

Comparison of the risk of left ventricular free wall rupture in Taiwanese patients with ST-elevation acute myocardial infarction undergoing different reperfusion strategies

A medical record review study

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Abstract

Ventricular free wall rupture (VFWR) is the second most common cause of death in patients with acute ST-elevation myocardial infarction (STEMI). Nevertheless, few reports have investigated the factors, including different treatment strategies, associated with VFWR in Taiwanese patients. Therefore, the aim of this study was to compare the risk of VFWR in Taiwanese patients with acute STEMI who had received primary percutaneous coronary intervention (PCI), rescue PCI, scheduled PCI, thrombolytic therapy, and pharmacologic treatment. In this medical records review study, records of patients with acute STEMI admitted to a regional hospital in south Taiwan between March 1999 and October 2013 were screened. Multivariate stepwise logistic regression analysis was used to evaluate the association between the risk of VFWR and its independent factors. The overall incidence of VFWR among the 1545 patients with acute STEMI in this study was 1.6%. Compared with primary PCI, the risk of VFWR was significantly higher in patients who had received thrombolysis (adjusted odds ratio = 6.83, $P=0.003$) or pharmacologic treatment alone (adjusted odds ratio = 3.68, $P=0.014$). The risk of VFWR in patients receiving rescue PCI or scheduled PCI was not significantly different from that in patients receiving primary PCI. In addition, older age and Killip class >I were associated with an increased risk of VFWR in patients with acute STEMI, whereas the use of angiotensin-converting enzyme inhibitors was associated with a lower risk of VFWR. In conclusion, findings from this medical record review study provide support for the use of primary PCI, rescue PCI, and scheduled PCI over thrombolytic therapy and pharmacologic treatment in reducing the risk of VFWR in Taiwanese patients with acute STEMI.

Abbreviations: ACC = American College of Cardiology, AHA = American Heart Association, CABG = emergency coronary artery bypass graft, CAG = coronary angiography, GUSTO-1 = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, LAD = left anterior descending artery, LMCA = left main coronary artery, OR = odds ratio, PCI = percutaneous coronary intervention, RCA = right coronary artery, STEMI = ST-elevation myocardial infarction, TIMI = Thrombolysis in Myocardial Infarction, VFWR = ventricular free wall rupture.

Keywords: cardiac rupture, myocardial infarction, primary angioplasty, reperfusion, thrombolysis

1. Introduction

Ventricular free wall rupture (VFWR) is the second most common cause of death in patients with acute ST-elevation

myocardial infarction (STEMI). The incidence can be as high as 6%, with high in-hospital mortality rate, in the era before widespread use of reperfusion therapy.^[1] This lethal complication may occur either early after the onset of myocardial infarction or in the subacute phase during cardiac remodeling and it can suddenly happen without any prodromal symptoms. Old age, female sex, and lower body mass index^[2,3] preceding event of rupture have been shown to increase the risk of VFWR.

With the introduction of reperfusion strategies and modern drug regimes, the incidence of VFWR has reduced to approximately 2% to 3%.^[1,4] Before the advent of thrombolysis or primary percutaneous coronary intervention (PCI), emergency coronary artery bypass graft (CABG) was the only option for therapeutic reperfusion in patients with evolving myocardial infarction. Today, in patients with acute STEMI, CABG is generally performed as an emergency procedure when primary PCI has failed or cannot be performed.

Both PCI and thrombolytic therapy are efficacious in patients with STEMI.^[5] The choice between the 2 reperfusion therapies is often dictated by logistic constraints and the timing of reperfusion therapy after symptom onset. Primary PCI is generally the treatment of choice in patients presenting in a hospital with PCI facility and expertise. In addition, primary PCI is preferred over thrombolysis if it can be achieved within the American College of

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Cardiology (ACC)/American Heart Association (AHA) recommended door-to-balloon time of less than 90 minutes.^[6] Furthermore, rescue PCI is recommended, if thrombolysis failed within 45 to 60 minutes after starting the administration.^[7]

