

Combined ECG, Echocardiographic, and Biomarker Criteria for Diagnosing Acute Myocardial Infarction in Out-of-Hospital Cardiac Arrest Patients

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Received: March 18, 2014

Revised: August 19, 2014

Accepted: September 1, 2014

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The authors have no financial conflicts of interest.

Purpose: Acute coronary lesions commonly trigger out-of-hospital cardiac arrest (OHCA). However, the prevalence of coronary artery disease (CAD) in Asian patients with OHCA and whether electrocardiogram (ECG) and other findings might predict acute myocardial infarction (AMI) have not been fully elucidated. **Materials and Methods:** Of 284 consecutive resuscitated OHCA patients seen between January 2006 and July 2013, we enrolled 135 patients who had undergone coronary evaluation. ECGs, echocardiography, and biomarkers were compared between patients with or without CAD. **Results:** We included 135 consecutive patients aged 54 years (interquartile range 45–65) with sustained return of spontaneous circulation after OHCA between 2006 and 2012. Sixty six (45%) patients had CAD. The initial rhythm was shockable and non-shockable in 110 (81%) and 25 (19%) patients, respectively. ST-segment elevation predicted CAD with 42% sensitivity, 87% specificity, and 65% accuracy. ST elevation and/or regional wall motion abnormality (RWMA) showed 68% sensitivity, 52% specificity, and 70% accuracy in the prediction of CAD. Finally, a combination of ST elevation and/or RWMA and/or troponin T elevation predicted CAD with 94% sensitivity, 17% specificity, and 55% accuracy. **Conclusion:** In patients with OHCA without obvious non-cardiac causes, selection for coronary angiogram based on the combined criterion could detect 94% of CADs. However, compared with ECG only criteria, the combined criterion failed to improve diagnostic accuracy with a lower specificity.

Key Words: Cardiac arrest, myocardial infarction, electrocardiography, diagnosis

INTRODUCTION

Sudden out-of-hospital cardiac arrest (OHCA) is a severe condition with a poor survival, estimated at 33% in 1990 and at 38% in 1997 in patients admitted to the hospital.^{1,2} Recent data from large studies estimated a mortality rate between 58% and 86% at one month after admission to the hospital in 3853 OHCA patients³ and a mortality rate of 71% in 24132 patients admitted to intensive care units after in-hospital or OHCA.⁴ Acute myocardial infarction (AMI) is known to be the most

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common cause of sudden cardiac arrest,^{2,5,6} and successful coronary angioplasty may improve survival in these patients.^{2,7,8} Even if the role of coronary angioplasty in OHCA is still under debate,⁹⁻¹² diagnosing and treating an ongoing AMI as early as possible after OHCA appears to be crucial to lowering mortality.

Determining whether to perform primary percutaneous coronary intervention (PCI) is classically based on electrocardiographic (ECG) findings after recovery of spontaneous circulation (ROSC). However, ECG changes may be difficult to interpret in patients resuscitated from OHCA, and the predictive value of ECG for acute coronary artery occlusion in this setting is poor.^{2,13} Therefore, it can be difficult to select candidates for primary PCI, especially in patients without ST-segment elevation, in whom this strategy has occasionally been challenged.⁹ Although echocardiography and biomarkers are commonly used in OHCA patients, their role in predicting the etiology of cardiac arrest has not been evaluated. In addition, the predictive value of diagnostic tools for acute coronary artery occlusion after ROSC may differ in Asian patients, compared to other races, due to differences in the prevalence of coronary artery disease (CAD).¹⁴⁻¹⁶

We hypothesized that ECG, echocardiographic, and biomarker changes might be useful in establishing an indication for emergency coronary angiogram (ECA). The need for triage is justified by the fact that not all OHCA patients benefit from ECA^{10,11} and by the limited availability and the cost of the technique. This study was performed to evaluate the efficacy and accuracy of combined criteria including ECG, echocardiography and biomarkers for predicting CAD as the cause of OHCA in resuscitated patients.

MATERIALS AND METHODS

Study design and population

This study analyzed data from a single-center registry of OHCA patients, and was conducted according to the principles of the Declaration of Helsinki (2008 version) of the World Medical Association. The Ethics Committee of our institution approved the study, and all subjects provided informed consent.

