

Impact of Direct Cardiovascular Laboratory Activation by Emergency Physicians on False-Positive Activation Rates

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Abstract

Introduction: Door-to-balloon (DTB) time is critical to ST elevation myocardial infarction (STEMI) patients' survival. Although DTB time is reduced with direct cardiovascular laboratory (CVL) activation by emergency physicians, concerns regarding false-positive activation remain. We evaluate false-positive rates before and after direct CVL activation and factors associated with false-positive activations. **Materials and Methods:** This is a retrospective single centre study of all emergency CVL activation 3 years before and after introduction of direct activation in July 2007. False-positive activation is defined as either: 1) absence of culprit vessel with coronary artery thrombus or ulceration, or 2) presence of chronic total occlusion of culprit vessel, with no cardiac biomarker elevations and no regional wall abnormalities. All false-positive cases were verified by reviewing their coronary angiograms and patient records. **Results:** A total of 1809 subjects were recruited; 84 (4.64%) identified as false-positives. Incidence of false-positive before and after direct activation was 4.1% and 5.1% respectively, which was not significant ($P = 0.315$). In multivariate logistic regression analysis, factors associated with false-positive were: female (odds ratio (OR): 2.104 [1.247-3.548], $P = 0.005$), absence of chest pain (OR: 5.369 [3.024-9.531], $P < 0.0001$) and presence of only left bundle branch block (LBBB) as indication for activation (OR: 65.691 [19.870-217.179], $P < 0.0001$). **Conclusion:** Improvement in DTB time with direct CVL activation by emergency physicians is not associated with increased false-positive activations. Factors associated with false-positive, especially lack of chest pain or LBBB, can be taken into account to optimise STEMI management.

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Introduction

Door-to-balloon (DTB) time has been shown to be a critical factor in the survival of patients with ST-elevation myocardial infarction (STEMI). A delay in DTB time is associated with higher adjusted risk of in-hospital mortality.^{1,2} Consensus guideline recommends a DTB or first medical contact (FMC) to device time goal of 90 minutes or less for STEMI patients to improve their survival.³ Although direct activation of cardiovascular laboratory (CVL) by emergency physicians without routine cardiology consultation has been shown to reduce DTB time,⁴⁻⁹ concerns regarding increased rate of false-positive activation with this strategy remain. Factors such as quality metric, potential

clinical and financial consequences associated with such false alarms need to be considered too.¹⁰ As such, the main objective of this study is to evaluate the rates of false-positive activation before and after direct CVL activation. We also studied the clinical factors associated with false-positive activations.

Materials and Methods

We conducted a retrospective longitudinal study in a large single tertiary referral centre. Since July 2007, emergency physicians have been autonomously activating the CVL directly for any clinical diagnosis of acute myocardial infarction (AMI) with significant reduction of DTB.¹¹ The

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eligibility criteria for direct CVL activation by emergency physicians were as follows: ≥ 2 mm ST elevation in anterior leads for 2 or more contiguous leads or ≥ 1 mm ST elevation in inferior leads for 2 or more contiguous leads and symptom onset of < 12 hours. All patients with a clinical diagnosis of AMI who presented to the emergency department (ED) for a period of 3 years before (1 June 2004 to 1 June 2007) and 3 years after (1 August 2007 to 1 August 2010) were retrospectively included in this study. There was also a 1-month blanking period before and after the start date of direct CVL activation on 1 July 2007.

The exclusion criteria were age ≥ 80 years old; significant comorbidities or poor premorbid status; contraindications to anticoagulation or antiplatelet therapy; collapsed or in a comatose state; heparin-induced thrombocytopenia; active gastrointestinal bleed or intravenous contrast allergy.

Data Collection

All patients who had direct CVL activation from the ED were identified via records kept in the CVL. Patient demographics, clinical presentation, 12-lead electrocardiograms (ECGs), treatment and outcomes were then obtained from a combination of patient electronic records, case notes and the National Heart Centre (NHC) Singapore Cardiac Data Bank. All angiographic data were similarly obtained from NHC STEMI database and CVL report. All false-positive activation cases were identified and subsequently verified through the review of their coronary angiograms and patient records by the senior author (HKW). The study protocol was approved by the Centralised Institutional Review Board (IRB) ethics committee.

Definitions

In our study, false-positive activation was defined as either: 1) absence of culprit vessel with coronary artery thrombus or ulceration, or 2) presence of chronic total occlusion of culprit vessel, with no cardiac biomarker elevations to suggest new myocardial infarction (MI) and no regional wall abnormalities in the corresponding cardiac segments.

For each of the verified false-positive cases, the final diagnoses were made based on the following definition.

