Long-term Predictive Factors of Major Adverse Cardiac Events in Patients with Acute Myocardial Infarction Complicated by Cardiogenic Shock

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Background : Cardiogenic shock (CS) after acute myocardial infarction (AMI) develops in 5~10% of patients and it is associated with high mortality. The aim of this study is to assess the predictive factors of mortality for patients with AMI and CS.

Methods : Two hundred fifty five AMI patients with CS (the mean age was 66.0±11.0 years, M:F=156:99) out of 1,268 AMI patients who admitted at Chonnam National University Hospital between July 2000 and June 2002 were analyzed according to the clinical characteristics, coronary angiographic findings and MACE during admission and for the 1-year clinical follow-up.

Results : Among the enrolled patients, 129 patients survived without MACE (Group I, mean age 64.2±10.6 years, M:F=76:53), and 126 patients had MACE (Group II, mean age 68.1±10.0 years, M:F=80:46) during admission or during the 1-year follow-up period. There were significant differences in age between the Groups I and II (64.2±10.6 vs. 68.1±11.0 years, respectively, *p*=0.004) and the previous MI history (0 vs. 17.4%, respectively, *p*<0.001). The left ventricular ejection fraction (EF) was lower in Group II (Group I vs. II: 49.1±13.0 vs. 39.1±12.9%, *p*<0.001). The levels of troponin (Tn) I and C-reactive protein (CRP) were higher in Group II (Group I vs. II: 29.2±7.72 vs. 50.8±5.17 ng/dL, *p*=0.017, 3.8±0.48 vs. 9.9±1.21 mg/dL, *p*<0.001 respectively). Left main stem lesion (LMSL) was more common in Group II than in Group I (0.7% vs. 22.0%, respectively, *p*=0.004). In-hospital death was associated with low Thrombolysis In Myocardial Infarction (TIMI) flow after coronary revascularization.

Conclusion : Old age, a previous MI history, high Tn and CRP, low EF and LMSL are associated with higher MACE for patients with AMI and CS. Coronary revascularization with TIMI 3 flow lowers the in-hospital mortality.

Key Words : Myocardial Infarction, Shock, Coronary diseases, Prognosis

INTRODUCTION

Acute coronary syndrome (ACS) is still one of the most important causes of death despite of improvements for its treatment. In Korea, the incidence of death from ACS has remarkably increased, and the annual death rate was 16.3 per 100,000 people/year in 1998, so intensive treatment of ACS is required[1].

Cardiogenic shock (CS) after acute myocardial infarction (AMI) is known to occur in 5~10% of patients and it is associated with a high mortality rate. According to the Thrombolysis in Myocardial Infarction (TIMI) 2B Trial[2], in which

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patients less than 75 years old were selected as subjects, the incidence of CS after AMI was 5.7%. Goldberg et al[3] have reported the incidence of CS after AMI was 6.2% from a large, multi-center prospective study from 1994 to 1997.

CS after AMI is associated with a high mortality rate despite of proper treatment such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Most of CS occurs in the first few days of the admission periods, so the mortality rate can be reduced by early invasive treatment[4].

The aim of this study is to assess the predictive factors of in-hospital mortality and long term prognostic factors from the clinical characteristics and procedural factors for patients with AMI and CS.

MATERIALS AND METHODS

Subjects

Between July 2000 and June 2002, there were 2,564 patients who had AMI as the first clinical impression on their arrival at the Gwangju-Chonnam Emergency Medical Center of Chonnam National University Hospital (CNUH). 1,268 patients out of these 2,564 patients were diagnosed as AMI, and 255 patients who were finally diagnosed as CS after AMI (the mean age was 66.0±11.0 years, M:F=156:99) were enrolled in our study. Among them, 129 patients survived without MACE (Group I, age 64.2±10.6 years, M:F=76:53), and 126 patients died or had MACE (Group II, age 68.1±10.0 years, M:F=80:46) during admission or during the one-year follow-up period.