Previous studies have evaluated various factors, including different reperfusion strategies, associated with VFWR in both Western^[8–10] and Asian^[11,12] patients presenting with STEMI. Nevertheless, few reports have investigated the factors associated with VFWR in Taiwanese patients. Yip et al^[2] studied clinical outcomes of 1250 Taiwanese patients with acute myocardial infarction who had received PCI. Multiple stepwise logistic regression analysis revealed that cardiac rupture was associated with advanced age, female sex, and a lower body mass index. As the incidences were found to be 0.3% for ventricular septal defect rupture and 0.7% for VFWR, which are lower than the 4% reported in the prethrombolytic therapy era, the authors concluded that early successful reperfusion might reduce the incidence of cardiac rupture after acute myocardial infarction. Nevertheless, their data did not allow a direct comparison of the risk of cardiac rupture between patients who had received different reperfusion strategies. Therefore, on the basis of a medical record review, we compared the risk of VFWR in acute STEMI patients who had received primary PCI, rescue PCI and scheduled PCI, thrombolytic therapy, and pharmacologic treatment. We also investigated other independent factors associated with VFWR in these patients.

2. Methods

2.1. Study design and patients

A retrospective medical record review study was conducted using the electronic patient record system of a regional teaching hospital in south Taiwan. Records of patients with acute STEMI admitted to the study hospital between March 1999 and October 2013 were screened. Exclusion criteria included patients with non-STEMI, unstable angina, and recent or remote myocardial infarction. Of the 1815 patients identified, 270 (14.9%) were excluded, and therefore, 1545 patients with STEMI were included in the analysis. The study was approved by the institutional review board of the Ditmanson Medical Foundation Chia-Yi Christian Hospital, Taiwan (No. 100061). The institutional review board waived the requirement for obtaining informed consent from the patients. All patient records were de-identified before analysis.

2.2. Diagnosis of ST-elevation myocardial infarction

Diagnosis of STEMI was based on the concurrence of chest pain or symptoms compatible with acute heart failure or unexplained syncope and ST-segment elevation ≥ 1 mm in 2 inferior or lateral leads or ≥ 2 mm in ≥ 2 precordial leads and elevation of creatine kinase-MB or troponin-I.

2.3. Predictor variables

Potential predictor variables evaluated in this study included demographic characteristics (age and sex), cardiovascular risk factors (smoking, hypertension, dyslipidemia, and diabetes mellitus), infarct location, infarct-related artery, numbers of diseased vessels, Killip's classification, laboratory data (creatinine, peak creatine kinase, peak creatine kinase-MB, peak troponin-I, peak activated partial thromboplastin time), reperfu-

sion strategy, medications use, intraaortic balloon pumping use, and complications. The major adverse cardiac events included cardiac rupture, paroxysmal atrial fibrillation, ventricular tachycardia or fibrillation, complete atrioventricular block, upper gastrointestinal tract bleeding, acute stroke, acute kidney injury, and death.

Echocardiographic assessment of left ventricular ejection fraction was conducted by the Teichholz method^[13] or by the biplane modified Simpson rule if regional wall motion abnormalities were noted.^[14]

Coronary lesions were evaluated by coronary angiography (CAG) evaluation criteria. The arteries of the coronary circulation system analyzed included the left main coronary artery (LMCA), left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). Luminal stenosis of 50% or more was defined as significant coronary stenosis. On the basis of the number of coronary arteries with lesion, 3 types of coronary lesion were defined and they included single-vessel coronary arterial lesion, 2-vessel coronary arterial lesions, and multi-vessel coronary arterial lesions.

2.4. Ventricular free wall rupture outcome

Diagnosis of VFWR was suspected by echo-free space on echocardiography when patients developed sudden onset of cardiogenic shock, conscious disturbance, and pulseless electric activity (electromechanic dissociation) after being in a stable condition. VFWR was confirmed by CAG, pericardiocentesis, or surgery.