Early repolarisation variant is defined by J point elevation manifested either as terminal QRS slurring (the transition from the QRS segment to the ST-segment) or notching (a positive deflection inscribed on terminal QRS complex) associated with concave upward ST-segment elevation and prominent T waves in at least two contiguous leads with no elevation of cardiac biomarkers.^{12,13} Old MI changes were defined as history of Q wave MI with ST-segment elevation that was either demonstrated on a previous ECG

or did not show any ST-segment evolutionary changes with no elevation of cardiac biomarkers.

Perimyocarditis was defined by typical ECG findings of widespread concave ST elevation, elevation of cardiac troponin levels and suggestive clinical history of preceding fever and presence of pericardial rub on examination. Takotsubo stress cardiomyopathy was defined as characteristic apical or mid-ventricular ballooning noted on left ventriculography, reversible left ventricular systolic dysfunction without significant coronary stenosis typically preceded by a stressful event.¹⁴

Pulmonary embolism (PE) was diagnosed from computed tomographic pulmonary angiography. Left ventricular hypertrophy (LVH) was diagnosed based on ECG voltage criteria. Brugada syndrome is by ECG findings of typical coved, down-sloping ST-segment elevation of at least 2 mm in the right precordial leads (V1-3).¹⁵

Statistical Analysis

Simple comparisons between patients diagnosed with true-positive and false-positive activations were performed with χ^2 test for categorical or binary data. For normally and non-normally distributed continuous data, the t-tests and Wilcoxon rank sum tests were used respectively. For univariate and multivariate analysis, logistic regression was used with the primary outcome variable of a false-positive activation.

The statistical output is reported as an odds ratio (OR) and 95% confidence interval. Non-normally distributed variables are presented as median values and interquartile range while continuous variables are presented as means and standard deviations. A P value < 0.05 is considered statistically significant.

All statistical analysis were performed using SPSS version 20.0

Results

A total of 1864 patients were identified from the CVL records in the study period, of which, 55 patients were excluded from the study (Fig. 1). These patients were excluded for the following reasons: CVL was activated from locations other than the ED, CVL was activated during the blanking period and aborted/incomplete coronary angiograms.

In total, 1809 patients were included in the study. Among these, 84 (4.6%) were identified as false-positives. The incidence of false-positives before and after implementation of direct CVL activation was 4.1% and 5.1% respectively, which was not statistically significant ($P = 0.315$).

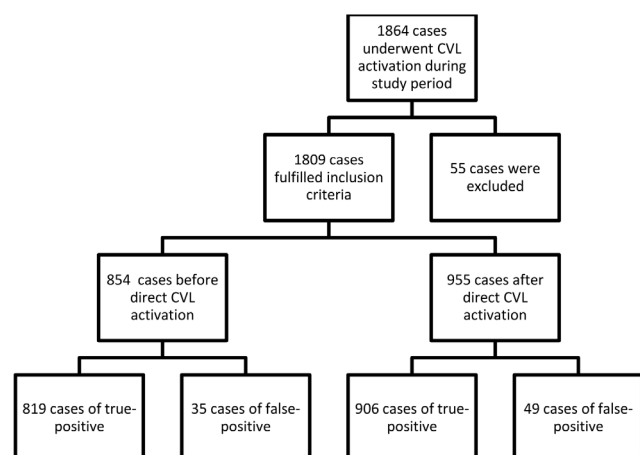


Fig. 1. Number of patients screened and the eventual study population.

Tables 1 and 2 show the univariate analysis of the patient's demographics, cardiovascular risk factors, previous cardiac history (including previous MI, previous coronary angioplasty or coronary artery bypass graft [CABG]), and clinical presentations. Female gender, non-smoker, absence of chest pain upon presentation at ED and presence of only left bundle branch block (LBBB) in ECG were associated with increased rates of false-positive CVL activation.

Table 1. Baseline Characteristics Comparison between True- and False-Positive STEMI Activation

Demographics	True-Positive (n = 1725)	False-Positive (n = 84)	P Value
Age, mean (SD), years	58.5 (11.5)	59.0 (12.6)	0.744
Female sex, no (%)	285 (16.5)	27 (32.1)	0.001
Race			
Chinese (%)	1103 (63.9)	60 (71.4)	0.199
Malay (%)	251 (14.5)	7 (8.3)	0.148
Indian (%)	281 (16.2)	11 (13.0)	0.543
Cardiovascular risk factors			
Non-smoker (%)	965 (55.9)	67 (79.7)	<0.005
Hypertension (%)	971 (56.3)	41 (48.8)	0.179
Diabetes (%)	530 (30.7)	21 (25.0)	0.331
Hyperlipidaemia (%)	914 (53%)	37 (44%)	0.118
Family history of CAD (%)	222 (12.8)	5 (5.9)	0.064
Previous cardiac history			
MI (%)	170 (9.8)	10 (11.9)	0.573
PCI (%)	254 (14.7)	14 (16.7)	0.637
CABG (%)	54 (3.1)	4 (4.8)	0.342

CABG: Coronary artery bypass graft; CAD: Coronary heart disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention

After multivariate logistic regression analysis, female gender (OR: 2.1 [1.2-3.5], $P=0.005$), absence of chest pain (OR: 5.4 [3.0-9.5], $P<0.001$) and presence of only LBBB (OR: 65.7 [19.9-217.2], $P<0.001$) were independently associated with an increased odds of false-positive CVL activation.

