likely to be women with a history of hypertension or an anterior infarct, whereas a previous history of MI and receiving reperfusion therapy were less common. Over the years, the prevalence of acute FWR decreased, whereas that of subacute FWR increased. The rate of emergent surgery increased over time (38.6%, 67.9%, 73.5%; P=0.003). In proportion with increases in the rate of emergent surgery, in-hospital mortality of CR decreased over the years (89.5% in 1977–1989, 56.6% in 1990–2000, and 50.0% in 2001–2011; P=0.002) (Figure 3). The mortality rate of CR was significantly lower in patients who underwent emergent surgery than in those who did not (emergent surgery, 51.8% versus no emergent surgery [medical therapy], 90.2%; P<0.001). In multivariable analysis, acute FWR was a significant determinant for in-hospital death in patients with CR. Emergent surgery seemed to be a protective factor against in-hospital death in patients with CR, but was only marginally significant (P=0.056) (Table 3). The median time from onset of AMI to death from CR was comparable among the 3 cohorts: 7 days (interquartile range: 2.0 to 14.0) for 1977–1989, 5 days (interquartile range: 3.5 to 8.5) for 1990–2000, and 6 days (interquartile range: 2.75 to 16.0) for 2001–2011 (P=0.83). CR occurred most frequently in the first 24 hours after AMI throughout the study period (33.3% in 1977–1989, 36.0% in 1990–2000, 48.5% in 2001–2011; P=0.34).

Table 4 shows the results of the univariable and multivariable analyses of Poisson regression for risk factors of CR. In the multivariable analysis, age >70 years, female sex, hypertension, first MI, and anterior MI were significant risk factors for CR. On the other hand, later time period (ie, recent cohort) and PPCI were significant preventive factors for CR. The interaction terms between time and PPCI and between time and hypertension were statistically significant (Tables 5 and 6), whereas those between time and other factors (age >70 years, female sex, first MI, and anterior MI) were not. Univariable analysis in each time period showed that hypertension was a significant determinant of CR in the periods from 1977 to 1989 and 1990 to 2000, whereas it was an

Table 2. Characteristics of Patients With CR (Total n=144)

	1977–1989 (n=57)	1990–2000 (n=53)	2001–2011 (n=34)	P for Trend
Age*, y	70.2±8.3	71.6±8.8	75.8±9.2	0.012
Female, n (%)	27 (47.4)	28 (52.8)	23 (67.7)	0.166
Hypertension, n (%)	44 (77.2)	36 (67.9)	25 (73.5)	0.548
Diabetes or IGT, n (%)	13 (22.8)	24 (45.3)	9 (26.5)	0.038
Dyslipidemia, n (%)	5 (8.9)	9 (17.0)	15 (44.1)	0.001
Previous MI, n (%)	5 (8.8)	4 (7.6)	1 (2.9)	0.558
Time from symptom onset to admission >12 h, n (%)	27 (47.4)	24 (45.3)	18 (52.9)	0.545
Infarct location, n (%)				
Anterior	39 (68.4)	30 (56.6)	28 (82.4)	0.043
Inferior	12 (21.1)	16 (30.2)	2 (5.9)	0.025
Lateral	4 (7.0)	7 (13.2)	4 (11.8)	0.545
Other	2 (3.5)	0 (0)	0 (0)	0.213
Reperfusion therapy, n (%)				
Fibrinolysis	2 (3.5)	12 (22.6)	1 (2.9)	0.001
PPCI	0 (0)	11 (20.8)	11 (32.4)	<0.001
CABG, n (%)	2 (3.5)	7 (13.2)	4 (11.8)	0.169
Type of rupture, n (%)				
Free-wall rupture, acute	32 (56.1)	18 (34.0)	10 (29.4)	0.016
Free-wall rupture, subacute	5 (8.8)	17 (32.1)	13 (38.2)	0.002
Ventricular septal rupture	24 (42.1)	23 (43.4)	16 (47.1)	0.897

Free-wall rupture and ventricular septal rupture occurred together in 4 patients from 1977 to 1989, 5 patients from 1990 to 2000, 5 patients from 2001 to 2011. CABG indicates coronary artery bypass grafting; CR, cardiac rupture; IGT, impaired glucose tolerance; MI, myocardial infarction; PPCI, primary percutaneous coronary intervention.
*Mean±SD data, Jonckheere–Terpstra test for trend.