2.5. Statistical analysis

Continuous and categorical variables were presented as mean with standard deviation and frequency with percentage, respectively. Student *t* test was used to compare the differences in the means of the continuous variables between patients with and without VFWR. Chi-square test or Fisher exact test, as appropriate, was used to compare categorical variables between patients with and without VFWR. Multivariate stepwise logistic regression analyses with a backward elimination procedure based on likelihood ratio test were used to obtain odds ratios (ORs) with 95% confidence intervals (95% CIs) for VFWR. All the variables included in Table 1 were evaluated for inclusion in the multivariate model during its development. The probabilities for variable entry and removal into the model were set at 0.05 and 0.10, respectively. A $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics software package, version 23.0 (IBM Corp., Armonk, NY).

3. Results

In this medical records review study based on the data from a regional hospital in south Taiwan, the incidence of VFWR among 1545 patients with acute STEMI was found to be 1.6%. Table 1 summarizes the demographic and clinical characteristics of patients with and without VFWR. The mean age was significantly higher in patients with VFWR ($P < 0.001$). The proportion of patients with hyperlipidemia was significantly lower in those with VFWR than in those without VFWR ($P = 0.003$). The mean length of hospital stay was significantly shorter in patients with VFWR ($P = 0.012$). In addition, there were significantly more

Table 1
Demographic and clinical characteristics of acute ST-elevation myocardial infarction patients with and without left ventricular free wall rupture (N = 1545).

Variable	Number (%)		P
	No free wall rupture 1521 (98.4)	Free wall rupture 24 (1.6)	
Age, y (mean ± standard deviation)	63.1 ± 12.9	72.8 ± 6.3	<0.001
Age category, y			
40–64	796 (52)	3 (13)	<0.001
65–95	725 (48)	21 (88)	
Sex			
Male	1159 (76)	17 (71)	0.541
Female	362 (24)	7 (29)	
Smoking (yes vs no)	641 (43)	6 (25)	0.082
Hypertension	816 (54)	12 (50)	0.720
Diabetes mellitus	585 (39)	11 (46)	0.462
Hyperlipidemia	646 (43)	3 (13)	0.003
Hospital stay, d	6.8 ± 5.6	3.9 ± 9.5	0.012
Body weight, kg	65.9 ± 13.0	60.3 ± 11.7	0.071
Systolic blood pressure at admission, mm Hg	132 ± 31	124 ± 34	0.182
Diastolic blood pressure at admission, mm Hg	80 ± 36	76 ± 23	0.587
Heart rate at admission, beats per min	82 ± 22	83 ± 25	0.754
Left ventricular ejection fraction (%)	51.8 ± 13.4	48.9 ± 8.7	0.178
Peak creatine kinase, U/L	2193 ± 2606	2777 ± 3637	0.441
Peak creatine kinase-MB, ng/mL	208 ± 320	209 ± 207	0.984
Peak Troponin-I, ng/mL	91.8 ± 174.0	68.2 ± 78.5	0.600
Peak activated partial thromboplastin time, s	53.1 ± 132.7	48.0 ± 30.6	0.852
Creatinine, mg/dL	1.5 ± 1.4	1.5 ± 0.9	0.904
Killip class			
I	840 (55)	4 (17)	<0.001
II–IV	681 (45)	20 (83)	
Infarct location			
Anterior	809 (53)	11 (46)	0.122
Inferoposterior	678 (45)	11 (46)	
Lateral	33 (2)	2 (8)	
Infarct-related artery			
LAD	684 (52)	5 (42)	0.961
RCA	540 (41)	6 (50)	
LCX	91 (7)	1 (8)	
LMCA	9 (1)	0 (0)	
SVG	2 (0)	0 (0)	
Number of vessels			
Insignificant lesion	1 (0)	0 (0)	0.187
1 vessel	507 (38)	3 (27)	
2 vessels	387 (29)	1 (9)	
3 vessels	447 (33)	7 (64)	
Number of total occlusion			
No	543 (41)	2 (18)	0.287
1 vessel	708 (53)	9 (82)	
2 vessels	77 (6)	0 (0)	
3 vessels	9 (1)	0 (0)	
Medications			
Tirofiban	469 (31)	4 (17)	0.135
Heparin	1352 (89)	22 (92)	>0.999
Aspirin	1412 (93)	19 (79)	0.027
Clopidogrel	953 (63)	6 (25)	<0.001
Ticlopidine	116 (8)	2 (8)	0.705
Dual antiplatelet agents	1412 (93)	19 (79)	0.027
Statin	529 (35)	0 (0)	<0.001
Beta blocker	382 (25)	3 (13)	0.156
ACE inhibitors	860 (57)	8 (33)	0.023
Nitrate	1256 (83)	19 (79)	0.594
Intra-aortic balloon pumping	74 (5)	3 (13)	0.114
Complications			
Death	112 (7)	22 (92)	<0.001
Ventricular septal defect	5 (0)	0 (0)	>0.999
Ventricular tachycardia, ventricular fibrillation	99 (7)	2 (8)	0.668