All consecutive patients resuscitated from an OHCA who had been admitted to our center between 2006 and 2012 were screened for inclusion. Patients aged 18 years or older with sustained ROSC (defined as >20 min)¹⁷ and who had undergone coronary evaluation by coronary angiography or

coronary computed tomography angiography (CCTA) were enrolled. Patients with any obvious extra-cardiac cause of OHCA or without available ECG traces post-ROSC were excluded. For each patient who fulfilled the inclusion criteria, demographic, clinical, and angiographic data were collected by reviewing clinical records. The initial rhythm of the OHCA was considered the heart rhythm present when a monitor or defibrillator was attached to the patient after collapse.¹⁷

On arrival at the hospital, an ECA with primary PCI, if indicated, was performed in all patients. The indication of ECA was ST-elevation on initial ECG. In patients without obvious indication for ECA, coronary angiography or CCTA was performed electively to rule out CAD. Patients were divided into two groups: Group 1, patients with CAD as a final cause of OHCA, and Group 2, patients who had other factors as a cause of OHCA. After ROSC, patients were transferred to the intensive care unit for standard management and optimal hypothermia. Patients discharged with a cerebral performance category (CPC)¹⁸ of 1 or 2 were counted as survivors with favorable neurological outcome, and patients with a CPC of 3 were regarded as survivors with unfavorable neurological outcome.

A diagnosis of AMI was made upon evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia according to the third universal definition of myocardial infarction endorsed by the European Society of Cardiology in 2012.¹⁹

Angiographic analysis

Coronary angiographies were retrospectively analyzed by two independent experienced observers and disagreement was arbitrated by a third party. Coronary flow was assessed according to the Thrombolysis in Myocardial Infarction (TIMI) classification.²⁰ Coronary angioplasty was considered successful if residual stenosis was <50% with TIMI 3 flow.²¹ In patients who were diagnosed by CCTA, coronary stenosis with a diameter reduction \geq 50% was considered significant.

ECG analysis

The reference ECG used for analysis was the first interpretable 12-lead ECG obtained after sustained ROSC (\geq 20 minutes). The reference ECGs were retrospectively analyzed by two experienced observers independently of the ECA and disagreement was arbitrated by a third party.

Recorded ECG changes included ST-elevation, ST-de-

pression, presence of left (LBBB) and right (RBBB) bundle branch block, hyperacute T wave, and a non-specific wide QRS complex. ST-elevation was considered significant if present in two or more contiguous ECG leads with an amplitude ≥ 2 mV for men and 0.15 mV for women in V2 or V3, and ≥ 0.1 mV in the rest of the leads.^{19,22} ST-depression was considered significant if ≥ 0.1 mV in two or more contiguous leads.²³ Reciprocal changes were defined as ST-depression ≥ 1 mm in leads reciprocal to those showing ST-elevation. LBBB was defined as QRS duration >120 ms with QS or rS pattern in V1 and broad R waves in lead I, V5, and V6. ST-elevation or depression and LBBB were analyzed because they represent major criteria of acute cardiac ischemia diagnosis.²² RBBB was defined as QRS duration ≥ 120 ms with rSR' complex in V1 and V2 and S wave in lead I and V5 or V6, and was analyzed because it is a conduction disturbance occurring in large AMI.²⁴ Hyperacute T waves were defined as T waves greater than 5 mm in the limb leads and greater than 10 mm in the precordial leads.

A non-specific wide QRS complex was defined as QRS duration ≥ 120 ms without LBBB or RBBB morphology. It was analyzed as a component of selection criteria for ECA because abnormal resting repolarization following wide QRS prevents accurate interpretation of ECG changes related to ischemia,²⁵ and AMI may be present in these patients. Moreover, myocardial ischemia is associated with slowing of ventricular conduction *in vitro*²⁶ and can increase QRS duration to up to 160 ms in patients without bundle branch block.²⁷

Brugada syndrome was definitively diagnosed when a type 1 ST-segment elevation was observed in more than right precordial lead (V1 to V3) in the presence or absence of a sodium channel-blocking agent: type 1 is diagnostic of Brugada syndrome and is characterized by a coved ST-segment elevation ≥ 2 mm (0.2 mV), followed by a negative T wave.²⁵ Early repolarization is characterized by an elevation of the junction between the end of the QRS complex and the beginning of the ST segment (i.e., the J point) from baseline on a standard 12-lead electrocardiogram (ECG).^{28,29}

Echocardiographic and biomarker analysis

The reference echocardiographic data used for analysis were the first interpretable data obtained after sustained ROSC. Resting 2-D echocardiogram and tissue Doppler measurements were obtained. Regional wall motion abnormality was evaluated by two experienced cardiologists. The value of biomarkers (Troponin T and CK-MB) sampled at the

time of admission were used. The normal reference values for troponin T and CK-MB were 0.0 to 0.014 ng/mL and 0.0 to 5.0 ng/mL, respectively.

