

# Magnitude and consequences of missing the acute infarct-related circumflex artery

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Emergent reperfusion strategies are integral to providing optimal patient outcomes in the setting of acute coronary artery occlusion. ST-segment elevation on the surface 12-lead electrocardiogram, although specific as a surrogate marker, is insensitive to acute posterior circulation coronary artery occlusion. Studies of non-ST-segment elevation acute coronary syndrome consistently identify patients who have epicardial vessel occlusion at the time of initial angiography, which is usually delayed for hours or days after the initial presentation. In addition, studies of ST-segment elevation myocardial infarction often divulge a disparity in identification of the infarct-related artery, with an underrepresentation of the left circumflex artery. Taken together, it is likely that many patients with left circumflex artery occlusion are “missed” during the early phases of myocardial infarction due to the electrocardiographically silent nature of the posterior territory, resulting in delayed myocardial salvage and worse cardiovascular outcomes. In this review, we report on the magnitude of missed left circumflex infarction and the consequences of this delay in diagnosis. We review the electrocardiographic findings of left circumflex occlusion and discuss strategies to enhance early identification. Heightened awareness of this clinical scenario and the available methods to avoid missing this elusive diagnosis are imperative in our quest to further improve the outcomes of patients with acute myocardial infarction. (*Am Heart J* 2009;158:706-12.)

Over the past 2 decades, clinical outcomes and survival in patients with acute myocardial infarction have substantially improved. This favorable outcome has been directly attributed to early and effective acute reperfusion strategies.<sup>1-3</sup> The goal of treatment in patients with ST-segment elevation myocardial infarction (STEMI) is to reestablish perfusion emergently using primary percutaneous coronary intervention (PCI) or fibrinolysis in situations where rapid access to primary PCI is limited.<sup>4</sup> Considerable resources have been directed at regionalization of STEMI care with a goal of improving the delivery of care in this time-sensitive environment.<sup>5</sup>

Conceptually, the initiation of an emergent reperfusion strategy is highly dependent on the presence of ST-segment elevation on the surface 12-lead electrocardiogram (ECG); the established noninvasive marker to identify epicardial vessel occlusion as well as infarct location. Less attention has been placed on the failure of the 12-lead ECG to identify those patients with epicardial vessel occlusion who do not have ST-segment elevation but otherwise present within the optimal reperfusion window (Figure 1).

In this article, we will specifically focus on the insensitivity of the conventional ECG to detect acute coronary occlusion in the posterior circulation and the clinical ramifications that result from this missed diagnosis. Highlighting this difficult to recognize subset will increase research in this area and hopefully translate into an increase in the number of patients benefiting from timely reperfusion.

## Culprit vessel in acute myocardial infarction: insights from clinical studies

The magnitude of our inability to identify the occluded infarct-related artery may be gauged by the following observations. Many patients undergoing angiography in trials of non-ST-segment elevation acute coronary syndrome (NSTEMI) are noted to have an occluded culprit artery (TIMI 0/1 flow) (Table I).<sup>6,9</sup> The frequency of infarct-related artery occlusion appears to be related to the timing of diagnostic coronary angiography. In patients undergoing early angiography, nearly 20% have an occluded culprit vessel. This incidence decreases to 10% at 65 hours, likely reflecting the natural history of the occluded infarct artery, which is characterized by spontaneous recanalization over time.<sup>10</sup> Extrapolation of these data to the number of individuals with NSTEMI in the United States alone implies that >200,000 patients annually may have a coronary occlusion that is missed by the standard 12-lead ECG.

The angiographic distribution of the infarct-related artery differs in trials of STEMI compared to NSTEMI, with an