In addition, we compared the clinical outcome of patients before and after implementation of direct CVL activation. There was no increase in mean length of stay, non-Killip 4 cardiac mortality and in lab complications between the 2 groups as shown in Table 3.

Final diagnoses of all 84 false-positive CVL activations are listed in Table 4. Common causes of false-positive activation in our study were early repolarisation ECG

Table 2. Clinical Factors Comparison between True-Positive and False-Positive STEMI Activation

Clinical Factors	True-Positive (n = 1725)	False-Positive (n = 84)	P Value
Indications for CVL activation			
Chest pain	1629 (94.4)	60 (71.4)	
Absence of chest pain (%)	96 (5.6)	24 (28.6)	0.001
Collapse	36 (2.0)	4 (4.7)	0.111
ECG changes	55 (3.1)	17 (20.2)	<0.001
Arrhythmias	2 (0.1)	2 (2.3)	0.012
Acute pulmonary oedema	3 (0.1)	0 (0)	1.000
After office hours presentation (%)	790 (45.8)	30 (35.7)	0.073
ECG localisation on presentation at ED			
Anterior (%)	806 (46.7)	35 (41.6)	0.373
Inferior (%)	787 (45.6)	16 (19.0)	0.000
Lateral only (%)	43 (2.5)	0 (0.0)	0.262
Posterior only (%)	6 (0.3)	0 (0.0)	1.000
LBBB only (%)	4 (0.2)	14 (16.7)	0.001

CVL: Cardiovascular laboratory; ECG: Electrocardiogram; ED: Emergency department; LBBB: Left bundle branch block

Table 3. Index Hospitalisation Outcomes Before and After Direct CVL Activation

Outcome	Before (n = 854)	After (n = 955)	P Value
Length of stay, mean, days	5.5	5.81	0.446
In lab complications (%)	98 (11.0)	37 (3.9)	<0.0001
Non-Killip 4 cardiac mortality (%)	16 (1.9)	17 (1.8)	1

CVL: Cardiovascular laboratory

Table 4. Breakdown of Causes of False-Positive CVL Activation in Our Series

Final Diagnosis	No. (n = 84)
Early repolarisation	23
Old myocardial infarction changes	14
Left bundle branch block	12
Perimyocarditis	8
Persistent chest pain with no ECG changes	7
Takotsubo cardiomyopathy	5
Pulmonary embolism	3
Subarachnoid haemorrhage	2
Ventricular tachycardia	2
Pulseless electrical activity	1
Brugada syndrome	1
Left ventricular hypertrophy	1
Coronary spasm	1
Others	4

CVL: Cardiovascular laboratory; ECG: Electrocardiogram

changes, old MI ECG pattern and presence of LBBB in ECG. We further stratified causes of false-positive activation according to female gender as shown in Table 5.

Discussion

In current literature, the reported false-positive AMI activation prevalence ranges from 9.5% to 36%.^{16,17} Our series reported a 5.1% false-positive rate after the introduction of direct CVL activation which is seemingly lower than those reported. One possible explanation is the lack of a universal definition of what constitutes as false-positive activation. McCabe et al included cases without any cardiac catheterisation lacking in 2 out of 3 lines of evidence supporting a STEMI diagnosis as false-positive, potentially explaining their relatively higher rate of false-positive activation of 36%. On the other hand, Larson et al adopted a more nuanced approach by giving a range of false-positive activation rate ranging from 9.5% to 14% depending on the definition of false-positive activation adopted. Regardless, the purpose of direct CVL activation as espoused by the American Heart Association (AHA) is such that patients with suspected STEMI are able to undergo urgent angiography and reperfusion therapy within the 90 minutes time frame.³ As such, our false-positive definition is based on absence of compelling angiographic findings that warrants reperfusion therapy which will impact the clinical outcome positively.