(continued)

Table 1
(continued).

Variable	Number (%)		P
	No free wall rupture 1521 (98.4)	Free wall rupture 24 (1.6)	
Complete atrioventricular block	80 (5)	1 (4)	>0.999
Paroxysmal atrial fibrillation	92 (6)	0 (0)	0.394
Upper gastrointestinal bleeding	94 (6)	2 (8)	0.658
Cardiac arrest	36 (2)	2 (8)	0.116
Stroke	11 (1)	0 (0)	>0.999
Acute kidney injury	71 (5)	1 (4)	>0.999

% are column percentages except in the header row where they are row percentages.

LAD=left anterior descending artery, LCX=left circumflex artery, LMCA=left main coronary artery, RCA=right coronary artery, SVG=saphenous vein graft.

patients in the Killip class II–IV in the patients with VFWR ($P < 0.001$). Regarding the medications used, the proportions of the use of aspirin ($P = 0.027$), clopidogrel ($P < 0.001$), dual antiplatelet agents ($P = 0.027$), statin ($P < 0.001$), and angiotensin-converting enzyme inhibitors ($P = 0.027$) were significantly lower in the patients with VFWR. Regarding the associated complications, the proportion of death was significantly higher in the patients with VFWR ($P < 0.001$). There were no significant differences in the remaining variables between patients with and without VFWR.

The results of the multivariate logistic regression analysis of VFWR in patients with acute STEMI are summarized in Table 2. Compared with patients who had received only primary PCI, the risk of VFWR was significantly higher in patients who had received only thrombolysis (adjusted OR = 6.83, $P = 0.003$) or those who had received pharmacologic treatment (adjusted OR = 3.68, $P = 0.014$). On the contrary, the risk of VFWR in patients who had received rescue PCI (thrombolytic therapy + PCI) or scheduled PCI was not significantly different from that of primary PCI.

In addition, patients 65 years or older exhibited an increased risk of VFWR compared with those who were 40 to 64 years old

(adjusted OR = 4.66, $P = 0.015$). Patients with Killip class II–IV were associated with a significantly higher risk of VFWR (adjusted OR = 4.69, $P = 0.007$). Conversely, patients who used angiotensin-converting enzyme inhibitors showed a lower risk of VFWR (adjusted OR = 0.32, $P = 0.014$).

Table 3 summarizes the distribution of time of rupture among the 24 patients with VFWR who had or had not received early reperfusion. Overall, 13 (55%) of the 24 patients had received early reperfusion and 7 (54%) suffered from VFWR within 48 hours. On the contrary, 5 (46%) patients developed VFWR within 48 hours among the 11 patients with no early reperfusion.

4. Discussion

VFWR is a lethal complication following acute STEMI. The present medical record review study revealed 4 significant independent factors associated with VFWR and they included the STEMI treatment, age, Killip class, and the use of angiotensin-converting enzyme inhibitors. First, the risk of VFWR was significantly higher in patients receiving thrombolytic therapy or pharmacologic treatment than those receiving primary PCI. This

Table 2
Multivariate logistic regression analysis of left ventricular free wall rupture in patients with acute ST-elevation myocardial infarction (N = 1428).