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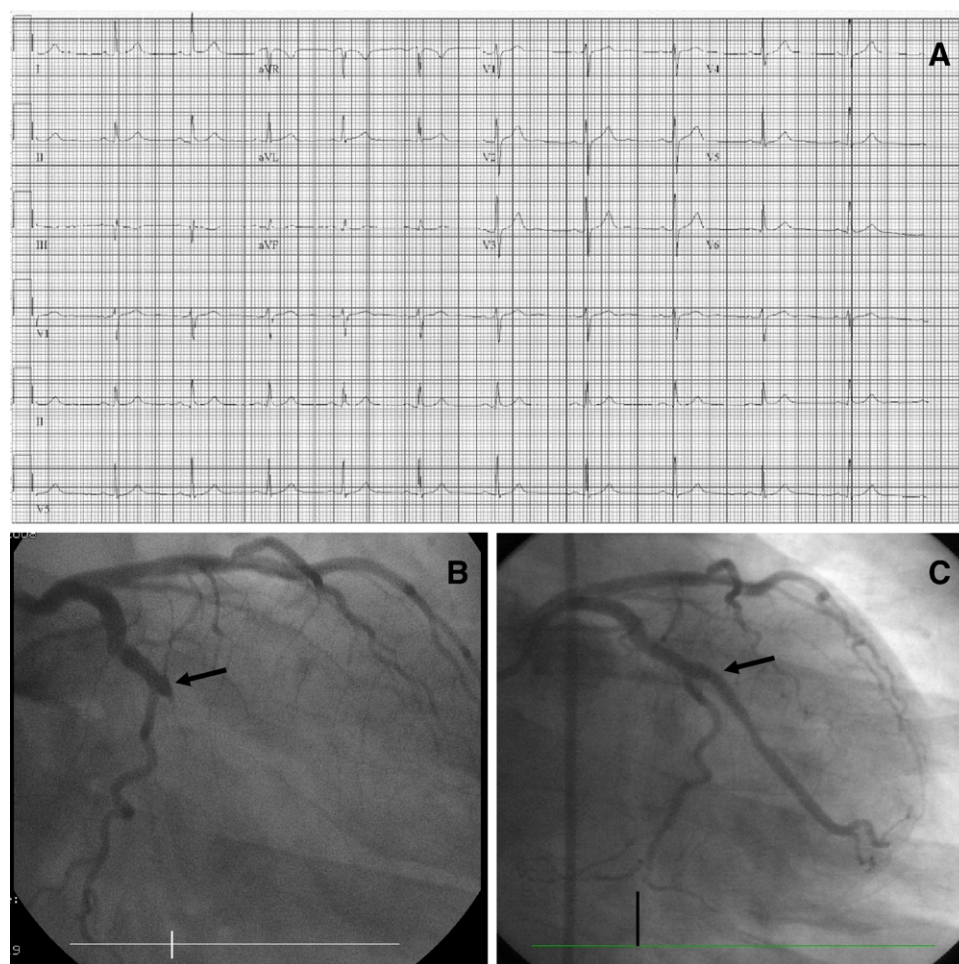
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**Figure 1**



**A**, Presenting ECG in a patient with acute myocardial infarction reveals no ST-segment changes. Coronary angiography in the same patient performed hours later reveals occlusion of a large lateral circumflex branch (panel **B**, arrow), and the same vessel after percutaneous coronary intervention (panel **C**, arrow).

underrepresentation of the left circumflex (LCx) as the culprit vessel in trials of STEMI (Figure 2).<sup>11-16</sup> Taking patients from the 5 studies included in our analysis in aggregate, identification of the left anterior descending coronary artery (LAD), LCx, and right coronary artery (RCA) as the culprit vessel occurred 40.3%, 14.8%, and 43.3% of the time, respectively. The LCx is likely underrepresented because of its underrecognition in the acute phase. In contrast, in studies of NSTEMI, the LAD, LCx, and RCA are all equally distributed as the culprit vessel, each implicated approximately one third of the time.<sup>6,8,17-20</sup>

### Missed diagnosis of LCx occlusion

It is unlikely that the LCx is less prone to plaque rupture and complete thrombotic occlusion. Rather, it may be

postulated that the discrepancy in infarct-related arteries identified in STEMI trials is because LCx occlusion is often missed by the routine 12-lead ECG, and thus, patients with LCx occlusion fail to meet inclusion criteria for these trials. Evidence for this assertion has been provided by multiple investigators.

In their characterization of the clinical ramifications of myocardial infarction due to angiographically confirmed LCx occlusion, Huey et al<sup>21</sup> found that in 40 patients with the LCx as the infarct-related artery, ST-segment elevation was present in only 48% and ST-segment depression noted in 45%. Furthermore, 38% of patients had no ST-segment deviation whatsoever on their presentation ECG.

