Clinical Utility of Serial and Continuous ST-Segment Recovery Assessment in Patients With Acute ST-Elevation Myocardial Infarction

Assessing the Dynamics of Epicardial and Myocardial Reperfusion

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Acute ST-segment–elevation myocardial infarction (STEMI) is a global source of mortality and morbidity and consequently is one of the most active areas of applied research. In the face of multiple reports of new combinations of medical and interventional therapies, the challenge to the clinician is both to understand data from key clinical trials and to translate that understanding to the individual patient at the bedside.

STEMI is defined by “ST elevation” on the ECG, which is the electrical manifestation of the pathophysiological changes that follow a thrombotic occlusion of an epicardial coronary artery.1 The ECG is ubiquitous in cardiology, applied as a diagnostic, prognostic, and management tool. Although a single ECG presents about 10 seconds of waveform morphology, acute STEMI displays its dynamic behavior over time, both spontaneously and in response to therapy.

The systematic use of serial and continuous ECG assessments has been one of the most fertile areas of advancement in the ability to measure and thereby recognize the presence, speed, quality, and stability of reperfusion of an infarct artery. In addition to providing insights into pathophysiological mechanisms and novel therapies in research protocols, serial or continuous use of this simple, noninvasive, quantitative measure has the potential to guide clinicians through the dynamic events surrounding the management of STEMI patients’ disease. This is illustrated in the following case studies of 3 patients, all of whom presented with 3 hours of chest pain with angiographically documented TIMI 3 flow, were managed with serial ECGs for clinical purposes, and were simultaneously monitored for research protocols with “black box” continuous 12-lead ECG monitors.

Case Reports

Patient 1

G.E. was a 67-year-old man with a history of hypertension and tobacco use who presented with 3 hours of chest pain. The initial ECG showed anterolateral ST-segment elevation with a maximum of 15 mm of ST-segment elevation in lead V2. He was treated with aspirin, heparin, and full-dose front-loaded tissue plasminogen activator. Although the patient had some pain relief, a repeat ECG 90 minutes later showed no interval change, with 15 mm of ST-segment elevation in lead V2. Acute angiography documented TIMI 3 flow through a 95% proximal left anterior descending coronary artery (LAD) stenosis, on which angioplasty was successfully performed. The patient subsequently did well.

Figure 1 graphically shows the ST-segment levels from continuously recorded 12-lead ECGs in this patient. In the 90 minutes between the first and second ECGs, ST-segment levels increased overall to a peak abnormality of 37-mm elevation in lead V2. Worsening condition from the time 0 ECG to these peak levels suggests ongoing occlusion of the infarct artery early after lytic therapy. By the 90-minute ECG, however, the 15-mm ST-
segment elevation was actually a recovery of >50% from the 37-mm peak, suggesting reperfusion of the infarct artery, as was documented at catheterization.

**Patient 2**
P.M. was a 72-year-old woman with a history of coronary disease, having undergone bypass surgery 4 years before. The patient presented with 3 hours of waxing-waning chest pain. On arrival in the emergency department, she had 7 mm of anterior ST-segment elevation but rapidly became pain free, with a nonacute ECG, when treated with sublingual nitroglycerine, aspirin, and heparin. She was admitted to the coronary care unit (CCU), but on arrival had recurrent pain. A repeat ECG showed recurrent anterior ST-segment elevation. She was quickly taken to cardiac catheterization. On arrival in the catheterization laboratory, she was pain free, with no ST-segment changes on ECG. Catheterization was deferred, and the patient was taken back to the CCU. She was stable for 2 hours, when she again experienced chest pain with anterior ST-segment elevation. She was taken back to the catheterization laboratory; on arrival she was again pain free, with a normalized ECG. Catheterization was performed, and a hazy mid-LAD lesion was defined with TIMI 3 flow. She was treated with abciximab in conjunction with angioplasty, and stenting was performed with a good result. The patient did well for ≈6 hours, when she experienced recurrent pain and ST-segment elevation because of stent thrombosis. She underwent urgent bypass with placement of a left internal mammary artery graft to the LAD.

Figure 2 shows the continuous ECG data from patient 2. Anterior ST-segment elevation evolves and resolves repeatedly, suggesting intermittent changes in epicardial coronary patency, or “cyclic flow.” Although the patient had 2 episodes of ST-segment re-elevation accompanied by chest pain, the vast majority of these episodes of ST-segment re-elevation were asymptomatic. Several episodes of ST-segment elevation and recovery were the result of balloon occlusion and reperfusion during angioplasty. Re-elevation is seen late from stent thrombosis, with the recording terminated as the patient went to bypass surgery.