The diagnosis of AMI was made by the criteria of American College of Cardiology/American Heart Association (ACC/AHA) guideline and Europian Circulation Society[5], and the clinical diagnosis of CS was made if all the following criteria were present: (1) a systolic blood pressure (BP) persistently less than 90 mm Hg or vasopressors were required to maintain the BP at more than 90 mm Hg (2) evidence of end organ hypoperfusion (e.g., urine output less than 30 mL or cold/diaphoretic extremities or altered mental status) and (3) evidence of elevated left ventricular filling pressures, for example, pulmonary congestion on examination or chest X-ray[6].

Methods

The enrolled patients were analyzed as to their clinical characteristics such as past history, family history and smoking, vital sign, physical examination and the laboratory, coronary angiographic and electrocardiographic findings. Among the risk factors, hypertension was defined if it was diagnosed and treated as hypertension in other hospital or the systolic blood pressure was more than 140 mmHg or the diastolic blood pressure was more than 90 mmHg more than two times after

the first visit, diabetes mellitus was defined if it was diagnosed and treated as diabetes in other hospital or there was a fasting blood glucose more than 126 mg/dL after admission, hyperlipidemia was defined if it was diagnosed and treated as hyperlipidemia in other hospital or there was a fasting serum cholesterol more than 200 mg/dL after the first visit, family history was defined if any family member had angina pectoris, MI, cerebrovascular disease or any peripheral vascular disease.

After the coronary angiogram (CAG), the types of lesions were classified according to ACC/AHA classification[7]; A and B1 were regarded as simple lesions whereas B2 and C were regarded as complex lesion. Critical stenosis was defined as more than a 75% diameter stenosis.

The number, location and characteristics of the target vessel, and the presence of thrombus or calcification were analyzed between the two groups. The Thrombolysis In Myocardial Infarction (TIMI) score[8] was checked for the infarct-related artery.

Emergency PCI was performed in patients who were capable of CAG. PCIs were performed 107±61 minutes after the emergency center visit. Successful reperfusion was defined as an obtained TIMI 3 flow in the infarct-related artery after PCI and less than 25% of the residual stenosis remained.

The enrolled patients were observed for the presence of major adverse cardiac events (MACE) such as death, AMI, target lesion revascularization (TLR) or stroke during admission and for a 1 year follow-up period.

Statistics

All the data were described as means±standard deviation. Nominal variables were analyzed by Chi-square testing and the various continuous variables were compared by t-testing and Chi-square testing. Results were considered significant if the p-values were less than 0.05. Also, predictive factors were sought by using binary logistic regression analysis after adjustments were made for age, sex, and the risk factors of coronary artery disease.

RESULTS

Baseline clinical characteristics

There were no significant differences in the risk factors between the two groups, except for age (64±11 vs. 68±10 for Group I and Group II, respectively, $p=0.009$) and previous MI history (0% vs. 18.5%, for Group I and Group II, respectively, $p<0.001$). The left ventricular ejection fraction was 43.6±13.8% for the total patients and it was significantly higher in Group I than in Group II (40.6±23.2% vs. 26.9±19.6% for Group I and Group II, respectively, $p<0.001$) (Table 1).

Table 1. Baseline clinical characteristics

	Group I (n=129)	Group II (n=126)	Total (n=255)	p value
Age (years)	64.2±10.6	68.1±10.0	66.0±11.0	0.004
Sex (M:F)	76:53	80:46	156:99	0.455
Ejection fraction (%)	49.1±13.0	39.1±12.9	43.6±13.8	<0.001
Risk factors (%)				
Hypertension	35 (27.1)	47 (37.3)	82 (32.2)	0.249
Diabetes mellitus	26 (20.1)	36 (28.5)	62 (24.3)	0.100
Smoking	63 (48.8)	72 (57.1)	135 (52.9)	0.286
Previous MI history	0 (0.0)	22 (17.4)	22 (8.6)	<0.001
Hyperlipidemia	24 (18.6)	13 (10.3)	37 (14.5)	0.145
Family history	9 (6.9)	5 (3.9)	14 (5.5)	0.803