Berry et al performed surface and intracoronary electrocardiography during percutaneous transluminal coronary angioplasty.<sup>22</sup> In 19 patients with balloon

**Table 1.** Incidence of TIMI 0/1 grade flow in trials of non-ST-segment elevation acute coronary syndrome

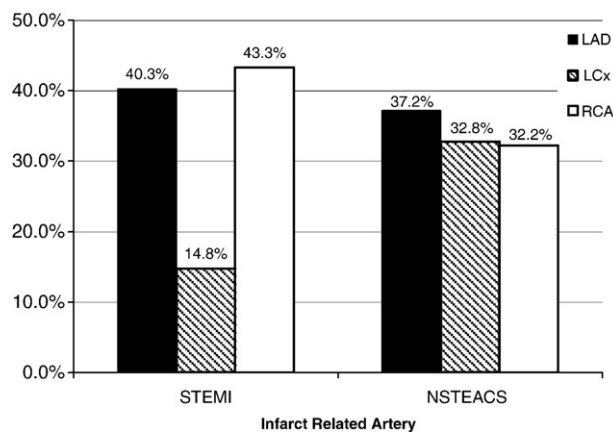
Trial	ISAR REACT 2 <sup>6</sup>	ACUITY <sup>7</sup>	PRISM PLUS <sup>8</sup>	Total
Patients	2022	7737	1491	11250
Time to PCI (h)	6.1	19.5	65	
Initial TIMI flow (%)				
0/1	19	13	10	13.7
2	23	10	11	12.5
3	59	77	79	74

inflation (and resultant occlusion) of the LCx, all of whom had intracoronary lead ST-segment elevation, only 32% manifested ST-segment elevation on the surface ECG, 42% had ST-segment depression, and 47% had no ST-segment deviation. This was in contrast to almost 90% of patients with LAD or RCA balloon inflation manifesting ST-segment elevation on the surface ECG. Consequently, it is reasonable to conclude that the underrepresentation of circumflex vessels in trials of STEMI arises due to our complete reliance on the standard surface ECG.

### Are there consequences to the delayed identification of an occluded LCx?

There are no large trials that provide insight into the clinical consequences of LCx occlusion missed by the standard 12-lead ECG. There are suggestions, however, that there are indeed negative outcomes related to this challenging scenario. Lindahl et al evaluated troponin T (TnT) levels in patients enrolled in the FRISC-II trial of patients with unstable angina/non-ST-segment elevation myocardial infarction.<sup>23</sup> As expected, they observed that higher TnT values were associated with a worse prognosis at 12 months. Importantly, there was a disproportionate number of patients with LCx subtotal or total occlusion compared to LAD or RCA occlusion in the groups with higher elevations in TnT.

O'Keefe et al<sup>24</sup> studied a group of patients undergoing primary percutaneous coronary intervention or thrombolysis with inferior infarction due either to RCA occlusion with ST-segment elevation, LCx occlusion with ST-segment elevation, or LCx occlusion without ST-segment elevation. All 3 groups had the same amount of myocardium at jeopardy, and all patients benefited equally from acute reperfusion irrespective of the presence or absence of ST-segment elevation. Another study by Rasoul et al compared the outcome of patients presenting with STEMI due to LCx versus RCA as the culprit vessel.<sup>25</sup> Those patients with LCx occlusion had greater enzymatic infarct size and comprised a larger percentage of the patients with significant post-MI left ventricular dysfunction despite an overall lesser magnitude of ST-segment elevation.

**Figure 2**

Identification of the culprit vessel in major trials of STEMI and NSTEMI/ACS.<sup>6-8,20</sup>

Similarly, a recent analysis of patients from the PARAGON-B trial found that 27% of patients in this large NSTEMI/ACS study had an occluded infarct-related artery, and this was more often the case in patients with inferolateral territory infarction.<sup>26</sup> Furthermore, those patients with epicardial occlusion had larger infarct size and a higher mortality at 6-month follow-up.