Statistical analysis

Continuous variables are expressed as medians and interquartile range (IQR 25–75). Differences in continuous variables were assessed using Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables are reported as absolute numbers and percentages. The chi-square test and Fisher's exact test were used to assess differences in categorical variables. The sensitivity and specificity of ECG for the detection of CAD were determined. The SPSS statistical package (SPSS Inc., Chicago, IL, USA) was used to perform all statistical evaluations. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

The selection of the study population and the final outcomes therein are shown in Fig. 1. Most patients were men aged 54 (45–65) years old, and 19% had a previous history of CAD. CAD as a cause of OHCA (Group 1) was noted in 49% ($n=66$) of the total study population. In Group 1, 42% of patients had ST-elevation myocardial infarction (STEMI), and non-ST elevation myocardial infarction (NSTEMI) was found in the rest of patients. Ventricular fibrillation or ventricular tachycardia as an initial rhythm was observed in 50 (76%) out of 66 patients in Group 1. In patients without CAD as a cause of OHCA (Group 2, $n=69$), 60 (87%) patients had ventricular fibrillation or ventricular tachycardia as an initial rhythm. Causes of OHCA in Group 2 were variant angina ($n=24$), idiopathic ventricular fibrillation ($n=14$), Brugada syndrome ($n=12$), long QT syndrome ($n=7$), heart failure ($n=7$), J wave syndrome ($n=3$), hypertrophic cardiomyopathy ($n=1$), and Wolf-Parkinson-White syndrome ($n=1$). A comparison of clinical characteristics between Group 1 and 2 is presented in Table 1. Compared with Group 2, patients in Group 1 were older and more frequently had hypertension, diabetes, hypercholesterolemia, and a history of CAD (p -value all <0.05).

Coronary angiogram analysis and AMI

Of the 135 patients, 39% had a normal coronary artery and 6% had non-significant coronary stenosis. Significant steno-

