Combined Prognostic Utility of White Blood Cell Count, Plasma Glucose, and Glomerular Filtration Rate in Patients Undergoing Primary Stent Placement for Acute Myocardial Infarction

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Although high white blood cell (WBC) count and plasma glucose (PG) and low glomerular filtration rate (GFR) on admission have been associated with poor outcomes after acute myocardial infarction (AMI), the combined prognostic utility of these 3 variables was unclear. The association of WBC count, PG, and GFR on admission to in-hospital outcomes was examined in 2,633 patients who underwent primary stent placement for ST-segment elevation AMI within 48 hours after symptom onset. In-hospital mortality progressively increased as the number of the variables of high WBC count (≥11,120/μl; upper tertile), high PG (≥10.4 mmol/L; upper tertile), and low GFR (≤60 ml/min/1.73 m^2; lower tertile) increased. Patients with all 3 variables had a strikingly higher in-hospital mortality rate (25.9%). After adjusting for baseline characteristics, multivariate analysis showed that compared with patients who had none of these variables, odds ratios for in-hospital mortality were 1.63 (95% confidence interval [CI] 0.88 to 3.03, p = 0.12) in patients with only 1 variable, 2.33 (95% CI 1.28 to 3.96, p = 0.047) in those with 2 variables, and 6.16 (95% CI 2.98 to 12.6, p <0.001) in those with all 3 variables. In conclusion, combined evaluation of WBC count, PG, and GFR on admission was a simple and useful method for the early prediction of risk of in-hospital death in patients undergoing primary stent placement for ST-segment elevation AMI. **(Am J Cardiol 2009;103:322–327)**

The evolution and widespread use of primary percutaneous coronary interventions, including stent implantation, has improved outcomes after acute myocardial infarction (AMI) compared with that after thrombolytic therapy.[1] However, clinical outcomes and survival rates after AMI were highly variable. Therefore, improved techniques for risk stratification and identification of high-risk subsets of patients most likely to benefit from a given therapeutic strategy were needed. Recently, several variables were used to stratify risk in patients with AMI. Both high white blood cell (WBC) count on admission and acute hyperglycemia were associated with a large infarct, impaired microvascular reperfusion, poor left ventricular functional recovery, and high mortality after AMI.[2–9] It also was shown that renal dysfunction (i.e., low glomerular filtration rate [GFR]) was associated with increased risks of mortality and morbidity after AMI.[10–13] These variables are universally available at the time of admission. However, the combined prognostic utility of these 3 variables has not been evaluated. We evaluated the impact of combinations of 1, 2, or all 3 variables on in-hospital outcomes in patients who underwent primary stent placement for AMI.

Methods

The Japanese Acute Coronary Syndrome Study (JACSS) was a retrospective and multicenter observational study conducted at 35 centers in Japan. From January 2001 to December 2003, consecutive patients admitted to participat-

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Table 1
Clinical characteristics of patients with low and high white blood cell (WBC) counts

Variable	WBC Count		p Value
	Low (n = 1,746)	High (n = 887)	
Age (yrs)	69 ± 11	64 ± 12	<0.001
Men	1,228 (70%)	713 (80%)	<0.001
Time from symptom onset to admission (h)	5.6 ± 7.6	5.5 ± 7.4	0.80
Killip class ≥2 on admission	239 (14%)	187 (21%)	<0.001
Cardiogenic shock on admission	91 (5%)	80 (9%)	<0.001
Previous infarction	210 (12%)	82 (9%)	0.032
Preinfarction angina	692 (40%)	303 (34%)	0.006
Diabetes mellitus	526 (30%)	317 (36%)	0.004
Hypertension	1007 (58%)	478 (54%)	0.064
Smoker	718 (41%)	505 (57%)	<0.001
Hyperlipidemia	571 (33%)	333 (38%)	0.013
Anterior wall AMI	822 (47%)	452 (51%)	0.060
WBC count on admission (/μl)	8,273 ± 1,826	14,102 ± 2,812	<0.001
PG on admission (mmol/L)	9.7 ± 4.1	10.9 ± 5.1	<0.001
GFR on admission (ml/min/1.73 m^2)	72 ± 25	74 ± 28	0.76
Multivessel disease	775 (44%)	383 (43%)	0.56
3-Vessel disease	250 (14%)	112 (13%)	0.23
TIMI flow grade 0 at initial coronary angiography	1,108 (64%)	615 (69%)	0.003
Final TIMI flow grade ≥2	1,675 (96%)	840 (95%)	0.15
Final TIMI flow grade 3	1,592 (91%)	780 (88%)	0.008
Peak creatine kinase (IU/L)	2,828 ± 2,773	3,927 ± 3,508	<0.001
In-hospital outcomes			
All-cause mortality	75 (4.3%)	73 (8.2%)	<0.001
Cardiovascular mortality	64 (3.7%)	60 (6.8%)	<0.001
Reinfarction	33 (1.9%)	19 (2.1%)	0.66
Heart failure	40 (2.3%)	32 (3.6%)	0.050
Stroke	20 (1.1%)	10 (1.1%)	0.97

Data presented as mean ± SD or number of patients (%). High WBC count indicates upper tertile of WBC count (≥1,1120/μl), and low WBC count indicates middle and lower tertiles of WBC count (<1,1120/μl).
TIMI = Thrombolysis In Myocardial Infarction.

Table 2
Clinical characteristics of patients with low and high plasma glucose (PG)

Variable	PG		p Value
	Low (n = 1,757)	High (n = 876)	
Age (yrs)	67 ± 12	67 ± 11	0.36
Men	1,334 (76%)	607 (69%)	<0.001
Time from symptom onset to admission (h)	5.8 ± 7.8	5.1 ± 6.9	0.024
Killip class ≥2 on admission	205 (12%)	221 (25%)	<0.001
Cardiogenic shock on admission	57 (3%)	114 (13%)	<0.001
Previous infarction	185 (11%)	107 (12%)	0.19
Preinfarction angina	704 (40%)	291 (33%)	0.001
Diabetes mellitus	290 (17%)	553 (63%)	<0.001
Hypertension	981 (56%)	504 (58%)	0.41
Smoker	847 (48%)	376 (43%)	0.010
Hyperlipidemia	580 (33%)	324 (37%)	0.043
Anterior wall AMI	866 (49%)	408 (47%)	0.19
WBC on admission (/μl)	9,878 ± 3265	10,960 ± 3,914	<0.001
PG on admission (mmol/L)	7.6 ± 1.6	15 ± 4.5	<0.001
GFR on admission (ml/min/1.73 m^2)	73 ± 24	70 ± 29	0.12
Multivessel disease	722 (41%)	436 (50%)	<0.001
3-Vessel disease	208 (12%)	154 (18%)	<0.001
TIMI flow grade 0 at initial coronary angiography	1,162 (66%)	561 (64%)	0.29
Final TIMI flow grade ≥2	1,672 (95%)	843 (96%)	0.21
Final TIMI flow grade 3	1,586 (90%)	786 (90%)	0.66
Peak creatine kinase (IU/L)	2,991 ± 2,743	3,621 ± 3,645	<0.001
In-hospital outcomes			
All-cause mortality	66 (3.8%)	82 (9.4%)	<0.001
Cardiovascular mortality	55 (3.1%)	69 (7.9%)	<0.001
Reinfarction	36 (2.0%)	16 (1.8%)	0.70
Heart failure	34 (1.9%)	38 (4.3%)	<0.001
Stroke	14 (0.8%)	16 (1.8%)	0.019

Data presented as mean ± SD or number of patients (%). High PG indicates upper tertile of PG (≥10.4 mmol/L) and low PG indicates middle and lower tertiles of PG (<10.4 mmol/L).
Abbreviation as in Table 1.

ing centers within 48 hours after the onset of AMI were enrolled in JACSS.[3,5,6,9] A diagnosis of AMI required ≥2 of the characteristics of typical chest pain persisting >30 minutes, ischemic electrocardiographic changes, and peak creatine kinase >2 times the upper limit of normal. The study protocol was reviewed and approved by the ethical committee of each participating hospital. Reperfusion therapy was performed in 4,237 patients, and coronary stents were used in 3,077 patients. Of these 3,077 patients, we studied 2,633 patients with ST-segment elevation AMI who had adequate clinical data, including baseline WBC count, plasma glucose (PG), and creatinine. Patients receiving antihypertensive drugs or with baseline blood pressure ≥140/90 mm Hg were considered to have hypertension. Diabetes mellitus was diagnosed according to criteria of the World Health Organization. Hyperlipidemia was defined as fasting total cholesterol ≥220 mg/dl, fasting triglycerides ≥150 mg/dl, or use of antihyperlipidemic therapy. Cigarette smoking was defined as active smoking. Preinfarction angina was defined as the presence of typical chest pain occurring at rest or during exercise and persisting for >30 minutes within 24 hours before the onset of AMI.[14]

Blood samples for measurement of WBCs, PG, and GFR were obtained on admission. GFR was calculated using the abbreviated Modification of Diet in Renal Disease Study formula.[15] Cutoffs used for WBC count and PG were the respective upper tertiles, and that for GFR was the lower tertile in this study population. Patients were classified into 2 groups according to admission WBC count (high, ≥11,200/μl [upper tertile], n = 887; low, <11,200/μL [low and middle tertiles], n = 1,746), admission PG (high, ≥10.4 mmol/L [upper tertile], n = 876; low, <10.4 [low and middle tertiles], n = ,1757), and admission GFR (low, ≤60 ml/min/1.73 m^2 [lower tertile], n = 852; high, >60 [middle and high tertiles], n = 1,781).