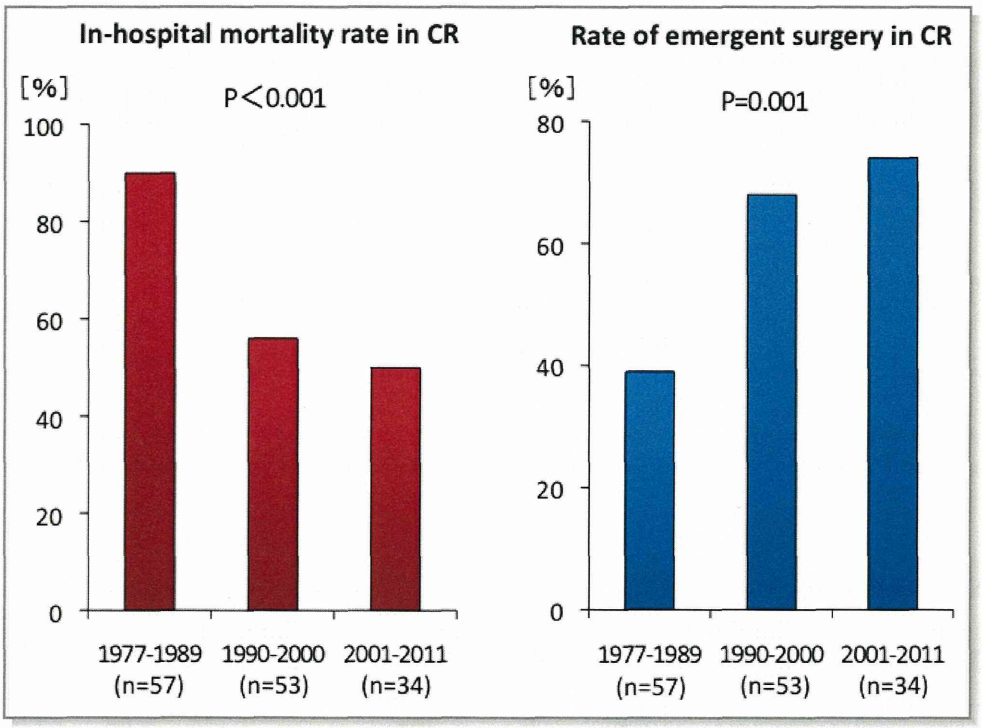

Figure 3. Decreased in-hospital mortality is associated with an increased rate of emergent surgery in 144 cardiac rupture (CR) patients. The left panel shows the in-hospital mortality rate in patients with CR. The right panel shows the rate of emergent surgery for CR.

Table 3. Multivariable Analysis of Poisson Regression for In-Hospital Deaths Due to CR

	IRR	95% CI		*P* Value
Emergent surgery	0.67	0.45	1.01	0.056
Free-wall rupture, acute	1.87	1.24	2.82	0.003

CR indicates cardiac rupture; IRR, incidence rate ratio.

insignificant factor from 2001 to 2011. Importantly, PPCI became a significant protective factor against CR beginning in 2001 (Table 7).

Pathological Examinations in 63 Autopsy Cases With CR

Between 1977 and 2011, 99 of the 144 patients with CR died. Autopsy was performed in 64 cases. One autopsy case was excluded from our analysis due to incomplete data on the pathological findings. The characteristics of 63 autopsy cases are summarized in Table 8. In the PPCI group, coronary stenting was performed in 4 of 6 patients, while in the fibrinolysis group, rescue percutaneous coronary intervention (without stenting) was performed in 2 of 7 patients. Regarding pathological findings, the rate of patency in the infarct-related artery was higher in patients with PPCI compared with those without reperfusion therapy. The incidence of myocardial hemorrhage in infarcted areas was higher in patients who underwent PPCI or fibrinolysis than those receiving no reperfusion therapy (Figure 4). In patients who did not undergo reperfusion therapy, Becker type 3 rupture was the most frequent type (no reperfusion therapy: type 1, 24.5%; type 2, 30.6%; type 3, 44.9%). In contrast, ruptures of Becker types 1 and 2 were more frequent in patients who underwent reperfusion therapy, especially PPCI, than in patients who did not (fibrinolysis: type 1, 28.6%; type 2, 42.9%; type 3, 28.6%) (PPCI: type 1, 50.0%; type 2, 33.3%; type 3, 16.7%); however, this difference in frequency was not statistically significant (55.1% with no reperfusion therapy versus 76.9% with reperfusion therapy (fibrinolysis or PPCI); P=0.154).