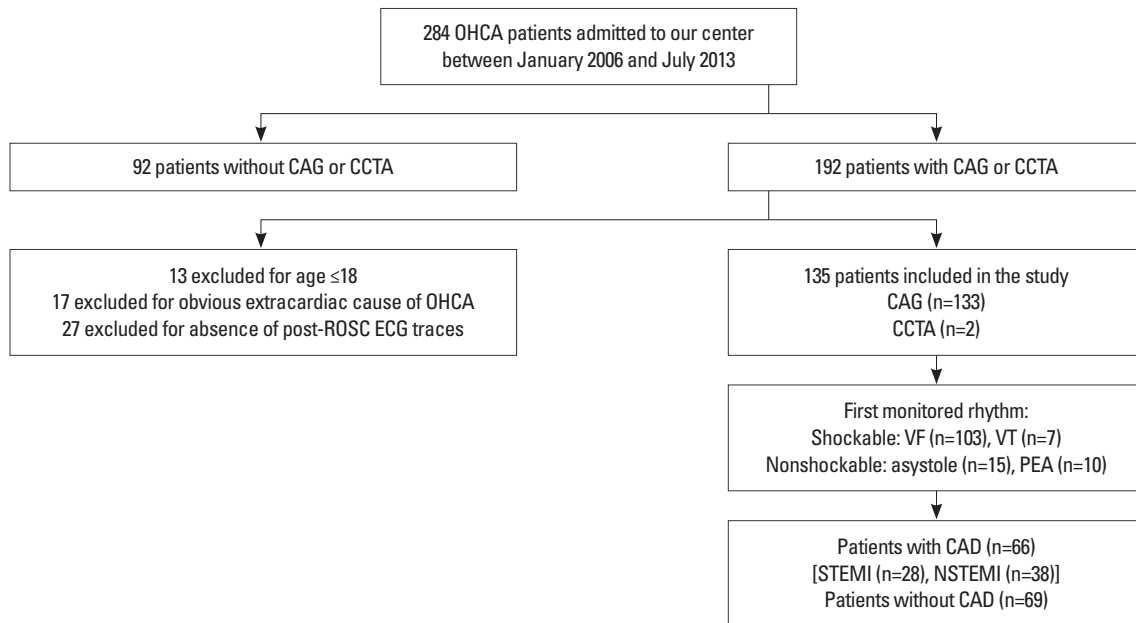


Fig. 1. Flow chart of OHCA patients included in the study. CAD, coronary artery disease; CAG, coronary angiography; CCTA, coronary CT angiography; ECG, electrocardiogram; NSTEMI, non-ST-segment elevation myocardial infarction; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; STEMI, ST-segment elevation myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

sis of \geq one coronary artery was observed in 72 (53%) patients, including 66 patients with CAD as a cause of OHCA (Group 1). In Group 1, the left anterior descending artery (LAD) was involved in 82%, the right coronary artery (RCA) in 70%, and the left circumflex artery (LCx) in 56%. In 68% of the patients, two or three arteries were simultaneously involved. In Group 2, two patients had two-vessel disease and four had one vessel disease. In these patients, five were diagnosed as having variant angina after provocation test, and one was diagnosed as having idiopathic ventricular fibrillation on electrophysiological study. Although these patients had CAD, these lesions were not considered as a culprit lesion after angiographic analysis.

In all patients, ECA was performed in 41 (30%) patients, and 11 of these 41 patients did not have CAD. One patient with Brugada syndrome was misdiagnosed with STEMI and had undergone ECA. Emergency angioplasty was successful in 83% patients. Among patients with STEMI ($n=28$), direct PCI was performed in 23 (82%) patients. The reasons for delay in coronary angiography in STEMI patients were as follows: coma ($n=3$) and refusal of the family ($n=2$). CCTA was performed in two patients (idiopathic DCMP, $n=1$; long QT syndrome, $n=1$) without obvious indications for ECA.

Management of the patients and outcome

Cardiac arrest was experienced in 95% and basic life sup-

port was performed in 97%. Initial rhythm was ventricular fibrillation or tachycardia in 81% patients. Therapeutic hypothermia (initially performed in 2008) was performed in 24% of the patients. Among all patients, 116 (86%) survived to hospital discharge (CPC 1–3).

ECG data

Among the 66 patients in Group 1, 42% had ST-elevation (Table 2): 54% in the anterior leads, 57% in the inferior leads, and 11% in the lateral leads (21% of Group 1 had ST-elevation in two territories). Reciprocal changes were present in 25% (7 patients) of Group 1.

Thirty eight patients (58% of Group 1) had NSTEMI: 17 had ST-depression, one had LBBB, and seven had non-specific wide QRS (the culprit artery in these patients was the left main coronary). In Group 1, 6 patients had RBBB without significant ST segment and three had a hyperacute T wave. Among all patients, six (4%) had supraventricular arrhythmia (atrial fibrillation) on the reference ECG. Serial change of ECG also did not discriminate CAD as a cause of OHCA successfully (Supplementary Table 1, only online).

Echocardiography and biomarkers data

A regional wall motion abnormality was more frequently observed in Group 1 than Group 2 ($p<0.001$). There was a trend towards an increased troponin T in Group 1, compared to Group 2. Nevertheless, there was no difference in the in-

Table 1. Characteristics and Demographics of the Study Population

Variable	Total	Group 1 (n=66)	Group 2 (n=69)	p value
Age, yrs	54 (45–65)	61 (53–70)	48 (34–56)	<0.001
Male sex	119 (88)	61 (92)	58 (84)	0.133
Risk factors				
Hypertension	51 (38)	36 (55)	15 (22)	<0.001
Diabetes	30 (22)	25 (38)	5 (7)	<0.001
Hypercholesterolemia	8 (6)	8 (12)	0	0.003
Current smoker	40 (30)	16 (24)	24 (35)	0.180
Family history of sudden cardiac death	14 (10)	3 (5)	11 (16)	0.030
History of coronary artery disease	25 (19)	20 (30)	5 (7)	<0.001
Unknown				
Witnessed cardiac arrest	128 (95)	63 (96)	65 (94)	>0.99
Place of cardiac arrest				
Public place	65 (48)	30 (45)	35 (51)	0.540
Home	70 (52)	36 (55)	34 (49)	0.540
Basic life support	131 (97)	64 (97)	67 (97)	>0.99
Initial rhythm				
Ventricular fibrillation	103 (76)	47 (71)	56 (81)	0.174
Ventricular tachycardia	7 (5)	3 (5)	4 (6)	>0.99
Pulseless electrical activity	10 (7)	8 (12)	2 (3)	0.052
Asystole	15 (11)	8 (12)	7 (10)	0.715
Arrest to ROSC duration (mins)	46 (34)	23 (8–31)	23 (10–33)	0.808