Coronary angiography was performed immediately after admission. Perfusion status of the infarct-related artery was assessed according to the Thrombolysis In Myocardial Infarction Study classification.[16] The recanalization method

Table 3
Clinical characteristics of patients with low and high glomerular filtration rates (GFRs)

Variable	GFR		p Value
	Low (n = 852)	High (n = 1,781)	
Age (yrs)	72 ± 10	64 ± 11	<0.001
Men	588 (69%)	1,353 (76%)	<0.001
Time from symptom onset to admission (h)	5.1 ± 7.2	5.8 ± 7.7	0.024
Killip class ≥2 on admission	216 (25%)	210 (12%)	<0.001
Cardiogenic shock on admission	111 (13%)	60 (3%)	<0.001
Previous infarction	142 (17%)	150 (8%)	<0.001
Preinfarction angina	289 (34%)	706 (40%)	0.005
Diabetes mellitus	286 (34%)	557 (31%)	0.24
Hypertension	533 (63%)	952 (54%)	<0.001
Smoker	305 (36%)	918 (52%)	<0.001
Hyperlipidemia	235 (28%)	669 (38%)	<0.001
Anterior wall AMI	349 (41%)	925 (52%)	<0.001
WBC count on admission (/μl)	10,356 ± 3,843	10,181 ± 3,370	0.24
PG on admission (mmol/L)	10.8 ± 5.4	9.7 ± 3.9	<0.001
GFR on admission (ml/min/1.73 m^2)	44 ± 12	86 ± 21	<0.001
Multivessel disease	439 (52%)	719 (40%)	<0.001
3-Vessel disease	147 (17%)	215 (12%)	<0.001
TIMI flow grade 0 at initial coronary angiography	535 (63%)	1,188 (67%)	0.048
Final TIMI flow grade ≥2	808 (95%)	1,707 (96%)	0.24
Final TIMI flow grade 3	762 (89%)	1610 (90%)	0.44
Peak creatine kinase (IU/L)	3,295 ± 3,541	3,154 ± 2,844	0.26
In-hospital outcomes			
All-cause mortality	97 (11.4%)	51 (2.9%)	<0.001
Cardiovascular mortality	79 (9.3%)	45 (2.5%)	<0.001
Reinfarction	15 (1.8%)	37 (2.1%)	0.59
Heart failure	39 (4.6%)	33 (1.9%)	<0.001
Stroke	13 (1.5%)	17 (1.0%)	0.20

Data presented as mean ± SD or number of patients (%). Low GFR indicates lower tertile of GFR (≤60 ml/min/1.73 m^2) and high GFR indicates middle and upper tertiles (>60 ml/min/1.73 m^2).
Abbreviation as in Table 1.

was left to the physicians' discretion. Stents were placed in all patients in whom the procedure was feasible.

Data were expressed as mean ± SD for continuous variables and percentage for categorical variables. Mean values were compared between groups using unpaired *t* tests. Differences in prevalence were assessed using chi-square tests. A p value <0.05 was considered to indicate a statistically significant difference. Multiple logistic regression analysis was used to examine predictors of in-hospital mortality that were available on admission. To test the independence of high WBC count, high PG, and low GFR, all variables were entered into a multivariate analysis. Other variables used for multivariate analysis included age, gender, time to admission, previous infarction, diabetes mellitus, hypertension, smoking, hyperlipidemia, Killip class on admission, anterior infarction, and preinfarction angina. Odds ratios (ORs) and 95% confidence intervals (CIs) were

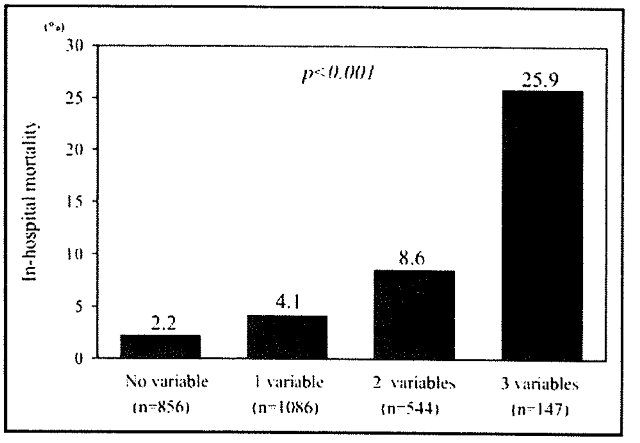

Figure 1. In-hospital mortality according to the number of the variables of high WBC count, high PG, and low GFR present.

calculated. Data were analyzed using SPSS software (release 10; SPSS Inc., Chicago, Illinois).

Results

The study group included 1,941 men (74%) and 692 women (26%) with a mean age of 67 ± 12 years. Clinical characteristics of patients in this study are listed in Tables 1 to 3.

Patients with a high WBC count were more likely to be younger and men; had higher incidences of Killip class ≥2, cardiogenic shock, diabetes mellitus, smoking, and hyperlipidemia; and had lower incidences of previous infarction and preinfarction angina. The frequency of initial Thrombolysis In Myocardial Infarction flow grade 0 was higher and that of final Thrombolysis In Myocardial Infarction flow grade 3 was lower in patients with a high WBC count. Patients with a high WBC count had a higher peak creatine kinase than those with a low WBC count. PG was higher in patients with a high WBC count, but GFR did not differ between the 2 groups (Table 1).

Patients with high PG were less likely to be men; had higher incidences of Killip class ≥2, cardiogenic shock, diabetes mellitus, and hyperlipidemia; and had lower incidences of preinfarction angina and smoking. Frequencies of multivessel and 3-vessel disease were higher in patients with high PG. Patients with high PG had higher peak creatine kinase than those with low PG. WBC count was higher in patients with high PG. There was a slight, but insignificant, trend toward lower GFR in patients with high PG (Table 2).

Patients with low GFR were more likely to be older and less likely to be men; had higher incidences of Killip class ≥2, cardiogenic shock, previous infarction, and hypertension; and had lower incidences of preinfarction angina, smoking, hyperlipidemia, and anterior AMI. Frequencies of multivessel and 3-vessel disease were higher and that of initial Thrombolysis In Myocardial Infarction flow grade 0 was lower in patients with low GFR. WBC count did not differ between the 2 groups. PG was higher in patients with low GFR (Table 3).

Table 4
In-hospital outcomes according to the number of variables present of high white blood cell count, high plasma glucose, and low glomerular filtration rate

Variable	No. of Variables				p Value
	0 (n = 856)	1 (n = 1,086)	2 (n = 544)	3 (n = 147)	
Cardiavascular mortality	14 (1.6%)	38 (3.5%)	41 (7.5%)	31 (21.1%)	<0.001
Reinfarction	17 (2.0%)	21 (1.9%)	13 (2.4%)	1 (0.7%)	0.62
Heart failure	13 (1.5%)	22 (2.0%)	24 (4.4%)	13 (8.8%)	<0.001
Stroke	3 (0.4%)	17 (1.6%)	8 (1.5%)	2 (1.4%)	0.07

Data presented as number of patients (%). High WBC count indicates upper tertile of WBC count (≥11,120/μl), high PG indicates upper tertile of PG (≥10.4 mmol/L), and low GFR indicates lower tertile of GFR (≤60 ml/min/1.73 m^2).

Table 5
Multivariate analysis of factors associated with in-hospital all-cause and cardiovascular mortality

	All-Cause Mortality			Cardiovascular Mortality		
	OR	95% CI	p Value	OR	95% CI	p Value
No. of variables*						
0	1			1		
1	1.63	0.88–3.03	0.12	1.04	0.55–1.98	0.70
2	2.33	1.28–3.96	0.047	1.74	0.91–3.36	0.08
3	6.16	2.98–12.6	<0.001	4.20	1.73–8.12	0.001
Age	1.07	1.04–1.09	<0.001	1.05	1.02–1.07	<0.001
Anterior wall AMI	1.76	1.14–2.73	0.011	1.67	1.06–2.62	0.026
Killip class ≥2 on admission	7.50	4.80–11.7	<0.001	8.53	5.34–13.6	<0.001
Previous infarction				2.07	1.21–3.55	0.010

* High WBC count, high PG, and low GFR.

During hospitalization (mean 14 days), 148 patients (5.6%) died. Patients with high WBC count, high PG, or low GFR had higher rates of all-cause death, cardiovascular death, and heart failure. Stroke was more frequently observed in patients with high PG. Reinfarction rates were not associated with WBC count, PG, or GFR (Table 3).