MI, myocardial infarction

Table 2. Laboratory findings

	Group I (n=129)	Group II (n=126)	p value
Creatine kinase (U/L)	1416.8±191.0	1829.8±189.2	0.117
Creatine kinase-MB (IU)	121.4±15.8	172.3±21.9	0.586
Troponin-I (mg/dL)	29.2±7.7	50.8±5.2	0.017
Troponin-T (mg/dL)	5.3±0.4	6.2±0.9	0.655
Total cholesterol (mg/dL)	199.0±36.8	202.0±54.7	0.752
Triglyceride (mg/dL)	127.0±59.1	171.0±62.3	0.452
HDL-cholesterol (mg/dL)	42.0±9.1	42.0±10.2	0.944
LDL-cholesterol (mg/dL)	122.0±29.7	125.0±26.3	0.888
C-reactive protein (mg/dL)	3.8±0.5	9.9±1.2	<0.001

HDL, high density lipoprotein; LDL, low density lipoprotein

Table 3. Coronary angiographic findings

	Group I (n=129)	Group II (n=126)	p value
Patient number underwent CAG	126 (99.6%)	50 (39.6%)	0.001
Infarct-related artery			
LM	1 (0.7%)	11 (22.0%)	0.004
LAD	90 (71.4%)	28 (56.0%)	0.782
LCX	12 (9.5%)	3 (6.0%)	0.193
RCA	23 (18.2%)	8 (16.0%)	0.885
Involved vessel number			
single vessel	73 (57.9%)	32 (64.0%)	0.548
Two vessel	45 (35.7%)	9 (18.0%)	0.074
Three vessel	8 (6.3%)	9 (18.0%)	0.228
ACC/AHA type			
B1	54 (42.8%)	18 (36.0%)	0.853
B2	32 (25.3%)	18 (36.0%)	0.692
C	40 (31.7%)	14 (28.0%)	0.958
TIMI flow			
0	44 (34.9%)	20 (40.0%)	0.813
1	4 (3.1%)	4 (8.0%)	0.535
2	24 (19.0%)	12 (24.0%)	0.074
3	54 (42.8%)	14 (28.0%)	0.072

CAG, coronary angiogram; LM, left main disease; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ACC/AHA, American Collage of Cardiology/American Heart Association; TIMI, Thrombolysis In Myocardial Infarction

Table 4. Therapeutic approaches and TIMI flow after revascularization

	Group I (n=129)	Group II (n=126)	p value
Door to needle time (min)	4.1±3.1	3.6±0.8	0.774
Door to balloon time (min)	162.5±23.7	182.9±11.5	0.863
IABP	26 (20.1%)	11 (8.7%)	0.043
PCI	106 (82.1%)	24 (19.0%)	<0.001
CABG	2 (1.5%)	7 (5.5%)	0.032
Medical treatment	21 (16.2%)	95 (75.3%)	<0.001
TIMI flow after revascularization			
0	4 (3.7%)	3 (12.5%)	0.016
1	6 (5.6%)	5 (20.8%)	0.021
2	13 (12.2%)	6 (25%)	0.823
3	83 (78.3%)	10 (41.6%)	0.044

IABP, intra-aortic balloon pump; PCI, percuatneous coronary intervention; CABG, coronary artery bypass graft; TIMI, Thrombolysis In Myocardial Infarction

Table 5. In-hospital mortality and long-term mortality in percutaneous coronary intervention, coronary artery bypass graft and medical therapy

	Mortality	In-hospital mortality	Long-term mortality
PCI (n=130)	24 (18.4%)	22 (16.9%)	2 (1.5%)
CABG (n=9)	7 (77.7%)	5 (55.5%)	2 (22.2%)
Medical treatment (n=116)	95 (81.9%)	92 (79.3%)	3 (2.6%)

PCI, percuatneous coronary intervention; CABG, coronary artery bypass graft

Laboratory findings

The level of troponin (Tn, Tn-I: 22.1±7.72 ng/dL vs. 40.5±5.17 ng/dL, p=0.05, Tn-T: 2.1±0.38 mg/dL vs. 4.5±0.88 mg/dL, p=0.011 for Group I and Group II, respectively) and C-reactive protein (CRP, 3.8±0.48 mg/dL vs. 9.9±1.21 mg/dL, p<0.001 for Group I and Group II, respectively) were lower in Group I than in Group II (Table 2).