Discussion

The major findings of this study were as follows: (1) over 35 years, the incidence of CR decreased in association with increased use of reperfusion therapy, especially PPCI; (2) in the past decade (2001–2011), first MI, anterior infarct, female sex, and age >70 years were risk factors for CR, whereas PPCI was a significant protective factor and hypertension was

Table 4. Univariable and Multivariable Analysis of Poisson Regression for CR

	Univariable				Multivariable			
	IRR	95% CI		*P* Value	IRR	95% CI		*P* Value
Age >70 y	3.11	2.2	4.4	<0.001	2.43	1.69	3.5	<0.001
Female	3.86	2.78	5.36	<0.001	2.58	1.83	3.64	<0.001
Hypertension	2.49	1.72	3.59	<0.001	2.77	1.89	4.07	<0.001
First MI	3.67	1.93	6.97	<0.001	3.38	1.77	6.45	<0.001
Anterior MI	2.68	1.89	3.79	<0.001	2.33	1.64	3.31	<0.001
Time	0.73	0.59	0.89	0.002	0.7	0.55	0.88	0.003
PPCI	0.36	0.23	0.57	<0.001	0.38	0.23	0.63	<0.001
Fibrinolysis	1.17	0.68	1.99	0.571	Not selected			

Time 1: 1979–1988; Time 2: 1990–2000; Time 3: 2001–2011. CR indicates cardiac rupture; IRR, incidence rate ratio; MI, myocardial infarction; PPCI, primary percutaneous coronary intervention.

Table 5. Interaction Effect Between Time and PPCI

	IRR	95% CI		*P* Value
Model 1				
Time	1.003	0.791	1.272	0.981
PPCI	3.577	0.433	29.535	0.237
Time×PPCI	0.415	0.179	0.963	0.041
Model 2 adjusted for other risks				
Age >70 y	2.44	1.7	3.5	<0.001
Female	2.59	1.84	3.64	<0.001
Hypertension	2.72	1.85	4	<0.001
First MI	3.42	1.8	6.53	<0.001
Anterior MI	2.31	1.63	3.28	<0.001
Time	0.74	0.58	0.94	0.014
PPCI	2.49	0.29	21.62	0.409
Time×PPCI	0.47	0.2	1.12	0.09

Model 1: Variables were selected by stepwise procedures. Model 2: Model 1+the interaction term between the time and PPCI. IRR indicates incidence rate ratio; MI, myocardial infarction; PPCI, primary percutaneous coronary intervention

Table 6. Interaction Effect Between Time and Hypertension

	IRR	95% CI		*P* Value
Model 1				
Time	1.18	0.8	1.74	<0.417
Hypertension	15.89	6.22	40.63	<0.001
Time×hypertension	0.4	0.25	0.63	<0.001
Model 2 adjusted for other risks				
Age >70 y	2.49	1.73	3.57	<0.001
Female	2.56	1.82	3.61	<0.001
Hypertension	13.82	5.36	35.67	<0.001
First MI	3.37	1.77	6.42	<0.001
Anterior MI	2.33	1.64	3.3	<0.001
Time	1.39	0.92	2.09	<0.115
PPCI	0.39	0.23	0.64	<0.001
Time×hypertension	0.4	0.25	0.63	<0.001

Model 1: Variables were selected by stepwise procedures. Model 2: Model 1+the interaction term between the time and hypertension. IRR indicates incidence rate ratio; PPCI, primary percutaneous coronary intervention.

no longer a significant risk factor for CR; and (3) based on pathological examination, the incidence of myocardial hemorrhage in infarcted areas and the proportion of Becker type 1 and 2 ruptures were higher in patients undergoing PPCI or fibrinolysis than in those who did not receive reperfusion therapy.

Decreased Incidence of CR in Patients With AMI and the Important Role of PPCI

Previous studies have reported that the incidence of CR was as high as 6% before the reperfusion era.[1–4] The incidence of CR in patients undergoing PPCI during the reperfusion era has ranged from 0.5 to 2.0%, which is lower than that observed in patients undergoing fibrinolysis or no reperfusion therapy.[11,12,22–25] However, there are very few longitudinal studies. Figueras et al[3] demonstrated that the incidence of CR before the reperfusion era was approximately 6%, and it decreased to 3.2% in 2001–2006 with increasing use of reperfusion therapy. The present study, with data over 35 years, clearly demonstrates in Figure 2 that the incidence of CR decreased with increasing use of reperfusion therapy over time. Indeed, PPCI became a significant protective factor against CR in the most recent period, 2001–2011 (Table 7).