On multivariate analysis, high WBC count (OR 1.73, 95% CI 1.11 to 2.70, p = 0.015), high PG (OR 1.32, 95% CI 1.04 to 2.16, p = 0.040), and low GFR (OR 1.66, 95% CI 1.05 to 2.63, p = 0.029) remained significant predictors of all-cause mortality. Other significant predictors were age (OR 1.06, 95% CI 1.04 to 1.09, p <0.001), anterior wall AMI (OR 1.88, 95% CI 1.19 to 2.98, p = 0.006), and Killip class ≥2 on admission (OR 7.39, 95% CI 4.67 to 11.6, p <0.001). Similarly, multivariate analysis showed that high WBC count (OR 1.62, 95% CI 1.10 to 2.63, p = 0.030), high PG (OR 1.42, 95% CI 1.02 to 2.43, p = 0.048), and low GFR (OR 1.56, 95% CI 1.04 to 2.59, p = 0.039) were significant predictors of cardiovascular mortality. Other significant predictors were age (OR 1.06, 95% CI 1.03 to 1.09, p <0.001), anterior wall AMI (OR 1.79, 95% CI 1.08 to 2.99, p = 0.006), Killip class ≥2 on admission (OR 10.8, 95% CI 6.47 to 18.8, p <0.001), and previous infarction (OR 1.55, 95% CI 1.11 to 2.64, p <0.001).

Because high WBC count, high PG, and low GFR were independent predictors of outcomes, we assessed whether the combined use of these variables improved the ability to predict mortality. All-cause and cardiovascular mortality progressively increased as the number of these 3 variables increased, and patients with all 3 variables had strikingly higher mortality (Figure 1; Table 4). Similar ORs were obtained when any combination of 2 variables was used. ORs were also similar when any 1 of the 3 variables was used. We therefore estimated ORs for mortality in the presence of any 1 or 2 of the 3 variables. Multivariate analysis showed that patients with only 1 variable had a 1.6-fold higher risk of all-cause mortality, those with 2 variables had a 2.3-fold higher risk of all-cause mortality and 1.7-fold higher risk of cardiovascular mortality, and those with all 3 variables had a 6.2-fold higher risk of all-cause mortality and 4.2-fold higher risk of cardiovascular mortality compared with patients with none of these variables (Table 5). Moreover, the presence of ≥2 of the 3 variables and the presence of all 3 variables were significantly related to all-cause and cardiovascular mortality, respectively.

Discussion

This study showed that high WBC count, high PG, and low GFR on admission were independent predictors of in-hospital mortality, and combined evaluation of these 3 variables enhanced the ability to predict in-hospital mortality in patients who underwent primary stent placement for ST-segment elevation AMI. Moreover, the prognostic independence of high WBC count, high PG, and low GFR suggested that all 3 of these variables should be included in risk assessment and that different mechanisms contributed to adverse outcomes.

Patients with a high WBC count had a higher rate of total occlusion of the infarct-related artery on initial coronary angiography. High WBC count has been related to a hypercoagulable or thromboresistant state.[17] Patients with high WBC count also had a lower rate of final Thrombolysis In Myocardial Infarction grade 3. Experimental and clinical studies showed that WBC was related to microvascular no-reflow phenomenon after reperfusion.[2,5,17,18] WBC count has also been linked to myocyte dysfunction.[19] These factors may contribute to a larger infarct size and increase the risk of mortality, but we cannot rule out the possibility that high WBC count was caused by severe myocardial damage.

Similar to previous studies,[3,6–9,20] our study confirmed a relation of admission hyperglycemia to larger infarct, heart failure, and higher mortality. Patients with high PG were likely to have had diabetes mellitus. Ishihara et al[21] showed that admission hyperglycemia in nondiabetic patients with AMI was not a sign of previously undiagnosed abnormal glucose tolerance. In our study, admission hyperglycemia was associated with increased mortality after AMI even after adjustment for diabetes mellitus, consistent with results of previous studies.[3,6,7,9] Hyperglycemia itself was related to microvascular dysfunction, larger infarct, and impaired left ventricular function.[22,23] However, admission hyperglycemia may be a marker of more extensive myocardial damage.[24]

We previously showed that combining WBC count with PG improved the ability to predict in-hospital mortality in patients with AMI,[3] in which primary stent placement was performed in 61% of patients, but did not consider renal function in that study. Renal dysfunction has negatively affected outcomes of patients with AMI.[10–13,25,26] GFR was considered a more accurate index of renal function than creatinine clearance.[27] The present study confirmed the finding that patients with renal dysfunction had adverse outcomes, but reasons are poorly understood. Extensive co-morbidities may have an important role, as indicated by our results. However, the contribution of renal dysfunction to mortality remained relevant even after adjustment for baseline characteristics, suggesting that these associated co-morbidities only partly explained the poor outcomes in patients with renal dysfunction. Factors such as anemia, oxidative stress, inflammation, altered cytokines, derangements in calcium-phosphate homeostasis, conditions conducive to coagulation, and less aggressive treatment were most likely involved.[10–13,25,26] Moreover, coronary atherosclerosis may be more severe and diffuse in patients with low GFR, indicated by the higher incidence of 3-vessel disease. Severer ischemia in noninfarcted myocardium and 3-vessel disease have been associated with poor outcome after percutaneous coronary intervention for AMI.[12]

Accurate risk stratification is critical to the implementation of personalized therapeutic strategies. Our results showed that combined evaluation of WBC count, PG, and GFR, variables that are routinely determined, was a simple and inexpensive technique that can be used on admission to predict the risk of in-hospital death. Availability of results soon after admission permitted early risk stratification and facilitated decision making before and during angiography. Patients with all 3 of these variables had strikingly higher in-hospital mortality because patients with cardiogenic shock on admission and those with renal insufficiency were included in our study, but were usually excluded from clinical trials.

The present study was a retrospective analysis and thus had several inherent limitations, including selection and referral biases. However, our database was relatively large and included patients treated at hospitals of various sizes and settings, making it more representative of current practice patterns than previous single-site databases. Our study showed that risk stratification based on combined use of WBC count, PG, and GFR on admission provided important prognostic information and facilitated early risk stratification (i.e., identification of high-risk patients) in patients undergoing primary stent placement for AMI.

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Current Status of Emergency Care for ST-Elevation Myocardial Infarction in an Urban Setting in Japan

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Background The door-to-balloon time (DTB) is an important predictor of the outcome for patients with ST-elevation myocardial infarction (STEMI). In Japan, percutaneous coronary intervention (PCI) can be performed at many hospitals, and the predominant strategy for reperfusion therapy is primary PCI. However, it remains unclear how rapidly reperfusion is achieved at these hospitals.
Methods and Results The study group comprised 369 patients with STEMI who presented within 12h of symptom onset to a tertiary emergency center (TEC) or at 11 community hospitals (CHs) in 2006 and underwent emergency coronary angiography. Median DTB was shorter in the TEC (63 vs 104 min, P<0.001), and the rate of DTB within 90 min was higher in the TEC (96% vs 39%, P<0.001). Lateral myocardial infarction, presentation during off-hours, and non-cardiologist as the first-contact physician were significantly associated with a prolonged DTB in CHs. There was a trend toward lower 30-day mortality from all causes in the TEC (2.0% vs 4.8%, P=0.08). Multiple logistic regression analysis demonstrated that prolonged DTB (>90 min) was an independent predictor of 30-day mortality (odds ratio 12.6; 95% confidence interval 1.85–86.2, P=0.01).
Conclusions Establishment of emergency cardiac care systems with the goal of DTB within 90 min is required in PCI-capable hospitals to improve clinical outcomes.

Key Words: Acute myocardial infarction (AMI); Door-to-balloon time; Mortality; Reperfusion

The time from hospital admission to reperfusion is an important predictor of the outcome for patients with ST-elevation myocardial infarction (STEMI).[1–3] Guidelines for the management of STEMI issued by the American College of Cardiology/American Heart Association and the European Society of Cardiology recommend primary percutaneous coronary intervention (PCI) for reperfusion therapy when it can be performed in a timely manner (ie, door-to-balloon time (DTB) or first medical contact-to-balloon time within 90 min) by experienced operators at high-volume centers.[4,5] However, emergency primary PCI is not always feasible, and treatment is frequently delayed. In Japan, PCI can be performed at many hospitals, and the predominant strategy for reperfusion therapy is primary PCI,[6–9] but how rapidly reperfusion is achieved in Japanese hospitals that routinely perform PCI remains unclear. Drugs, devices, and techniques for primary PCI have been actively debated, whereas shortening the time to reperfusion has only recently received attention. This study evaluated DTB and analyzed its components in patients with STEMI who were admitted to emergency hospitals in an urban setting in Japan and examined differences in DTB according to the type of hospital.