There were several factors associated with false-positive activation, one of them being the absence of chest pain on presentation. From our study, we found that cardiovascular

Table 5. Causes of False-Positive Activation in Female Gender

Causes	No. (n = 27)
Takotsubo cardiomyopathy	5 (18.5%)
Early repolarisation	5 (18.5%)
Myopericarditis	3 (11.1%)
Left bundle branch block	3 (11.1%)
Old myocardial infarction changes	3 (11.1%)
Subarachnoid haemorrhage	1 (3.7%)
Pulmonary embolism	1 (3.7%)
Others	6 (22.2%)

collapse, arrhythmias and ECG changes were indication for direct CVL activation in such patients. Although these presentations may arise due to AMI, other conditions can account for them and as such, false-positivity is not surprising. Similarly, other studies have also reported varying percentages of false-positive activation in the absence of chest pain on presentation, ranging from 17.9% to 33%.^{16,18} However, 80% of all patients without chest pain on presentation had an acutely occluded culprit artery in our study. In light of higher prevalence of false-positive CVL activation of patients without chest pain, evaluation should be done to identify high risk features such as haemodynamic instability, cardiogenic shock and life threatening arrhythmias as recommended by current guidelines for immediate invasive evaluation and institution of appropriate therapy or revascularisation, accepting potentially higher rates of false-positive activations in this high risk population.¹⁹

The European Society of Cardiology (ESC) recommends urgent coronary angiogram for patients with chest pain suggestive of MI presenting with new or presumed new onset LBBB. However, our study showed that presence of only LBBB in the ECG is an independent predictor of false-positive activation. Several studies have also corroborated our findings, with incidence of AMI in patients with both chest pain and only new or presumed new LBBB ranging from 12.2% to 33%.^{20,21} On the other hand, patients with ECG showing pre-existing LBBB, Sgarbossa criteria, ie. ST elevation of at least 1 mm that is concordant with the QRS complex, or ST depression of at least 1 mm in leads V2 and V3 should be used to determine the presence of AMI.²² In our study, of the 16 patients that had CVL activation based on the presence LBBB only on ECG, 14 (87.5%) had false-positive activations. Although we concur with guideline recommendations for CVL activation in appropriate patients with new LBBB and chest pain with acceptance of high false-positive activations, efforts should be made to determine if the LBBB changes were pre-existing and if so, Sgarbossa criteria be used to diagnose AMI to



Fig. 2. Graph showing early repolarisation ECG changes.

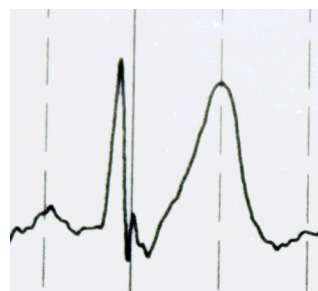


Fig. 3. Graph showing hyperacute T wave ECG changes.

reduce false-positive rates. The chronicity of LBBB at the time of presentation cannot be established for most patients because old ECGs are not available for comparison. Hence, given the heterogeneity of the causes of LBBB other than AMI, the 2013 American College of Cardiology (ACC)/AHA guidelines recommended that new or presumed new LBBB should not be considered diagnostic of AMI in isolation without other clinical presentations, e.g. chest pain, suggestive of AMI.

With regard to gender, females have a higher prevalence of false-positive activation in our study, with the commonest cause being Takotsubo stress cardiomyopathy, occurring exclusively in the females. Other studies have also reported increased prevalence of false-positives in the female gender.¹⁶

Contrary to previous studies,^{16,17} our data did not show a significant increase in the risk of false-positives in patients with previously known MI, CABG or coronary artery disease. One possible explanation could be the slightly selective inclusion criteria for which these patients may not fulfill and as such may have had a cardiology consult at the ED to further stratify the patients for CVL activation.

Our study identified early repolarisation changes as the most common underlying cause for false-positive CVL activation accounting for 23 out of 84 false-positive activations (27%). This represents a common diagnostic dilemma in the ED which typically occurs in a young male patient occurring with chest pain. Characteristic early repolarisation ECG changes include a notch at the J point most prominently seen in V4, concave ST-segment elevation and tall asymmetrical T waves (Fig. 2).²³ This is in contrast to hyperacute ECG changes with MI where there is presence of sloped ST-segment elevation with loss of the normal ST concavity and tall symmetrical T waves (Fig. 3). If present, a previous ECG showing early repolarisation changes when the patient had no chest pain can help differentiate the ECG changes from AMI.

Limitations

Being a single centre study, we are unable to assume that our data is representative of patients with suspected STEMI presenting to ED around the world or even in Singapore for that matter. However, this is partially offset by factors such as the small size and predominantly urban setting of Singapore for which there is unlikely to be significant inter-hospital differences within Singapore.

Conclusion

In this series, we demonstrated that there was no significant increase in false activation rates through the introduction of direct CVL activation by emergency physicians. In addition, this emphasis on reduction of DTB time through such strategy did not result in worse clinical outcome. Factors associated with increased false-positive CVL activations especially the lack of chest pain or LBBB only should be taken into account with the clinical presentation when making a diagnosis of AMI. Larger studies or meta-analysis of similar studies are needed to confirm our findings and to derive a predictive model to accurately identify AMI patients who will benefit from CVL activations.

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