**Patient 3**
M.L. was a 57-year-old man with diabetes who otherwise was in generally good health. He presented to the emergency department with a history of 3
hours of chest fullness. An ECG showed posterior infarction with ST-segment depression in the anterior leads, maximal at −11 mm in lead V2. He was treated with aspirin, heparin, morphine, and full-dose tissue plasminogen activator. During the course of 90 minutes, his symptoms resolved; however, an ECG at 90 minutes showed worsening symptoms, with 14 mm of depression in lead V2. He was taken to cardiac catheterization, where TIMI 3 flow was observed through a 95% proximal circumflex stenosis. Stenting of the lesion was successfully performed, with persistence of TIMI 3 flow but minimal ECG recovery. The patient was subsequently treated with pressors and intraaortic balloon pump support, but he died 8 hours after percutaneous coronary intervention (PCI).

Figure 3 shows the ST-segment levels recorded during the entire 11 hours from presentation to death in patient 3. Although it was documented angiographically that the epicardial infarct artery had reperfused within 90 minutes of the onset of lytic therapy, the persistence of ST-segment deviation in the presence of TIMI 3 flow suggests that microvascular myocardial perfusion remained poor, with ongoing cellular injury and death. Further manipulation of the epicardial vessel with angioplasty, although angiographically successful, did not improve myocardial perfusion, and the patient finally succumbed to a massive infarction.

Discussion
Pathophysiological insight into the thrombotic occlusion of an epicardial vessel1 and the associated “wavefront” of cell death2 revolutionized the clinical management of patients experiencing acute STEMI. Mortality reduction with thrombolytic therapy and aspirin3,4 generated a new standard of care for medical therapy. Mechanical revascularization of the infarct artery, although logistically more challenging, appears to offer an even greater clinical benefit to these patients.5,6

Exploration of optimal therapy for acute STEMI continues to advance the clinical armamentarium, with safer, more effective lytic agents7,8 and novel anticoagulant and antiplatelet adjuncts9,10 in both medical and facilitated PCI strategies. Unique devices inducing hypothermia or providing distal protection from thrombotic embolization are also under study.

The principles guiding these research directions are conceptually and mechanistically familiar to the clinician at the bedside. Conceptually, optimal therapy for STEMI must minimize cell death by interrupting the
infarction and begin to reverse the ischemic metabolic derangement of still-viable cells. ST-segment recovery over serial ECGs in STEMI represents both reversal of ischemia and interruption of infarction.\textsuperscript{11} Mechanistically, optimal therapy is mediated through 2 related but independent phenomena, the speed and stability with which the epicardial vessel is recanalized and the quality of the nutritive response to reperfusion at the cellular level.\textsuperscript{12–14}

The speed and stability of reperfusion at the epicardial level can be both unpredictable and dynamic. Cyclic flow, such as illustrated in patient 2, has been reported in 35% to 50% of patients treated with thrombolytic therapies.\textsuperscript{15–19} Although the waxing and waning of chest pain may be a clinical signal of such events, reocclusion of the infarct vessel is also frequently asymptomatic.\textsuperscript{15} Serial and continuous ECG assessments over time provide a noninvasive modality for tracking the status of epicardial patency. The more frequently ECGs can be taken, the more precisely the timing of reperfusion and the stability of patency over time can be characterized.\textsuperscript{20,21} As shown in patient 2, cyclic flow changes can be both dramatic and rapid, with more frequent or continuous ECG assessment progressively correcting potential temporal undersampling errors.\textsuperscript{20}

Recanalization of the infarct vessel can be recognized by >50% ST-segment recovery.\textsuperscript{20,22,23} As shown in patient 1, however, this “absolute relative” calculation depends on the initial as well as the current ECG used for comparison. Thus, in patient 1, the 90-minute ECG was no different from the time 0 ECG, but it was >50% recovered from the much worsened peak ECG that evolved within the 90-minute window. Although waiting 60 to 90 minutes to assess the adequacy of thrombolytic therapy is a clinically reasonable strategy, taking more frequent serial or continuous ECGs during the course of the waiting period may correct undersampling of the true peak levels of injury current from which “percent recovery” is measured.