Methods

Study Population

We retrospectively studied 369 patients (283 men, 86 women; mean age, 65 years) with STEMI who were admitted to 12 emergency hospitals in an urban setting in Japan and underwent emergency coronary angiography within 12h after symptom onset. Patients with out-of-hospital cardiac arrest were excluded. All subjects had to have typical chest pain lasting for 20 min or more and ST-segment elevation in at least 2 adjacent leads (>0.1 mV in leads II, III, aVF, aVL, V4–6 and >0.2 mV in leads V1–3) on the admission electrocardiogram (ECG). The diagnosis of acute myocardial infarction (AMI) was confirmed by an increase in the creatine kinase level to more than twice the upper limit of normal. Another 20 patients with STEMI within 12h after symptom onset were hospitalized during the study period, but did not undergo urgent cardiac catheterization because of advanced age or comorbidity. No patient

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Table 1 Capabilities of the 2 Types of Hospitals

	TEC (n=1)	CHs (n=11)
No. beds	720	239–601*
No. cardiologists	14	4–8*
Annual no. total PCI ≥200	+	3/11
Interventional capability for 24 h/7 days	+	10/11
Cardiologists on duty for 24 h/7 days	+	3/11
Cardiologists always initially evaluate patients with chest discomfort in the emergency department	+	1/11
On-site cardiac surgical back-up	+	3/11
Pre-hospital 12-lead ECG transmission system	+	–

*Range.
TEC, tertiary emergency center; CHs, community hospitals; PCI, percutaneous coronary intervention; ECG, electrocardiogram.

Table 2 Baseline Characteristics of the Patients

	TEC (n=98)	CHs (n=271)	P value
Age (years)	62.3±10.8	66.6±11.7	0.002
Gender, M	80 (82%)	203 (75%)	0.18
Medical history			
Hypertension	57 (58%)	148 (55%)	0.54
Dyslipidemia	44 (45%)	116 (43%)	0.66
Diabetes mellitus	36 (37%)	102 (38%)	0.93
Previous myocardial infarction	8 (8%)	20 (7%)	0.81
Previous bypass surgery	2 (2%)	4 (1%)	0.51
Infarct location			
Anterior	38 (39%)	130 (48%)	0.12
Inferior	48 (49%)	105 (39%)	0.08
Lateral	7 (7%)	21 (8%)	0.85
Time and mode of presentation			
Presentation during regular hours	49 (50%)	134 (49%)	0.93
Presentation by self-transport	4 (4%)	69 (25%)	<0.001
Inter-hospital transfer	30 (31%)	57 (21%)	0.06
Cardiologist as 'first-contact' physician	94 (96%)	117 (45%)	<0.001
Killip class ≥2	10 (10%)	34 (13%)	0.54
Fibrinolytic therapy with facilitated PCI	42 (43%)	93 (34%)	0.13

Abbreviations see in Table 1.

received thrombolytic therapy without coronary angiography. All clinical data were collected from medical records by a single researcher. The 12 participating institutions consisted of 1 tertiary emergency center (TEC) and 11 community hospitals (CHs), all of which could perform PCI. The study period was from January through December 2006.

Data Analysis and Definition

We compared the institutional and patients' baseline characteristics between the TEC and CHs. Time factors such as DTB and its components were also compared. We then analyzed variables associated with treatment delays and clinical outcomes.

Door time was defined as the arrival time at the emergency department where emergency cardiac catheterization was performed (not the arrival time at referral hospitals for transferred patients). Balloon time was defined as the time of first balloon inflation, or the time of stent implantation if the patient underwent primary stenting. PCI was considered successful if a Thrombolysis In Myocardial Infarction (TIMI) flow grade of 2–3 was obtained in the infarct-related artery in the presence of <50% residual stenosis with balloon angioplasty or <20% residual stenosis with stent implantation. If initial angiography showed TIMI grade 3 flow with >75% stenosis, additional PCI was left to the discretion of the attending physician.

Presentation time was divided into "regular hours" (defined as weekdays from 08.30–19.59 h) and "off-hours" (weekdays from 20.00–08.29 h and weekends).

Statistical Analysis

Statistical analysis was performed with SPSS 11.0 for Windows (SPSS, Inc, Chicago, IL, USA). The Kolmogorov-Sminov test was used to analyze the normality of the distribution of the study variables. Values are expressed as mean ± SD or median with interquartile ranges. Univariate comparisons of continuous variables between groups were done with unpaired t-tests for normally distributed variables and Mann-Whitney tests for skewed variables. Categorical variables were compared with chi-square tests or Fisher's exact test. Multivariable logistic-regression analysis was performed with the variables that were significantly related to outcome variables in the univariate analyses to determine predictors of DTB within 90 min and of 30-day mortality. Differences were considered significant at $P<0.05$.

Results

Hospital Characteristics

Table 1 shows the characteristics of the hospitals. The TEC was a high-volume center with many strategies to reduce the DTB. An attending cardiologist is always available to examine patients who present with chest discomfort at the emergency department, as compared with only 1 of the 11

Table 3 Angiographic Findings and Interventional Procedure Rates

	TEC (n=98)	CHs (n=271)	P value
Initial TIMI flow grade 0	46 (47%)	124 (46%)	0.84
POBA and/or stent implantation	80 (82%)	231 (85%)	0.40
Thrombectomy	13 (13%)	83 (31%)	0.001
Distal protection	9 (9%)	3 (1%)	<0.001
Pre intravascular ultrasound	74 (76%)	47 (17%)	<0.001
Temporary pacing	1 (1%)	22 (8%)	0.001
Final TIMI flow grade 3	86 (88%)	242 (89%)	0.68
PCI success	77 (96%)	226 (98%)	0.34

TIMI, Thrombolysis In Myocardial Infarction; POBA, plain old balloon angioplasty. Other abbreviations see in Table 1.

Table 4 Time Factors Related to Reperfusion

	TEC	CHs	P value
Symptom onset-admission (min)	83 (51, 142)	100 (56, 180)	0.08
Admission-ECG (min)	4 (3, 5)	4 (2, 7)	0.67
ECG-catheterization laboratory (min)	20 (16, 25)	45 (35, 69)	<0.001
Catheterization laboratory-CAG (min)	13 (11, 16)	18 (15, 23)	<0.001
CAG-balloon (min)	24 (20, 31)	26 (19, 38)	0.28
Door-balloon (min)	63 (55, 70)	101 (83, 134)	<0.001
DTB within 90 min	96%	39%	<0.001

Values are median with interquartile ranges.
CAG, first coronary angiography; DTB, door-to-balloon time. Other abbreviations see in Table 1.

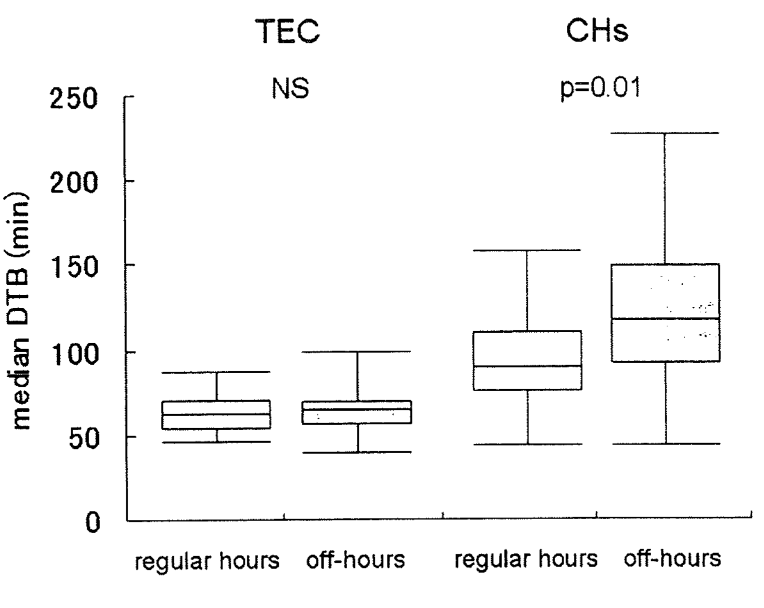

Fig 1. Median door-to-balloon time (DTB) during regular hours and off-hours in each hospital type. TEC, tertiary emergency center; CHs, community hospitals.

CHs. The TEC has a pre-hospital 12-lead ECG transmission system from the ambulance to the emergency department, and ECG transmission was performed in approximately 50% of the TEC patients.

Patients' Characteristics

Within the overall study group, 98 (27%) patients were admitted to the TEC and 271 (73%) to CHs. There was no difference in sex, infarct location, or the rate of Killip class ≥2 between the 2 types of institution. The patients admitted to TEC were younger than those admitted to CHs. Fibrinolytic therapy with low-dose tissue plasminogen activator with facilitated PCI was performed in 42 patients (43%) in the TEC and in 93 (34%) patients in the CHs. Overall, 15 patients who received fibrinolytic agents did not undergo PCI because of successful reperfusion as confirmed by coronary angiography, without balloon angioplasty. These patients were excluded from the analysis regarding the time from CAG to first balloon inflation. First-contact physicians were more frequently cardiologists in the TEC. The proportion of patients transferred from other hospitals was higher in the TEC, whereas the rate of self-transport to the hospital was significantly lower (**Table 2**).