Variable	Number (%)		Odds ratio (95% confidence interval)	P
	No free wall rupture 1404 (98.4)	Free wall rupture 24 (1.6)		
Treatment				
Primary PCI	657 (47)	6 (25)	1.00	
Rescue PCI	198 (14)	1 (4)	0.75 (0.08–6.34)	0.788
Scheduled PCI	284 (20)	1 (4)	0.33 (0.04–2.80)	0.311
Thrombolytic therapy	79 (6)	5 (21)	6.83 (1.93–24.11)	0.003
Pharmacologic treatment	186 (13)	11 (46)	3.68 (1.30–10.37)	0.014
Age category, y				
40–64	733 (52)	3 (13)	1.00	
65–95	671 (48)	21 (88)	4.66 (1.34–16.16)	0.015
Killip class				
I	803 (57)	4 (17)	1.00	
II–IV	601 (43)	20 (83)	4.69 (1.54–14.28)	0.007
ACE inhibitors				
No	596 (43)	16 (67)	1.00	
Yes	808 (58)	8 (33)	0.32 (0.13–0.80)	0.014

Variables evaluated during the development of multivariate logistic regression included all the variables listed in Table 1.

Patients with coronary artery bypass grafting (CABG) ($n = 96$) or thrombolytic therapy + CABG ($n = 21$) were excluded from the multivariate logistic regression analysis because none of them had ventricular free wall rupture and odds ratios for them could not be estimated.

Pharmacologic treatment is based on the American Heart Association Advanced Cardiac Life Support (ACLS) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.

% are column percentages except in the header row where they are row percentages.

ACE=angiotensin-converting enzyme, PCI=percutaneous coronary intervention.

Table 3**Distribution of time of rupture among patients with left ventricular free wall rupture with and without early reperfusion (N=24).**

Time of rupture since symptom onset	Number (%)					
	Total 24 (100)	Early reperfusion			No early reperfusion	
		Thrombolytic therapy 6 (25)	Thrombolytic therapy + PCI (rescue PCI) 1 (4)	Primary PCI 6 (25)	Scheduled PCI 1 (4)	Pharmacologic treatment 10 (42)
≤24h	4 (17)	1 (17)	0 (0)	1 (17)	0 (0)	2 (20)
>24–48h	8 (33)	2 (34)	1 (100)	2 (34)	0 (0)	3 (30)
3–5 d	9 (38)	2 (34)	0 (0)	3 (50)	0 (0)	4 (40)
6–10 d	3 (13)	1 (17)	0 (0)	0 (0)	1 (100)	1 (10)

% are column percentages except in the header row where they are row percentages.

PCI=percutaneous coronary intervention.

finding is consistent with previous reports. In a study of 706 patients aged 75 years or older, those who treated with thrombolytic therapy showed an excess risk of cardiac rupture (OR=3.62; 95% CI 1.79–7.33) compared with patients treated with primary PCI.^[9] In another study based on retrospective chart reviews, thrombolytic therapy was associated with an increased risk of cardiac rupture (OR=3.32; 95% CI 1.75–6.54) compared with no acute reperfusion.^[8]

Although thrombolytic therapy has found to be able to reduce total mortality rate of STEMI by increasing reperfusion of infarct-related artery, its use is associated with a higher early mortality rate due to VFWR as a result of increased myocardial hemorrhage and activation of plasmin.^[15] It accelerates the timing of rupture with a peak occurrence at 24 to 48 hours rather than 3 to 5 days.^[16,17] In our study, we found a significant increased risk of VFWR in patients who had received thrombolytic therapy alone and half of them suffered from VFWR within 48 hours. However, the risk in patients who had received rescue PCI (thrombolytic therapy+PCI) (OR=0.75; 95% CI 0.08–6.34) was not significantly different from that of primary PCI alone. We also observed that patients without reperfusion strategy had a significantly higher risk of VFWR (OR=3.68; 95% CI 1.30–10.37) and half of the 10 patients receiving pharmacologic treatment with VFWR had the rupture occurred between 3 and 10 days. Pathologic findings of VFWR in STEMI revealed different mechanisms according to the reperfusion strategies. In patients without reperfusion strategy, rupture tends to involve perforation in the central portion of aneurysm associated with thinning of myocardium and will lead to an abruptly developed cardiac tamponade with mortality in 3 to 5 days after STEMI. On the contrary, rupture in patients with reperfusion therapy, either primary PCI or thrombolytic therapy, is usually characterized as myocardial hemorrhage with slit-like myocardial tear or myocardial erosion and the rupture occurs subacutely in 24 to 48 hours.^[3]