It is now widely appreciated that recanalization of the epicardial vessel is a necessary but insufficient condition of nutritive reperfusion that actually reverses ischemia and interrupts infarction.\textsuperscript{12,13,24,25} Mechanistic observations with contrast echo perfusion and myocardial blush\textsuperscript{25–27} suggest that in \approx 30% of patients in whom recana-
lization produces TIMI 3 flow, the quality of nutritive reperfusion is compromised. Characterization of the quality of reperfusion with both of these biomarkers is strongly correlated with the extent of ST-segment recovery observed over serial ECGs.26,28 The “gold standard” defining nutritive reperfusion is mortality, and it is well established that successful recanalization of the infarct artery with TIMI 3 flow yields a mortality benefit as compared with failed recanalization.29 The extent of ST-segment recovery further stratifies mortality significantly in patients with TIMI 3 flow.30–32 In patients treated with thrombolytics, the prognostic information provided by ST-segment recovery analyses can be assessed over an array of time periods, from 60 to 240 minutes after administration of thrombolytic therapy.33–36 At any given time, the extent of ST-segment recovery, corresponding with the quality of reperfusion, appears to provide the key information, as patients with ≥70% ST-segment recovery have superior survival to those with 30% to 70% recovery, who in turn do better than those with <30% recovery.32,33,35 ST-segment elevation on the surface ECG is a physiological reflection of a focal area of myocytes so deprived of oxygen that ATP-dependent transmembrane ion gradients are lost. Fast, stable, and complete ST-segment recovery quantifies the reversal of this state and thus has proved to be one of the most predictive and clinically practical measures of the cellular response to reperfusion. As seen in patient 3, despite recanalization of the infarct artery, elimination of the stenosis, and brisk TIMI flow at the epicardial level, worsening ST-segment deviation identified the absence of nutritive benefit at the cellular level (despite reperfusion), with ongoing cell death and ultimately death of the patient.

For clinical purposes, the use of serial or continuous ECG measurements must not only have a sound rationale for its application but must also be logistically feasible in the flow of acute care. Accurate manual measurements of severely abnormal ST segments over serial ECGs can be challenging, and digital ECG tools may be helpful. Digital tools may be susceptible to artificial information if the measurement point is taken at or close to the J point because subtle shifts of key fiducial points in the digital instrumentation may intermittently pull the measurement point of interest into the S wave.

Similarly, the summation of multiple measurements over combinations of affected leads may be quite complex and too time consuming for clinical use. With regard to the prognostic value for patients, the information content from absolute, relative, and temporal measurements based on the single-peak lead selected from the standard 12-lead ECG seems similar to the information content from multiple-lead measures,37 and it is certainly simpler for clinical use.

Acquiring serial ECGs in the clinic is easily done with any standard ECG. Care must be taken to ensure that the lead positions are marked or stay in place during the course of serial acquisitions to avoid artifact from reposi-
tioning. How frequently to check the ECG is best guided by the recognition that STEMI is a highly dynamic pathophysiology and undersampling may significantly affect the interpretation of serial ECG information.20 In this setting and within reason, the simple maxim “more is better” is applicable, ideally with no more than 5 to 10 minutes (or less) between assessments during the first 60 to 90 minutes of care.

Historically, the perceived complexity of continuous multilead ST-segment monitoring equipment and the absence of guidelines and standards have limited widespread use in clinical care despite a relatively low cost. In Sweden, however, real-time continuous ST-segment monitoring has become a standard of care in the management of CCU patients,38–40 and in the United States, several centers have applied this technology in chest pain observation units.41,42 Radiolucent electrodes allow continuous monitoring during chest x-ray or angiography. The emergence of consensus standards for ST-segment monitoring43 and more facile devices and user interfaces from all of the major commercial manufacturers of monitoring equipment have enhanced the clinical potential of modern ECG and vectorcardiogram monitoring for patients with acute coronary syndromes.

In research studies of new therapeutics in populations presenting with acute STEMI, serial and continuous multilead ST-segment recovery assessment has emerged as one of the most robust and widely used measures to quantify the speed, stability, and quality of reperfusion. In the clinical setting, this application of the ECG signal provides an inexpensive, noninvasive, and highly reliable approach to patient management and risk stratification that can be individualized to every patient during the dynamic course of his or her illness.

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