Angiographic Findings and Interventional Procedure Rate

The frequency of PCI-related procedures such as thrombectomy, use of distal protection devices, and pre-intravascular ultrasound differed between the 2 types of institution. Balloon angioplasty (POBA), stent implantation, or both were performed in 82% of the patients in the TEC and in

Table 5 Variables Associated With Prolonged DTB (>90 min) in Patients Admitted to CHs

	Univariate analysis	P value	Multivariate analysis	95%CI	P value
Annual PCI procedures <200 in admitting hospital*	1.09	0.76	–	–	–
Cardiogenic shock	0.36	0.045	–	–	0.16
Lateral wall infarction	3.45	0.043	3.85	1.01–14.8	0.049
Presentation during off-hours	3.39	<0.001	2.94	1.63–5.31	<0.001
Presentation by self-transport	2.3	0.014	–	–	0.10
Inter-hospital transfer	0.41	0.004	–	–	0.37
Non-cardiologist as 'first-contact physician'	4.13	<0.001	3.63	2.02–6.52	<0.001

ORs of prolonged DBT are shown. Variables reaching P<0.05 on univariate analysis were entered into the multivariate analysis.
**Although annual PCI volume is included, it was not associated with prolonged DBT and was not entered into the multivariate analysis.*
CI, confidence interval; OR, odds ratio. Other abbreviations see in Tables 1,4.

Table 6 Multivariate Predictors of All-Cause 30-Day Mortality

	OR	95%CI	P value
Age >75 years	11.4	2.05–63.3	0.005
DTB >90 min	12.6	1.85–86.2	0.01
Killip class ≥2	34.3	5.56–211.2	<0.001
Final TIMI flow grade ≤2	25.5	2.75–236.7	0.004
Anterior myocardial infarction	11.8	1.34–103.3	0.03

Variables reaching P<0.05 on univariate analysis were entered into the multivariate analysis.
Abbreviations see in Tables 3,4.

85% of those in CHs. PCI was successful in 95% of the patients treated in the TEC and in 98% of those treated in CHs. The proportion of patients with a final TIMI flow grade of 3 did not differ between the TEC and CHs (**Table 3**).

Time Factors Related to Reperfusion and Clinical Outcome

The time from symptom onset to admission was slightly but not significantly longer in the CHs. The time from admission to ECG recording and the time from first coronary angiography to first balloon inflation were similar in the 2 types of hospital. However, the time from ECG recording to the cardiac catheterization laboratory was significantly longer in the CHs, resulting in a longer DTB. The TEC had a median DTB of 63 min and achieved a guideline-recommended DTB within 90 min in 96% of patients, whereas the CHs had a median DTB of 101 min and only 39% of patients achieved a DTB within 90 min (**Table 4**). Presentation during off-hours significantly prolonged the DTB for 27 min as compared with presentation in regular hours in the CHs, whereas the time of presentation did not influence the DTB in the TEC (**Fig 1**). Moreover, treatment was markedly delayed (DTB >150 min) in 18% of the patients treated at CHs, and this increased to 30% when a non-cardiologist was the first-contact physician. There was a trend toward lower 30-day mortality from all causes in the TEC in the overall study group (2.0% vs 4.8%, P=0.08).

Variables Influencing DTB in CHs

Because a guideline-recommended DTB was achieved in most of the patients treated in the TEC, the variables that influence the DTB were analyzed among the patients who were admitted to a CH. Hospitals that performed more than 200 PCI per year did not have a shorter DTB than hospitals that performed less procedures. After multivariable adjustment, lateral MI, presentation during off-hours, and non-cardiologist as first-contact physician were significantly associated with a prolonged DTB (**Table 5**). Inter-hospital transportation occurred in 21% of patients admitted to a CH, but was not a significant factor for DTB >90 min on multivariate analysis. After excluding referred patients and analyzing data only from patients with direct transportation, the results for time factors were similar to those obtained for the study group as a whole.

Analysis of Predictors of 30-Day Mortality

Table 6 shows the predictors of 30-day mortality from all causes in patients who underwent emergency PCI. Multiple logistic regression analysis showed that age >75 years, anterior MI, Killip class ≥2, final TIMI flow grade ≤2, and DTB >90 min were independent predictors of mortality within 30 days.

Discussion

Our study showed that CHs achieved the guideline-recommended DTB in less than 40% of patients with STEMI, and that prolonged DTB was an independent predictor of 30-day mortality. Delayed treatment was associated with patient presentation during off-hours and non-cardiologists as the first-contact physician. In contrast, the TEC, which specialized in cardiac emergency care, performed rapid reperfusion therapy in most patients.

Prompt PCI significantly reduces mortality and morbidity in patients with STEMI, and prolonged DTB has been associated with poor outcomes.[1–5,10] However, most previous studies were performed in Western countries at medical centers with experienced PCI providers. We investigated whether a similar situation exists in Japanese hospitals. In contrast to Western countries, many hospitals in Japan can perform PCI and consequently, 75–94% of patients with STEMI undergo primary PCI for reperfusion therapy,[6–8] including those treated at low-volume centers.[11,12] Our findings showed that PCI volume at the CHs was unrelated to either DTB or 30-day mortality in contrast to results obtained by Western studies, where a prolonged DTB was associated with higher 30-day mortality. This outcome suggests that the establishment of emergency cardiac care systems is a more important factor in the reduction of DTB than the treatment of patients with STEMI at high-volume centers, consistent with the recommendations of "Development of System of Care for ST-Elevation Myocardial Infarction," issued by the American Heart Association.[13] A recent study has shown that hospital policies that emphasize having a well-equipped catheterization laboratory staffed by attending cardiologists and other dedicated care providers contributes to a reduced DTB.[14] In another study, the establishment of protocols requiring that the cardiac catheterization laboratory is activated by emergency department physicians and that patients with cardiac problems are immediately transferred and treated at catheterization laboratory significantly reduced DTB by 38 min overall,[15] contributing to a decrease in mean infarct size.

Our study found that non-cardiologists as first-contact physician and off-hour presentation were associated with prolonged DTB in Japan. In the CHs, more than half of the patients with STEMI were initially treated by a non-cardiologist, who quickly obtained a 12-lead ECG for patients who had symptoms suggesting STEMI, but the time from ECG to the catheterization laboratory remained prolonged. The time from first coronary angiography to first balloon inflation, the PCI success rate, and the proportion of patients with a final TIMI flow grade of 3 did not differ between the CHs and TEC, suggesting the cardiologists were unaware of treatment delays that occurred before they were consulted. Ideally, all patients with symptoms suggesting STEMI should be examined by a cardiologist immediately after admission; however, most CHs do not have a 24-h on-site attending cardiologist 7 days per week because of limited human and financial resources. Non-cardiologists should therefore be aware of the clinical significance of the DTB and immediately transfer patients suspected to have STEMI to the cardiac catheterization laboratory.

In Vienna, Austria, the establishment of a cooperative network and implementation of the guidelines for the treatment of STEMI led to earlier reperfusion therapy and significantly improved clinical outcomes.[16] Pre-hospital ECG transmission enables on-call cardiologists to be notified before the patient arrives in the emergency department and reduces PCI-related delays, with earlier activation of the catheterization laboratory.[17–19] We believe that pre-hospital ECG transmission and analysis contributed substantially to the higher rate of a DTB within 90 min at the TEC in our study.

In conclusion, our results suggest that the design and implementation of appropriate guidelines and the improvement of hospital performance through the organization and establishment of emergency cardiac care systems will consistently ensure rapid reperfusion in patients with STEMI. Optimal policies tailored to meet the needs of specific communities are likely to reduce the DTB and lead to improved outcomes.

Study Limitations

This study included a small number of patients and was performed in a single region of Japan. Overall, 37% of patients underwent facilitated PCI with a half-dose of tissue plasminogen activator; negative results after facilitated PCI have been reported,[20,21] but several studies, including the Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) trial,[22] the Vienna registry,[16] and the National Registry of Myocardial Infarction (NRMI),[18] have demonstrated the effectiveness of fibrinolytic therapy early after the onset of MI. In addition, the former 2 trials also confirmed the efficacy of immediate PCI after fibrinolytic therapy.[16,22,23] We therefore administered a half-dose of fibrinolytic therapy followed by PCI in younger patients who presented early after onset.

Although the DTB at the TEC was within guideline recommendations in nearly all patients with STEMI, a direct comparison with the results of previous Western studies is precluded by differences in the definition of the DTB for transferred patients. Indeed, inter-hospital transfer has been found to be a strong independent predictor of a delayed time from first hospital arrival to first balloon inflation,[24] but the present study focused on hospital performance to identify in-hospital problems that need to be solved. Furthermore, we must recognize that emergency care systems in Japan might differ considerably from those in Western countries.

Conclusion

A DTB longer than 90 min was associated with a higher 30-day mortality in Japanese patients with STEMI. Guideline-recommended DTB was achieved in most of the patients in the TEC, as compared with less than 40% in CHs. Although the DTB was frequently longer in CHs, there was no correlation between PCI volume and DTB. Establishment of emergency systems for STEMI care with the goal of a DTB within 90 min is required in PCI-capable hospitals to improve clinical outcomes.