ROSC, recovery of spontaneous circulation.

Table 2. Serial ECG, Biomarker, and Echocardiography Findings after Initial Resuscitation

Variable, n (%)	Group 1 (n=66)	Group 2 (n=69)	p value
ST-segment elevation	28 (42)	9 (13)	<0.001
ST-segment depression without ST-segment elevation	35 (53)	21 (30)	0.008
Left bundle branch block	3 (5)	7 (10)	0.330
Nonspecific wide QRS complex	11 (17)	4 (6)	0.050
RBBB without other significant changes	15 (23)	11 (16)	0.320
Hyperacute T wave	3 (5)	2 (3)	0.68
Patients without significant ECG changes	6 (9)	23 (33)	0.001
RWMA	41 (64)	12 (18)	<0.001
LAD territory	10 (24)	1 (8)	
LCx territory	3 (7)	2 (17)	
RCA territory	12 (29)	0 (0)	
Multi-vessel territory	14 (34)	0 (0)	
Not compatible with coronary territory	2 (5)	9 (75)	
Troponin T elevation	41 (64)	27 (49)	0.100
Troponin T (mean±SD, ng/mL)	0.32±0.69	0.13±0.37	0.091
CK-MB (mean±SD, ng/mL)	18.6±75.5	7.5±12.1	0.244

ECG, electrocardiogram; LAD, left anterior descending artery; LCx, left circumflex artery; RWMA, regional wall motion abnormality; SD, standard deviation; RBBB, right bundle branch block; RCA, right coronary artery.

cidence of troponin T elevation and mean value of CK-MB between the two groups ($p=0.10$, and 0.244 , respectively).

Combined ECG and other test data

While ST-elevation predicted CAD as the cause of OHCA with a sensitivity of 42% and a specificity of 87%, the com-

bined criterion (ST-elevation and/or depression) showed a sensitivity of 68% and a specificity of 52% (Table 3). The extended criterion and/or elevated troponin T increased the sensitivity to diagnose CAD as the cause of OHCA to 94% with a decreased specificity of 17%. Therefore, the addition of echocardiography did not improve diagnostic accuracy.

DISCUSSION

Major findings

The main finding of this study is that the prevalence of CAD was lower in Asian patients undergoing coronary evaluation after resuscitation for OHCA. Second, the ST-segment and/or depression provided important information for primary PCI in a patient population with a relatively low incidence of CAD. Third, the combined ECG, echocardiography and biomarker criteria showed a sensitivity of 94% for the selection of patients with AMI; however, the specificity of the test was low. This is the first evaluation of such combined criteria in patients resuscitated from an OHCA. Our study suggests that ischemic changes in ECG should be primarily considered when deciding whether to perform ECA.

Low incidence of CAD in Asian patients with ROSC from OHCA

AMI is the most frequent cause of OHCA, in nearly 37.5% to 70% of all cases.^{2,9,10,30} Many studies from Western countries have confirmed a high incidence of obstructive CAD and the presence of one or more coronary occlusion in patients with aborted sudden cardiac death.^{2,9,30} In a recent study, significant CAD was observed in more than 80% of patients referred for coronary angiography.³¹ However, in our study, CAD was found in 53% of total study population, and only 49% of patients had CAD as a cause of OHCA. The relatively high proportion of primary rhythm disorders in this study is also noteworthy. Inherited arrhythmogenic diseases occur in the absence of structural heart disease, and sudden cardiac death is often the first manifestation.