Coronary angiographic findings

There were no significant differences in the CAG findings except for the less frequent left main stem disease in Group I than Group II (0.7% vs. 34.3%, for Group I and Group II, respectively p=0.004) (Table 3).

Percutaneous coronary intervention and coronary artery bypass graft

In procedural characteristics, there were no significant difference for the "door to needle" time or for the "door to balloon time", but there was more PCI performed for Group I (80.7% vs. 14.7%, for Group II and Group II, respectively p<0.001) and IABP insertion (19.1% vs 9.2%, for Group I and Group II, respectively p=0.043), and there was more TIMI 3 flow after PCI observed in Group I than Group II (77.1% vs. 41.1%, for Group I and Group II, respectively p=0.044) (Table 4).

The in-hospital and long-term mortality rate according to PCI, CABG and medical treatment were analyzed (Table 5).

Major adverse cardiac events (MACE) during in-hospital and long-term clinical follow up

One hundred nineteen (46.7%) patients died during the in-hospital period and 139 patients (54.5%) had reperfusion therapy such as PCI or CABG. The mortality rate after reperfusion therapy was 17.2%, so about a 30% of mortality reduction was observed after reperfusion therapy (the total mortality rate was 46.7% and the mortality rate after reperfusion therapy was 17.2%). According to binary logistic regression analysis, the factor related to the in-hospital mortality was TIMI 3 flow after PCI (p<0.001, OR=12.40) (Table 6). On the one-year follow-up of the surviving patients, there were 2 cases of recurrent MI and 5 cases of target lesion revascularization due to recurrent ischemia.

DISCUSSION

Cardiogenic shock resulting from acute myocardial infarction is a serious complication with a high mortality rate. According to Goldberg et al[9], the incidence of CS was 7.1% for all the AMI patients they studied from 1975 to 1997, and in the GUSTO-III[10] trial, 5.2~5.5% of the AMI patient that underwent thrombolytic therapy experienced CS.

At Chonnam National University Hospital, CS occurred in 8.6% of the 201 AMI patient treated with PCI from 1997 to

Table 6. Binary logistic regression analysis for cardiac death during long-term clinical follow-up

	p value	OR	95% CI
PCI	0.67	1.46	0.25~8.49
Low TIMI flow after PCI	<0.001	12.40	3.32~46.39
Age>70 years	0.86	0.90	0.28~2.89
Old MI history	0.55	0.43	0.03~6.89
DM	0.49	1.64	0.39~6.83
EF<40%	0.38	0.58	0.17~1.96
CK>10 fold increase	0.49	0.63	0.17~2.36
CRP>1 mg/dL	0.87	0.00	0.00~7.13
Multi-vessel disease	0.92	1.07	0.18~4.00
Left main disease	0.86	0.00	0.00~1.09
IABP insertion	0.19	0.32	0.05~1.87
CABG	0.90	0.22	0.01~0.25

PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; DM, diabetes mellitus; EF, ejection fraction; CK, creatine kinase; CRP, C-reactive protein; IABP, intraaortic balloon pump; CABG, coronary artery bypass graft

1999, and there were more CS patients in the rescue PCI patients than the primary PCI patients (22.6% vs. 6.2%, respectively)[11]. Although the incidence of CS was decreased with early treatment, the incidence of CS was still high (20.1%) in our study.

According to Goldberg et al[9], the mortality rate of CS has been highly decreased, especially after 1990: the in-hospital mortality rate was 70% in 1975~1990, 61% in 1993, and 59% in 1997. However, the 30-day mortality rate was still high in cases of thrombolytic therapy[10]. In this study, there were 119 in-hospital deaths (46.7%) and it was relatively high in the recent period.

Hands et al[12] have reported that a history of diabetes mellitus and previous myocardial infarctions were associated with the in-hospital development of cardiogenic shock. Other studies have reported that old age, diabetes mellitus, previous myocardial infarction, a left ventricular ejection fraction on hospital admission of less than 35%, large infarct as estimated from a serial enzyme assay, presence of left anterior descending artery occlusion or multiple vessel disease, prolonged occlusion of infarct related artery, decreased left ventricular ejection fraction, and high creatine kinase or lactate dehydrogenase levels when admitted to the hospital were also associated with cardiogenic shock[13, 14].