A study composed of 63 autopsy patients with cardiac rupture revealed that the reperfusion rate of thrombolytic therapy was only approximately 60%. Although the proportion was numerically higher than that among patients receiving no reperfusion (32%), the difference between the 2 proportions did not reach statistical significance. On the contrary, primary PCI was able to achieve close to 100% patency in the infarct-related arteries.^[3] In our study, we found that the risk of VFWR was not significantly different between patients undergone primary PCI and rescue PCI. Rescue PCI appeared to be able to reduce the risk of VFWR in patients who have unsuccessful reperfusion after thrombolytic therapy. In a randomized study of

151 patients with anterior myocardial infarction, rescue PCI appeared to prevent death or severe heart failure compared with conservative management alone.^[18] Another study of 198 patients treated in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) angiographic trial reported that rescue PCI was very effective in restoring patency. The study also demonstrated that rescue PCI did not increase catheterization laboratory or postprocedural complication rates.^[19] Previous research also revealed that the risk of VFWR in thrombolytic therapy was inversely correlated with the presence of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the infarct-related arteries.^[20] If thrombolytic therapy fails to perfuse the infarct-related arteries or the reperfusion time is delayed, myocardial necrosis and thinning can develop. This will increase the possibility of VFWR as a result of myocardial hemorrhage after the use of a thrombolytic agent.

Age over 65 years was found to increase the risk of VFWR in patients with STEMI in this study. Old age has been consistently reported as a risk factor for VFWR in many previous reports.^[21–23] On the contrary, female sex did not emerge as a significant independent predictor for VFWR in our study. Several studies have shown higher incidences of VFWR in women even without thrombolytic therapy.^[17,22,24] Nevertheless, in a study of 10,202 patients in China with acute myocardial infarction, female sex did not remain as a significant factor in the multivariate regression model when other factors were adjusted for.^[25] Further studies are required to delineate the association between sex and VFWR in different populations.

Killip's classification is a useful method for risk stratification in patients with acute myocardial infarction. Our study revealed that patients with Killip class >I were associated with a significantly higher risk of VFWR. Our finding is consistent with studies showing that Killip class >I was an independent predictor of poor outcome in patients with or without ST-segment elevation on the presenting electrocardiogram.^[26,27]

Patients who used angiotensin-converting enzyme inhibitors showed a lower risk of VFWR. Angiotensin-converting enzyme inhibitors and β -blocker have been reported to prevent VFWR in previous studies.^[4,28] Observations from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9 Study showed that angiotensin-converting enzyme inhibitors or beta-blockers use was inversely associated with cardiac rupture (OR=0.27; 95% CI 0.16–0.46).^[29] In animal studies, β -blocker and angiotensin-converting enzyme inhibitors were found to reduce the activation of matrix metalloproteinase and synthesis of collagen.^[30,31] In the present study, the use of angiotensin-

converting enzyme inhibitors but not β -blocker was found to associate with a lower risk of VFWR.

A few limitations of this study deserve mention. First, this study inherited potential limitations of all studies that required abstraction of medical record data for research purposes. Second, the study population was composed of patients from a single regional teaching hospital, and therefore, the results may not necessarily be generalizable to patients in other hospitals. Third, patients who died of cardiac arrest with pulseless electrical activity might not have an opportunity to undergo echocardiography, and therefore, it is possible that the true incidence of VFWR is underestimated. Fourth, the effects of unmeasured confounding factors cannot be completely ruled out in this type of study.

5. Conclusions

VFWR is a serious complication following acute myocardial infarction. Our observational data provide support for the use of primary PCI, rescue PCI, and scheduled PCI over thromolytic therapy and pharmacologic treatment in reducing the risk of VFWR in patients with acute STEMI. In addition, older age and Killip class higher than I were associated with an increased risk of VFWR in patients with acute STEMI. Use of angiotensin-converting enzyme inhibitors was associated with a lower risk of VFWR.

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