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8．縦隔炎と感染予防

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I．基本的な考え方

近年，心臓血管外科領域においては手術手技の改良や人工材料の発達により，その手術成績は飛躍的に向上してきている．しかしながら現在においても，術後に遭遇する感染症は患者の予後を左右するもっとも重篤な合併症の一つである．心臓血管外科手術は本来無菌手術であるが，体外循環や多数の血管内留置カテーテル，さまざまな人工材料の体内留置などにより，術中・術後に体内に病原微生物が移入されやすく，また感染への抵抗性も低下して宿主と病原菌の力関係が逆転し，術後に感染症を発症するリスクは高い．心臓血管外科医にとって，この感染ならびに感染準備状態をいかにコントロールするかは，手術成績を左右する重大な問題となる．

本稿においては，心臓血管外科周術期における感染予防対策，術後に問題となる感染症対策および縦隔炎の診断と治療方針について述べる．

II．心臓血管外科手術後の感染症予防対策

術後の感染には，患者自身が有する常在菌による感染（内因性感染）と，ICU や病室に存在する院内環境汚染菌による感染（外因性感染）がある．これらの術後感染を防止するためには，すべての体内への細菌の侵入をいかに防止するかにある．その対策として，これまでに Centers for Disease Control and Prevention（CDC）をはじめとするさまざまな「感染症対策ガイドライン」[1]が示されているが，院内環境や感染対策状況は施設によってさまざまであり，通常の標準的感染予防対策（standard precaution）に加えて，各施設，各診療科に応じた「感染対策マニュアル」を作成し対応していくことが必要である（表 1）．そこで，心臓血管外科手術後の感染症予防対策について，その特徴的対策としてわれわれの施設が行っている方法を中心に，術前・術中・術後について述べる．

❶ 予防的抗菌薬投与

心臓血管外科手術は無菌手術であるが，皮膚切開を必ず伴うため皮膚に常在する表皮ブドウ球菌や黄色ブドウ球菌による内因性感染を対象とし抗菌薬を投与する．一般的に第一世代セフェム系薬（cefazolin）やペニシリン系薬（ampicillin と sulbactam の合剤）などが用いられる．定期的なメチシリン耐性黄色ブドウ球菌（MRSA）prevalence rate 調査を行うことを原則とし，特に MRSA 保菌例や院内環境で MRSA が多いと判断される状況のときは，発症阻止のため vancomycin を使用する[2]（健康保険非適用）．手術部位の細菌汚染が始まるのは皮膚切開時であり，そのときに抗菌薬が血中および組織中の殺菌的濃度に達していることが必要であり，皮膚切開の 30 分前に投与する．Cefazolin は半減期が約 2 時間であり，組織中の抗菌薬濃度を閉創まで十分に殺菌的な水準に維持するため，手術開始 3〜4 時間後には追加投与が必要となる．半減期の長い vancomycin においても手術開始 6 時間後には追加投

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表 1. 心臓血管外科手術後の感染症予防対策

1. 環境対策
standard precaution の徹底
感染対策マニュアルの作成
2. 術前対策
術前禁煙，術前シャワー浴
手術直前にクリッパーによる除毛
術前監視培養(mupirocin 塗布，povidone-iodine 希釈液によるうがい)
3. 術中対策
maximal barrier precaution の徹底
手術時間の短縮
3 時間ごとの手袋の交換
4. 術後対策
気管チューブ・血管カテーテル・尿道カテーテルの早期抜去
早期離床，早期経口摂取開始，厳格な血糖コントロール
適切な創部管理

与が必要である．投与期間については，これまでにさまざまな臨床研究がなされてきたが，米国胸部外科学会のガイドラインでは，耐性菌の出現も考慮し，心臓血管外科手術後 48 時間までの投与が推奨されている[3]．

❷ 術前予防対策

術後の感染症を予防するために，入院時にう歯の有無，喫煙，血糖管理状況など術前のリスクファクターについて評価する．MRSA の鼻腔内保菌が手術部位感染（surgical site infection：SSI）のリスクファクターであることは多数報告されており[4]，鼻腔・咽頭の監視培養を行う．監視培養で MRSA が検出された場合には，緊急例以外は mupirocin 塗布による除菌や povidone-iodine 希釈液によるうがいを行う．当施設では週 1 回の検査で連続 2 回の陰性を確認してから手術に臨んでいる．原則的に，手術前日には液体石鹸を用いシャワー浴を行う．術前の剃毛は原則的に行わず，必要な場合のみ手術当日，手術室にてハサミやクリッパーを用いて行う．

❸ 術中予防対策

十分な手洗いの後でも 3 時間経過すると手指に表皮常在細菌が認められることが報告されており，手術時間の短縮を心がけ，約 3 時間ごとに速乾性手指消毒剤を使用し手袋の交換や，再度手洗いをするなどの配慮が必要である．閉胸前に縦隔，心嚢内を生理食塩水で十分に洗浄し，落下細菌や血腫などを十分に除去する．術後感染症の原因菌の多くは術中・術後に体内に移入するので，外科医のみならず麻酔医，看護師，臨床工学技師などの無菌操作もきわめて重要である．手術室への入室人数が増加すると浮遊粉塵が多くなり，病原微生物が混入しやすくなるため，手術室への入室を制限することも重要である．血管内用具留置時，静脈内投与薬剤の準備，および投与に際しては，無菌法の原則を順守する．特に中心静脈カテーテル挿入の際には，maximal barrier precaution に沿って帽子，マスクを着用し，手洗いの後，滅菌ガウンと滅菌手袋を着用して行う．すなわち術中においては，① 手術室の環境対策，② 血管確保時の無菌対策，③ 手術操作に関する感染対策が重要である．

❹ 術後予防対策

感染起因菌の侵入部位は，創部のみならず血管ライン刺入部，ドレーン挿入部，気管チューブ，尿道カテーテルなどさまざまであり，それらのラインを早期に抜去することが重要である．また栄養管理を考慮し，早期離床，早期経口摂取開始を行う．一期的に閉鎖した切開創は，72 時間以内に接合面が接着する．そのため原則的に術後 3 日間，術中の滅菌ドレッシング剤で保護し，それ以降は開放とする．ただし創部より滲出液などがあった場合には，その症例ごとに対応する．包交の前後では必ず手洗いを行い，手袋を着用し包交を行う．高血糖時には白血球の機能（遊走，接着，貪食，殺菌能）が障害されると考えられており，周術期において感染を生じやすい状態となるため，特に術後 48 時間以内は血糖を厳格にコントロール（血糖値を 200 mg/dl 以下）する[5]．

すなわち術後は，① 体内への挿入ライン（カテーテルやドレーン）および創部の管理，② 術後の栄養，血糖管理が重要である．

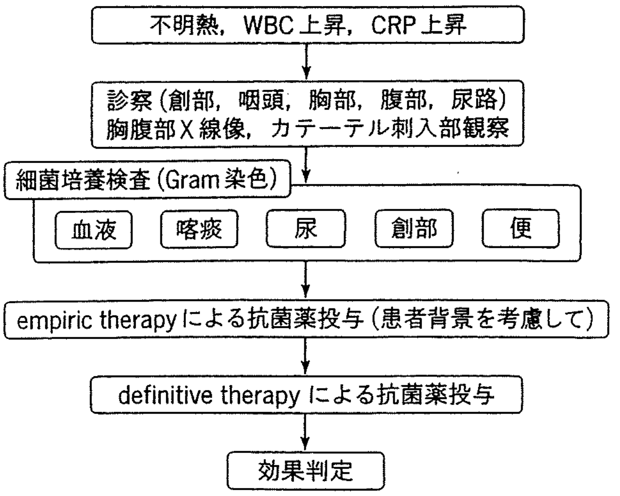

図1．術後感染症に対する抗菌薬投与方針

❺ 術後感染症対策

予防的抗菌薬を終了後，発熱や炎症所見が遷延，再上昇した場合には，盲目的に広域スペクトラムの抗菌薬を用いるのではなく，感染部位，起因菌の同定に努め，感受性，感染部位に応じた抗菌薬を選択することが重要である（図1）．起因菌検索のため，病歴の問診と同時に必ず身体診察を行い，局所の圧痛，腫脹，痰，咽頭痛，歯痛，排尿痛，頭痛，下痢，関節痛など丹念に聴取しながら診察する．臨床検査では末梢血液検査，尿検査などのほかに，喀痰，尿，血液の細菌培養検査は必須である．それ以外に，局所に排膿があった場合には同部位の培養，または必要に応じて便培養を採取する．起因菌の特定がもっとも基本であるが，培養検査では菌の同定や感受性試験の結果までに時間がかかるため，Gram染色による鏡検が抗菌薬投与の手がかりとなる．鏡検によってGram陽性球菌による重症感染症が疑われた場合には，初期治療からvancomycinを投与する．起因菌と感受性が判明した時点において，より抗菌力が強く，毒性が低く，抗菌スペクトラムの狭い薬剤に変更する．抗菌薬を投与する場合には，pharmacokinetics（PK）/pharmacodynamics（PD）を考慮し，投与回数，投与量を十分に検討することが重要である．心臓血管外科手術後の感染症には，①SSIと②術野外感染（remote infection）があり，その双方への留意が必要である．