A subgroup analysis from the TRITON-TIMI-38 presented recently evaluated patients with isolated anterior ST-segment depression.<sup>27</sup> An occluded culprit artery was identified 26% of the time, and was most often the LCx. Furthermore, those patients with infarct-related artery occlusion had a significantly higher rate of death or myocardial infarction at 30-day follow-up. Similarly, Ripa et al<sup>28</sup> have shown that the magnitude of ST-segment depression in the early precordial leads correlates well with the ultimate size of myocardial infarction and recommend consideration of this feature during the emergency triage of patients without ST-segment elevation.

The benefits of infarct-related artery reperfusion are time dependent. The benefits of acute reperfusion therapy on clinical outcomes beyond the 12-hour reperfusion window have not been demonstrable with fibrinolytic therapy and have not been systematically assessed with primary percutaneous coronary intervention. In the current American College of Cardiology/American Heart Association guidelines, reperfusion with percutaneous coronary intervention or fibrinolysis is a class IA indication for patients within 12 hours of infarct onset.<sup>4</sup> The OAT investigators found that percutaneous coronary intervention for asymptomatic patients presenting with an occluded infarct-related artery (TIMI 0/1 flow) 3 to 28 days after acute myocardial infarction resulted in outcomes that were similar to optimal medical therapy alone.<sup>29</sup> In a post hoc analysis of this trial, Menon

**Table II.** Electrocardiographic indicators of LCx occlusion

ST-segment elevation in lead II > III <sup>30</sup>
ST-segment elevation in leads I and aVL <sup>31</sup>
ST-segment depression in leads V <sub>1-3</sub> <sup>32,33</sup>
R-wave prominence in lead V <sub>1</sub> or V <sub>2</sub> (R/S > 1) with upright T waves <sup>39,40</sup>
ST-segment elevation in extended leads V <sub>7-V<sub>9</sub></sub> <sup>41</sup>
ST-segment depression in lead aVR during inferior ST-segment elevation <sup>30</sup>

et al have found that patients in the Occluded Artery Trial with NSTEMI on presentation were far more likely to have an occluded LCx as the culprit vessel than their STEMI counterparts (personal communication). Although speculative, it is plausible that some of these patients would never have been enrolled in the trial if immediate clinical suspicion of an occluded infarct-related artery had resulted in earlier angiographic definition and reperfusion within the beneficial time window.

Taken together, these studies provide the basis for the assertion that missed LCx occlusion may have significant negative clinical ramifications including larger infarct size, worse post-MI left ventricular dysfunction, and mortality. Acute reperfusion strategies may provide similar benefit to these patients as for those currently receiving guideline-based therapy on the grounds of an ECG that is diagnostic for coronary occlusion.

## Useful strategies for diagnosing LCx occlusion

The ECG remains the first and most important part of the diagnostic process in the assessment and triage of patients with suspected acute myocardial infarction. Electrocardiogram-diagnosed inferior or posterior infarction may be the result of involvement of either the LCx or RCA. Because of the difficult nature of diagnosing posterior myocardial infarction, many investigators have proposed criteria to help identify acute myocardial infarction electrocardiographically (Table II).

When ST-segment elevation is noted in the inferior leads, a greater degree of elevation in lead II than lead III is often seen with LCx occlusion, owing to the leftward course of the vessel.<sup>30</sup> For the same reason, concomitant elevation in lead I or aVL in this setting is also more characteristic of LCx occlusion.<sup>31</sup> In addition, ST depression in lead aVR in the setting of inferior ST elevation may be seen in the setting of LCx occlusion, as opposed to aVR elevation with RCA occlusion.<sup>30</sup>

As demonstrated, however, the standard ECG may miss >50% of patients with LCx occlusion if evaluated only for ST-segment elevation. Therefore, a thorough evaluation for other potential changes due to LCx infarction is necessary. Depression of the ST-segments in the precordial leads may be indicative of either nonocclusive ischemia or complete occlusion of an epicardial coronary vessel in the inferoposterior territory.<sup>32</sup> In the