The most common cause of CS after AMI is left ventricular failure (74.5%), and other causes are mitral regurgitation, ventricular septal rupture and right ventricular infarction etc[15]. In addition, it is well known that an elevated C-reactive protein level (CRP) is associated with the occurrence of acute coronary syndrome[16-18]. In Chonnam National University Hospital, we found that a high level of CRP was related with a poor prognosis for ACS patients[19].

According to the TRandolapril Cardiac Evaluation (TRACE)

registry[20], 59% of CS occurred within 48 hours after AMI, and according to another study, CS occurred earlier in the ST segment elevated group than the non-elevated group, so it is important to aggressively treat CS during the early in-hospital period[10].

In this study, there was no difference in risk factors such as hypertension, diabetes and hyperlipidemia, but old age, a previous coronary artery disease history and high levels of troponin and CRP were associated with death after AMI complicated with CS. So, it was thought that aggressive lipid lowering therapy to reduce arterial inflammatory changes may decrease the incidence of CS after AMI.

Hochman et al[21] reported that for patients with CS, emergency revascularization did not significantly reduce the overall mortality at 30 days, but it did show a significant survival benefit (50.3% vs. 63.1%, respectively, p=0.027) after six months. Holmes et al[10] reported that the mortality rate for CS was 32% when revascularization was done, but the mortality rate was 75% in thrombolytic therapy group. In the SHOCK trial[21], early revascularization reduced the mortality for patients less than 75 years; the 30-day mortality rate was 41.4% in the revascularization group and 56.8% in the medical therapy group. So it was concluded that early revascularization should be strongly considered for patients with AMI complicated by CS.

In this study, 83.6% of patients in group I underwent revascularization, whereas only 24.5% of patients in group II underwent revascularization, and the revascularization therapy resulted in about a 30% reduction of the in-hospital mortality, so the revascularization strategy is suggested to improve the short term and long term survival. Yet group II included critically ill patients were not able to undergo reperfusion therapy; thus it is hard to draw a correct conclusion.

Recently, the TIME trial[22] reported that patients aged 75

years or older with angina, despite standard drug therapy, benefited more from revascularization than from optimal medical therapy in terms of their symptom relief and quality of life. Therefore, old patients should be offered invasive assessment, despite their high risk profile, and this should be followed by revascularization when feasible.

For the early revascularization strategy, several studies have shown that the mortality rate depends on the "door to needle time", the TIMI flow grade after revascularization, the presence of more than two vessel disease, and left main stem lesions: these were all associated with a higher mortality rate[23-26].

In this study, there were no significant difference in the "door to needle" time or the "door to balloon" time, but the TIMI flow grade was significantly lower in group II, and left main stem lesions were more common in group II. Also, as we found on the multivariate analysis, obtaining adequate TIMI 3 flow after PCI was the most important factor to reduce in-hospital mortality.

On the other hand, Barron et al[27] reported that patients with AMI complicated by CS may substantially benefit from an intra-aortic balloon pump (IABP) procedure when this is used in combination with thrombolytic therapy. The use of IABP before primary PCI for AMI in all patients with CS has been shown to be beneficial in patients with heart failure or depressed left ventricular function[28-30]. In this study, more IABP insertion procedures were done in the survival group, so IABP insertion was beneficial for the primary PCI of CS after AMI. But we could not perform IABP in many cases because of the limitations of the Korean medical insurance reimbursement.

There were some limitations of this study. First, CS occurred at a relatively high rate (20%) in AMI patient, and this was mainly because critically ill patients were transferred in from local hospitals to our hospital. Second, the mean ejection fraction of the enrolled patients was relatively high because the echocardiogram was performed after emergency PCI in many patients. Third, the selection bias could have occurred because this is not a prospective study, and it is possible that patient's condition with CS was so poor that we did not perform diagnostic work ups and extensive procedures.

In conclusion, early reperfusion therapy using PCI with IABP insertion and the acquisition of adequate TIMI 3 flow after PCI may reduce the mortality from CS. A prospective randomized study concerning the prognostic significance of CS and PCI in elderly people more than 75 years should be performed.

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