表2．縦隔炎発症のリスクファクター

宿主要因	手術要因	術後要因
高齢	手術時間延長	長期ICU滞在（長期挿管）
肥満	術後出血	気管切開
MRSA保菌	両側内胸動脈使用	術後肺炎
糖尿病	輸血	
慢性閉塞性肺障害		
喫煙		
術前心不全		
腎不全		
再手術		
緊急手術		

Ⅲ．術後感染性心内膜炎

心臓血管外科手術後に感染性心内膜炎を合併する危険性は2%以下[6]と報告されているが，一度罹患した場合には敗血症を伴い，死亡率が約20%と重篤な合併症である．特に人工弁置換術後の心内膜炎では，予後は不良である．原因菌としては連鎖球菌，ブドウ球菌，腸球菌が多く，菌種に応じた抗菌薬の投与が重要である．原因菌が同定できない場合においても，ガイドラインに従い抗菌薬を投与する[7]．診断は，心臓超音波検査でvegetationを認め，血液培養で菌血症を証明する．内科治療に抵抗性で抗菌薬の投与でも炎症反応が改善しない場合，vegetationが増大傾向にあるときや心不全がコントロールできない場合には外科治療が必要となる．

Ⅳ．縦 隔 炎

❶ リスクファクターと診断

縦隔炎は，現在においても心臓血管外科手術後の0.5〜3.3%に発症し，その死亡率も5.4〜23%と高く[8〜12]，術後のSSIの中でもっとも重篤な感染症の一つである．宿主側の要因としては高齢，肥満，MRSA保菌，糖尿病，慢性閉塞性肺障害，喫煙，腎不全，再手術，緊急手術などであり，手術要因としては手術時間，術後出血，両側内胸動脈使用，輸血であり，術後要因としては長期ICU滞在（長期挿管），気管切開などがあげられている（表2）．

手術後に発熱やWBC数やCRPの上昇に加え，胸骨の痛みや発赤および動揺，創部やドレーンから膿汁が認められた場合には縦隔炎を疑う．診断

には局所の細菌培養検査のほか，胸部CTが有用である．胸部CTで縦隔内にair bubbleやring enhanceされる液体の貯留，胸骨離開や骨髄炎像が認められた場合には縦隔炎と診断する．臨床症状が乏しくCTなどで診断が困難な場合には，FDG-PETによって胸骨や胸骨裏面のブドウ糖の異常消費を調べることも，診断の補助手段として有用である．起因菌は表皮ブドウ球菌と黄色ブドウ球菌が約40～70％と多く，その半数がMRSAと報告されている[6,8～12]．

❷ 縦隔炎の治療

治療には，抗菌薬に加えて外科的処置が必要になる．胸骨の破壊が軽度の場合や膿瘍が限局している場合には，局所のデブリドマン，生理食塩水による洗浄およびSBバック（住友ベークライト社，東京）などによる持続陰圧吸引で治療する．消毒薬は創傷治癒に働く細胞を傷害し創の治癒を遷延させるため，局所の消毒薬での洗浄や抗菌薬の塗布は行わない．炎症が強く胸骨が大きく破壊されている場合には，これまでに抗菌薬や消毒薬による洗浄の後，二期的な胸骨閉鎖や抗菌薬による閉鎖式縦隔洗浄，大網や大胸筋充塡などが行われてきたが，最近では胸骨を開放しスポンジとSBバックなどを用いた陰圧閉鎖式持続吸引ドレナージ（vacuum assisted closure：VAC）が行われるようになり，治癒率をより向上させている．またVAC療法と併用し，死腔に大網や大胸筋などを充塡することや，胸骨閉鎖，有茎筋皮弁なども有効であると報告されている[13～15]．胸骨の破壊や炎症の程度は症例によってさまざまであるため，十分なデブリドマンの後，①胸骨閉鎖，②VAC，③大網充塡などを組み合わせて対応していくことが肝要である．

V．結　論

心臓血管外科手術後の感染を予防するためには，以下のことを日々実践していくことが肝要である．

1）ガイドラインに沿って各施設，各診療科ごとの「感染対策マニュアル」を作成し，感染予防に努める．

2）予防的抗菌薬はcefazolinまたはampicillinとsulbactamの合剤を用い，手術開始前に投与し術後48時間で終了とする．

3）術後感染症が疑われた場合には，必ず各種細菌培養検査を行ってから抗菌薬を投与する．

4）縦隔炎が疑われた場合にはただちにCTを撮影し，外科的治療を開始する．症状に応じてvacuum-assisted systemを用いた持続陰圧吸引療法を行う．

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SUMMARY

Management of Mediastinitis and Preventions of Perioperative Nosocomial Infection after Cardiovascular Surgery

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This article reviews risk factors and treatment of perioperative nosocomial infections. The primary prophylactic antibiotic is recommended to be a cefazolin or penicillin with sulbactam, because the most frequent organism cultured in cardiac surgical site infection (SSI) is *Staphyloccocus*. Antibiotic prophylaxis of 48 hours' duration after cardiovascular surgery is clinically effective in minimizing infectious complication. In patients considered at high risk for a staphylococcal infection, vancomycin may be recommended. In the treatment of postoperative infections, Gram-stain-based antibiotic selection is necessary and the initial empirical therapy to ensure adequate coverage of potentially infective organisms should be accompanied by de-escalation until microbiological data become available. Mediastinitis, which is one of the important infectious complications after cardiovascular surgery, requires surgical drainage and debridement, as well as antimicrobial therapy. Vacuum-assisted closure (VAC) is an effective therapy compared with the conventional technique of open packing. Continuous clinician's efforts and prolonged infection control programs are very important for prevention of perioperative nosocomial infection after cardiac surgery.

KEY WORDS
cardiovascular surgery/antibiotic prophylaxis/mediastinitis/risk factor

臨床経験

未破裂の心外型 Valsalva 洞動脈瘤

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はじめに

Valsalva 洞動脈瘤はまれな疾患であり，その未破裂例はさらにまれである．未破裂例は無症状で偶然発見されるために，その治療方針は議論のあるところである．今回，未破裂の心外型 Valsalva 洞動脈瘤を経験したので報告する．

I．症　例

症　例 49 歳，女．

主　訴：労作時息切れ．

家族歴：特記すべきことはない．

既往歴：36 歳時に子宮腺筋症，慢性閉塞性肺疾患．

現病歴：2005 年 1 月ごろから労作時息切れを自覚し，当院内科を受診した．慢性閉塞性肺疾患として外来治療していたが，2007 年 9 月にたまたま施行した心臓超音波検査で Valsalva 洞動脈瘤を指摘され，手術目的にて当科へ紹介となった．

現　症：身長 160 cm，体重 41.2 kg，体温 36.8℃，血圧 136/76 mmHg，脈拍 60 回/分・整であった．心雑音はなかった．漏斗胸と両下肢静脈瘤を認めた．

血液・生化学所見：血液一般，生化学，血清検査はすべて正常で，炎症反応も陰性であった．

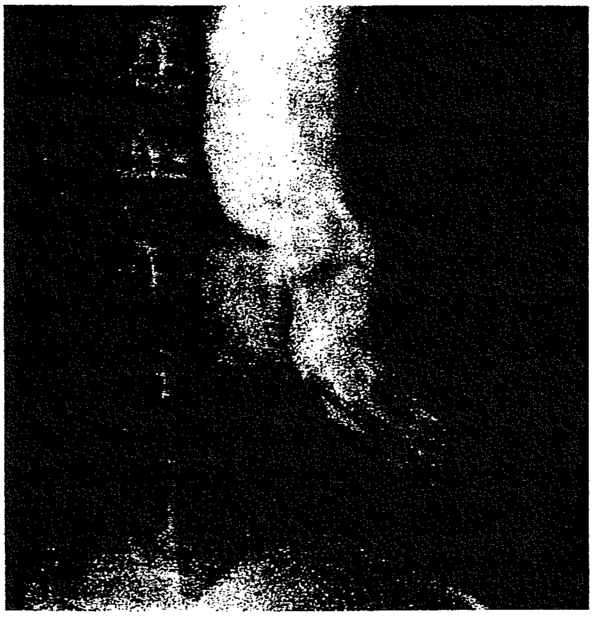

図 1．術前左室造影像
無冠状動脈洞の瘤化を認める．

胸部 X 線所見：心胸郭比 45.7%，肺気腫様変化を認めた．

呼吸機能所見：1 秒率 48.2%，%肺活量 92%であった．

心電図所見：洞調律，不完全右脚ブロックを認めた．

心臓超音波所見：無冠状動脈洞に 3.5×4.2 cm の動脈瘤を認めた．左室駆出率は 77%と良好で，

キーワード：Valsalva 洞動脈瘤，心外型動脈瘤，パッチ閉鎖

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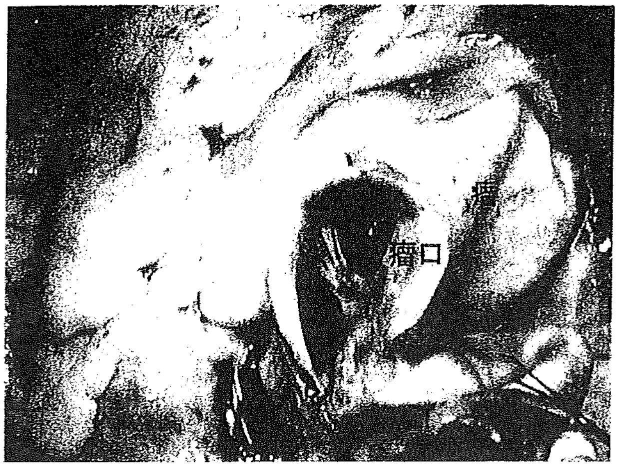