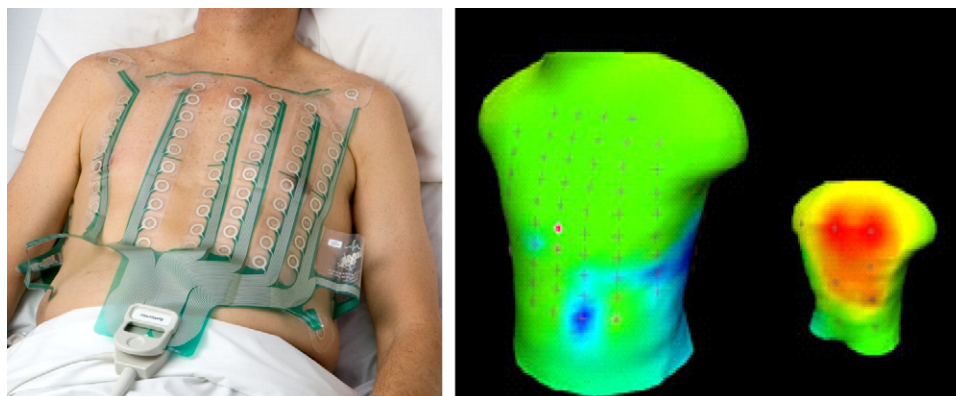
setting of infarction, leads V<sub>1</sub> to V<sub>3</sub> predominate as the areas of maximum depression, whereas greater involvement of the lateral precordial leads (V<sub>4</sub>-V<sub>6</sub>) and inferior leads (II, III, aVF) is more indicative of nonocclusive ischemia.<sup>33</sup> ST-segment depression in the early precordial leads does not reliably discriminate between RCA and LCx involvement, although depression of leads I and/or aVL is seen more often in patients with RCA involvement.<sup>21,34</sup> Similarly, ST-segment elevation in the early precordium (along with inferior infarction) may be seen in the setting of proximal RCA occlusion as a result of right ventricular infarction due to involvement of a marginal branch of the RCA.<sup>35</sup> The use of right ventricular precordial leads (V<sub>3R</sub>, V<sub>4R</sub>, V<sub>5R</sub>) is also beneficial in evaluating a patient with suspected inferoposterior or right ventricular infarction, although ST-segment elevation in this distribution does not reliably distinguish between RCA or LCx involvement.<sup>36,37</sup>

Early precordial R-wave prominence may be noted in patients with posterior myocardial infarction, as well as nonischemic etiologies such as right ventricular hypertrophy, hypertrophic cardiomyopathy, Wolff-Parkinson-White syndrome, and Duchenne muscular dystrophy.<sup>38</sup> The likelihood of posterior infarction as a cause of tall R-waves in the early precordium is increased by the concomitant finding of upright or hyperacute T waves in the same distribution.<sup>39</sup> Almost 50% of patients with LCx infarction may display a prominent R wave in V<sub>1</sub> or and R/S ratio in V<sub>1</sub> or V<sub>2</sub> ≥ 1, although it may take up to 24 hours for this finding to manifest and may not necessarily be indicative of acute versus old infarction.<sup>40</sup>

Another strategy to improve the recognition of posterior infarction is the use of extended posterior chest leads V<sub>7</sub> to V<sub>9</sub> (placed in the plane of V<sub>6</sub> from the posterior axillary line to the paravertebral line). Matetzky et al<sup>41</sup> studied a group of 33 patients who presented with acute myocardial infarction based on positive creatinine kinase, none of whom had ST-segment elevation on the standard 12-lead ECG. In all of these cases, the posterior leads revealed ST-elevation. Twenty of the patients went on to coronary angiography, and all were diagnosed with LCx occlusion. Other notable ECG findings in this series included ST-depression in leads V<sub>1</sub> to V<sub>3</sub> in 61%, a positive R-wave in lead V<sub>1</sub> in 9%, and a positive R-wave in lead V<sub>2</sub> in 44%.