The prediction of CAD using ECG in patients after ROSC

ST-segment elevation on post-ROSC ECG was sensitive for the diagnosis of STEMI. ST elevation on post-ROSC ECG was associated with the presence of a presumed acute culprit lesion in 76% of cases. This is consistent with a recent study, where ST-segment analysis on a post-ROSC ECG showed a good positive predictive value, but a low negative predictive value, in diagnosing the presence of acute or presumed recent coronary artery lesions (85% and 67%, respectively).¹³ Sideris, et al.³² evaluated the diagnostic characteristics of post-resuscitation ECG changes and found that by using combined ECG criteria AMI can be detected with high sensitivity.³²

Although recent studies found coronary angiography and PCI to be independent predictors of in-hospital survival after OHCA,^{31,33} there are no specific recommendations for the need for routine performance or specific timing of coronary angiography. In this study, total occlusive lesions were found in 16.8% (18/107) of patients without STEMI, indicating their role as an indication for urgent invasive coronary intervention regardless of the presence of ST elevation. Recent guidelines also support this concept.³⁴ Furthermore, because some ECG changes, as in Brugada syndrome or J wave syndrome, are hard to distinguish from ST-elevation due to STEMI, a more offensive approach with ECA is reasonable.

The prediction of STEMI and CAD using other tests in patients after ROSC

Several studies have reported that an acute culprit lesion may be present when angiography is performed, even in the absence of obvious ischemic ECG changes.^{32,34} In this study,

Table 3. Combinations of Different ECG Criteria and Echocardiographic Findings Used to Differentiate CAD Patients

	Sensitivity (%) (CI)	Specificity (%) (CI)	PPV (%) (CI)	NPV (%) (CI)	Accuracy (%)
ST-elevation (n=37)	42 (30–55)	87 (77–94)	76 (59–88)	61 (51–71)	65
ST-elevation or depression (n=78)	68 (56–79)	52 (40–64)	58 (46–69)	63 (49–76)	60
ST elevation with or without RWMA (n=66)	70 (57–80)	71 (59–81)	70 (57–80)	71 (58–81)	70
ST elevation with RWMA or TnT (n=108)	90 (79–96)	29 (19–41)	55 (45–64)	74 (54–89)	59
Combined ST-elevation or depression with RWMA (n= 95)	83 (72–91)	42 (30–55)	58 (47–68)	73 (56–85)	62
Combined ST-elevation or depression with RWMA or TnT (n=119)	94 (85–98)	17 (9–28)	52 (43–61)	75 (48–93)	55

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; ECG, electrocardiogram; CAD, coronary artery disease; RWMA, regional wall motion abnormality.

combination of EKG, echocardiography and biomarkers criteria showed 94% sensitivity in diagnosing CAD, although the specificity was decreased substantially. However, no large cohort study has evaluated the efficiency of echocardiography in diagnosing CAD in OHCA patients.

Study limitations

Our study has several potential limitations. First, post-ROSC ECG has been observed to change over time and may show a STEMI not noted after ROSC. Because only patients who underwent angiographic evaluation were included, many patients who were too unstable to undergo invasive procedures or who died prior to the procedure were excluded. Therefore, it is possible that the incidence of CAD was underestimated. Second, the low specificity of cardiac markers for identifying CAD may be caused by cardiac masses. The aim of this study was to find patients who require immediate intervention based on available evidence at the time of arrival at the emergency room. Therefore, we considered TnT above the normal reference value as an elevated cardiac marker. A different value for TnT might have improved the diagnostic accuracy. Third, the relatively low application of therapeutic hypothermia might affect the results of the study. Lastly, this is a single center study. A multicenter study is warranted to further elucidate the prognostic value of ECGs, cardiac marker, and echocardiographic findings.

Conclusion

The prevalence of AMI in resuscitated Asian patients was much lower than that in Western patients. ST elevation was a good predictor of STEMI, while other combined criteria, including RWMA on echocardiography, were not sufficient to exclude CAD as a trigger of OHCA. Therefore, emergent coronary angiography should be performed without delay to detect culprit coronary lesions and to allow for their proper management.

ACKNOWLEDGEMENTS

This study was supported in part by the Basic Science Research Program through the National Research Foundation of Korea, funded by the Ministry of Education, Science and Technology (NRF-2010-0021993, NRF-2012R1A2A2A02045367), and the Korean Healthcare Technology R&D Project, Ministry of Health & Welfare (HI12C1552).

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