図 2．術中所見
無冠状動脈洞に 20×15 mm の瘤口があり，
その右側に瘤を認める．

大動脈弁閉鎖不全を認めなかった．

心カテーテル所見：無冠状動脈洞から生じた巨大な Valsalva 洞動脈瘤を認めた（図 1）．

以上から無症状であるものの，巨大瘤破裂の危険性を考慮して手術適応とした．

手術所見：胸骨正中切開にて開胸した．Valsalva 洞動脈瘤は心内腔と接しない心外型であった．上行大動脈送血，上下大静脈脱血にて人工心肺を確立した．上行大動脈を遮断し，右上肺静脈ベントを行いながら心筋保護液を順行性および逆行性に注入して心停止を得た．上行大動脈を横切すると無冠状動脈洞に 20×15 mm の瘤口を認めた（図 2）．ウマ心膜パッチ（XAG-400：Edwards Lifesciences 社，Irvine）を用い，5-0 プロリン糸の連続縫合で瘤口を閉鎖した．人工心肺からの離脱は容易であった．

術後経過：術後は順調に経過し，CT で瘤の血栓閉塞を確認した（図 3）．

Ⅱ．考　察

Valsalva 洞動脈瘤は井上[1]の分類が一般的に用いられ，心外型と心内型に分類される．心外型は通常 1 個の Valsalva 洞から発生した嚢状動脈瘤であり，心外に発育してしばしば巨大化するが，右心房を外から圧迫することはあっても右心房内に突出することはない．一方，心内型は瘤口を有する瘤が心腔内に突出するが，通常みられる破裂性の瘤では小指頭ないし母指頭大で，windsock，balloon type と表現されるように吹き流し状あるいは指サック状を呈し，その先端が穿孔することが特徴とされる[1]．

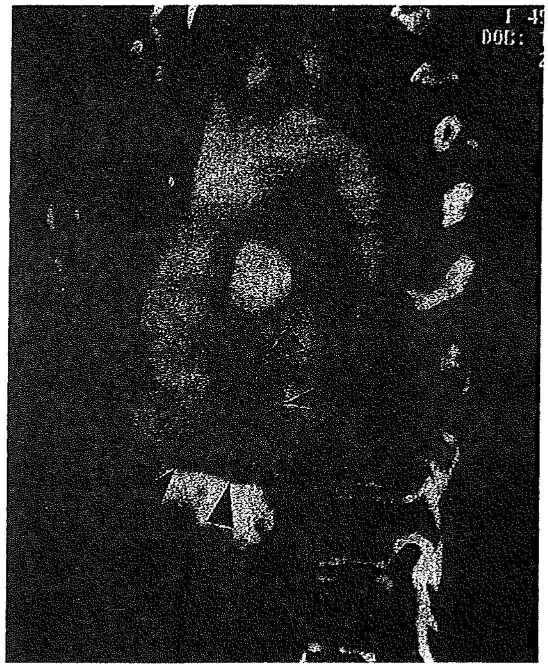

図 3．術後 CT
無冠状動脈洞動脈瘤の血栓化（矢印）
を認める．

Valsalva 洞動脈瘤の原因は先天性と後天性に分けられる．先天性としては胎生期の円錐部隆起および心内膜床の融合不全や Marfan 症候群などの中膜変性によるものが考えられ，後天性としては外傷，大動脈炎症候群，梅毒，結核などによるものが考えられる[2,3]．心外型の原因は大動脈壁と大動脈弁輪間の中膜の連続性が欠如していることであり[4]，心内型はこれに中隔筋性組織の欠損が加わるとする説[5]があり，合理的な説明であると考えられる．

本稿では特に心外型について述べることにする．本邦ではこれまでに文献上 20 例の心外型 Valsalva 洞動脈瘤が報告されている（表 1）．平均年齢 51.5（24〜69）歳，男女比は 10：10 と同等であった．主訴は合併する心疾患によるものが多く，14 例（70%）に大動脈弁閉鎖不全症，8 例（40%）に冠状動脈病変，このほかに右室流出路狭窄 2 例，上行大動脈瘤 2 例を認めた．瘤の発生部位は左冠状動脈洞 5 例，右冠状動脈洞 7 例，無冠状動脈洞 6 例とほぼ同等の比率であったが，すべての冠状動脈洞に認めたものが 1 例，右〜無冠状動脈洞に発生したものが 1 例あった．

表1　本邦における未破裂の心外型 Valsalva 洞動脈瘤の報告例

報告者（年）		瘤径(mm)	瘤の部位	合併心疾患	手　術
[illegible]	(1983)	60	L	AR，LMT 圧迫	パッチ閉鎖，AVR
[illegible]	(1987)	100	N	上行瘤	パッチ閉鎖 & 上行置換術
[illegible]	(1989)	100	R	AR，RCA 閉塞	パッチ閉鎖
東[illegible]	(1989)	80	L	AR，LMT 閉塞	パッチ閉鎖，AVR，CABG
加　藤	(1993)	30	R	AR, 右室流出路狭窄, 狭心症	パッチ閉鎖，AVR，CABG
Okita	(1995)	70	R	RCA 圧迫	パッチ閉鎖，RCA 再移植
浜　田	(1995)	70	N	AR	パッチ閉鎖
水　島[7]	(1996)	140	R	なし	パッチ閉鎖，瘤縫縮
本　多	(1997)	60	R-N	AR	パッチ閉鎖，AVR
Yasuda[8]	(2000)	70	L	AR，RCA 拡張症	大動脈基部置換術
		50	N	AR，上行瘤	パッチ閉鎖，上行置換術
下　山	(2001)	80	R	AR，RCA 閉塞	パッチ閉鎖，AVR，CABG
Kusuyama[9]	(2002)	15	R	AR	パッチ閉鎖
佐　藤	(2002)	35	N	なし	パッチ閉鎖，瘤切除
横　山	(2003)	50	L	RCA 瘤	パッチ閉鎖，CABG
内　川[6]	(2003)	35	N	AR	パッチ閉鎖，AVR→出血：上行置換術
近　江	(2004)	66	L	AR	大動脈基部置換術
石　神	(2004)	70	R	AR，右室流出路狭窄	パッチ閉鎖，AVR，CABG
Akashi	(2005)	60，42，20	N，L，R	AR	大動脈基部置換術
木　村[10]	(2006)	52	N	なし	大動脈基部置換術

L：左冠状動脈洞，R：右冠状動脈洞，N：無冠状動脈洞，AR：大動脈弁閉鎖不全，RCA：右冠状動脈，LMT：左冠状動脈主幹部，AVR：大動脈弁置換，CABG：冠状動脈バイパス術

瘤径は 15～140 mm とさまざまであった．手術術式は 16 例（80%）でパッチ閉鎖が行われており，これに合併心疾患に対する AVR や CABG が追加されていた．パッチ使用例の中には閉鎖部位からの出血のため上行置換へ変更した症例もあった[6]．パッチ閉鎖が困難な 4 例に対しては大動脈基部置換術が行われた．

病理組織学的に動脈瘤壁が特異的所見を示したのは 5 例あったが（Ehlers-Danlos 症候群，好酸球増多症候群，Marfan 症候群，Behçet 病，大動脈炎症候群）[7~10]，動脈瘤様変化の所見が 8 例と多く，ほかに粘液腫様変性が 2 例，記載なしが 5 例であった．

手術術式はパッチ閉鎖術が標準と思われるが，合併心疾患や Valsalva 洞動脈瘤の性状，上行大動脈の性状を考慮して決定すべきであろう．手術適応については議論のあるところである．本症はまれな疾患であり，動脈硬化性動脈瘤のような瘤径に基づいた手術適応基準はない．本症の原因が大動脈壁と大動脈弁輪の中膜の連続性の欠如であることから，瘤破裂のリスクは高いと考えられる，本症の報告例中，Behçet 病に伴った Valsalva 洞動脈瘤では瘤径 15 mm で手術が施行されていた[9]．合併疾患を考慮しながら，発見後早期の手術が望ましいと考えられた．

本例は大動脈壁や瘤壁を採取していないため病理組織学的検討ができず，Valsalva 洞動脈瘤の原因確定にはいたらなかった．

おわりに

未破裂の心外型 Valsalva 洞動脈瘤の 1 例に対して瘤口パッチ閉鎖術を行い，良好な結果を得た．

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