Comprehensive bedside body surface mapping (BSM) is a technique currently under clinical investigation to improve diagnostic accuracy in assessment of the patient suspected of acute myocardial infarction, and uses an extended array of ECG leads to measure cardiac potentials. A study by McClelland et al of 53 patients with myocardial infarction documented by positive cardiac biomarkers found that 17 patients missed by the 12-lead ECG were diagnosed by the body surface map, a finding that has been substantiated by other investigators.<sup>42-44</sup> The increased sensitivity of body surface



**Figure 3**

Eighty-lead ECG body surface mapping system; application (left panel) and color map in a patient with posterior myocardial infarction (right panel). Images reproduced with permission from HeartScape Technologies, Inc, Columbia, Maryland.

mapping to detect posterior infarction has also been demonstrated in studies of acute myocardial infarction as well as during angioplasty, providing further impetus for the use of this technique.<sup>45</sup>

There have been different iterations of the body surface mapping system using between 18 and 120 leads, but the most readily available apparatus currently consists of a vest containing 80 electrodes, which are apposed to the torso (Figure 3).<sup>46</sup> Measurements are then made by the included software to construct a color-coded “map” corresponding to areas of ST-segment elevation and depression. A prospective multicenter trial evaluating the 80-lead PRIME body surface mapping system (OC-CULT-MI) was recently completed and publication of the results are awaited.<sup>47</sup> A multicenter emergency department registry (BEACON) is also currently underway.<sup>48</sup>

In situations of acute myocardial infarction where LCx occlusion is suspected but not evident on the 12-lead ECG, imaging with transthoracic echocardiography may be of value.<sup>49</sup> Hypokinesis or akinesis of the ventricular myocardium manifests before the development of ST-segment changes on the ECG.<sup>50</sup> Therefore, the use of transthoracic echocardiography to identify isolated lateral or posterior wall motion abnormalities during NSTEMACS may identify those patients who have LCx infarction and may benefit from emergent angiography. Unfortunately, previous MI or baseline wall motion abnormalities complicate the use of this strategy to identify acute changes.

Taking all patients with suspected NSTEMACS emergently to the cardiac catheterization laboratory is a potentially effective, although logistically difficult, strategy by which to diagnose LCx occlusion in a timely fashion. Recent trials of an immediate invasive (compared to an early invasive) strategy for all patients with

NSTEMACS have not shown an improvement in major cardiovascular outcomes.<sup>51</sup> Based on the rationale presented, though, it is possible that a reanalysis of the data concentrating on LCx occlusion patients alone may show a benefit to immediate angiography and intervention. In fact, “high-risk” patients (defined by the Global Registry of Acute Coronary Events score) in the TIMACS trial of NSTEMACS did indeed show a benefit to an immediate intervention strategy.<sup>52</sup> However, data on distribution of the culprit vessel and degree of TIMI flow at the time of angiography have not yet been presented.

An aggressive but more discretionary strategy of immediate angiography only in patients with precordial ST-segment depression may also be of value. Based on the analysis presented above from TRITON-TIMI-38, more than one fourth of these patients would be diagnosed with an occluded epicardial vessel, most likely the LCx. Whether this diagnostic strategy would translate into a clinically therapeutic benefit is only hypothetical at this time.

## Conclusions

It is not surprising in clinical practice to encounter a patient who has a history and laboratory picture consistent with acute myocardial infarction, but an ECG that does not provide an evidence-guided pathway to emergent angiography and revascularization. These patients are often brought to the catheterization laboratory with a diagnosis of NSTEMACS 24 to 48 hours after initial presentation, at which time they may be diagnosed with a complete occlusion of the LCx or one of its marginal branches. Clinical experience and extrapolation of data from clinical trials do not imply that left coronary dominance is a prerequisite for this scenario. These patients with a “missed” STEMI may indeed have

benefited from emergent angiography and reperfusion within the time frame assigned to patients with coronary occlusion in a more “ECG-sensitive” location. Knowledge of the subtle ECG findings that may be present with LCx occlusion, the use of extended lead ECG systems, and use of bedside echocardiography may all be of value in situations in which LCx occlusion is suspected but presents without ST-segment elevation. Furthermore, although taking all patients with NSTEMI to emergent angiography has not been shown to produce a clinical benefit, an aggressive angiographic approach to patients with precordial ST-segment depression alone may be warranted (although at this point based only on conjectural evidence). Ultimately, the immediate identification of “silent” posterior occlusion is imperative as we seek to improve the overall outcome of patients with acute myocardial infarction, and further research into methods of achieving this goal is necessary.

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