Time Is Myocardium and Time Is Outcomes

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As an interventional cardiologist and a clinical trialist, I am often asked, “what do we need to do to improve mortality by another 1% in the setting of acute myocardial infarction?” Indeed, nearly a decade and a half of effort and many hundreds of millions of dollars have been spent in pursuit of this elusive “1% reduction” in mortality by both the pharmaceutical and the device industry. As the report by the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT 2) investigators in the present issue of Circulation highlights,1 this kind of advance may not be achieved exclusively with new drugs or devices, but in also reducing time to treatment and in modifying patient behavior to seek these potentially life-saving treatments earlier.

Time and the ECG: Complementary Risk Stratification Tools

In a time of dizzying advances in diagnostic modalities, it is refreshing to see what a useful, simple, noninvasive, broadly accessible, easily repeatable/applied, and affordable tool the ECG is.1 Time to treatment and ST-segment resolution were roughly similar in their ability to risk-stratify patients in the study by Fu et al.1 For both time to treatment and ST-segment resolution, there was an ~2-fold gradient between the lowest risk category and the highest risk category (<2 hours versus >4 hours for time to treatment and >70% resolution versus <30% resolution for ST-segment resolution). Although time to treatment may reflect the extent of necrosis before therapy (with greater myocardial salvage observed with shorter times to treatment), ST-segment resolution may instead reflect the response to therapy. It is notable that these 2 variables allow further risk stratification within each category of the other. As a result, limitations of ST-segment resolution as a sole end point become apparent: patients with electrocardiographic success (ie, complete ST resolution) but with symptoms who were treated in >4 hours than patients with partial ST-segment resolution who were treated in <2 hours. This illustrates how no end point is monolithic in its ability to predict outcomes and that life (and death in this case) is multivariate.

Timing to Assess ST-Segment Resolution

Several questions remain unanswered. For instance, is earlier ST-segment resolution better? It is unclear which is more predictive of outcomes: ST-segment resolution at 60, 90, or 180 minutes or the data provided at 24 to 36 hours in the report by Fu et al,1 because these time points were not compared. Although static2 and dynamic3 ST-segment resolution at several such time points have been associated with mortality, the incremental value of data at each time point was not addressed in this study. It could be speculated that ST-segment resolution data at early and late time points may be complimentary and additive in their value. Although early ST-segment resolution may reflect the patency of the artery and microvasculature, late ST-segment resolution may instead identify patients who have reoccluded the artery, patients with aneurysms or those who are more likely to have adverse remodeling, patients who may show limited recovery in infarct zone wall motion, and patients who may undergo a progressive decline in ejection fraction. In a time when early, full reperfusion by both angiography and electrocardiography has been emphasized, the observation at 24 to 36 hours in the study by Fu et al1 emphasizes that sustained ST-segment resolution is also critical (other studies have emphasized the same for patency on angiography).

It is unclear how percutaneous coronary intervention alters the 24-hour ECG. Indeed, better, early tools are needed before 24 hours to identify those patients who have failed reperfusion therapy who might benefit from rescue interventions. My colleagues and I recently demonstrated the potential value of the early ECG in this regard.4 Other point-of-contact biomarkers, such as troponins and myoglobin and the TIMI risk score,3 may add to these early risk stratification efforts.

Time to Change End Points?

Although the r value relating ST-segment resolution to mortality in the report by Fu et al1 is quite high (0.963, P<0.001), it should be noted that this value is based on a regression model of the average values in 10 different strata and is not based on individual patient values, which may artificially inflate the predictive power of the end point. Thus, the explanatory value reported here needs to be interpreted with caution. One limitation noted in previous studies is the fact that a substantial number of ECGs may be uninterpretable or of poor quality. The fact that only 77% of patients were included in the analysis speaks to the limitation of ST-segment resolution as an end point in clinical trials. No information is provided about the prognosis of patients with missing ECG data in this report. Furthermore, as pointed out by the authors, the early lability of ST-segment resolution and the lack of clarity about the optimal timing of ECG resolution in its relation to outcomes is another limiting factor.

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ST-segment resolution was a multivariate correlate of 1-year mortality after adjusting for known critical ECG confounders, such as the location of the anterior myocardial infarction (associated with poor ST-segment resolution in several reports) and other, well-established predictors of mortality, such as age, heart rate, blood pressure, and time to treatment. The Kaplan-Meier curves are provocative between 30 days and 1 year. They suggest a potential late divergence in mortality, such that the complete ST-segment resolution group fares better relative to the other 2 groups after 30 days. No formal comparison is made of late outcomes between 30 days and 1 year, which again may be confounded by infarct location.

Clearly, ST-segment resolution is associated with mortality and, as such, can be considered a “marker.” However, whether the marker of ST-segment resolution satisfies stricter criteria to qualify as a “surrogate” for mortality has not yet been fully defined. This would require a tripartite association, as follows: (1) ST-segment resolution would need to be shown to be associated with mortality (which it has been); (2) a treatment would need to lower mortality; and (3) that treatment would need to be associated with ST-segment resolution. Angiographic data from the Global Use of Strategies to Open Occluded Arteries (GUSTO) 1 trial does demonstrate that (1) TIMI grade 3 flow is associated with mortality; (2) tissue plasminogen activator administration lowered mortality by 1% compared with streptokinase; and (3) tissue plasminogen activator administration was associated with a 22% improvement in TIMI grade 3 flow.6

Recently, the 7% improvement in TIMI 3 flow observed in the dose-confirmation phase of the Strategies for Patency Enhancement in the Emergency Department (SPEED) pilot study (from 47% to 54%) yielded the anticipated 0.3% change in mortality in the subsequent GUSTO V trial.7 In contrast, unpublished data from an ECG substudy of GUSTO V showed the time to steady-state ST-segment resolution was significantly improved among those patients who received combination therapy compared with those who received full-dose reteplase (66 versus 100 minutes, n=207, P=0.012); however, this large improvement did not translate into a mortality benefit. Clearly, there is no monolithic end point to assess reperfusion efficacy, and different end points provide different insights into the mechanism of benefit (ie, epicardial patency, tissue perfusion, reduced reoclusion, improved safety) of reperfusion strategies. What is critical is to assure that the end point matches the presumed underlying biological mechanism of benefit and that there is consistency in the directionality among end points in assessing the efficacy of a reperfusion strategy.

How does this information alter the way we practice cardiology? This is a valuable additional risk stratification tool; however, it seems unlikely that people will risk-stratify patients solely on the basis of the 24-hour ECG rather than performing a submaximal exercise tolerance test. The greatest value of this data may lie in reemphasizing the critical role of time to treatment.

**Time to Treatment**

The time from symptom onset to the initiation of therapy in large-scale clinical trials has remained unchanged at a 2.7- to 2.9-hour delay over the past decade (Figure). Although these data from the clinical trials arena look somewhat disappointing, there are encouraging registry data which indicate that the medical community has collectively improved modifiable delays once the patient arrives at the hospital. Among patients treated with thrombolytic agents, door-to-needle times in the National Registry of Myocardial Infarction have improved from 60 to 36 minutes during the 1990s.8 Door-to-balloon times have improved only slightly from 116 to 108 minutes from 1994 to 1999, and times remain prolonged in many systems.8 Although “high tech” advances in performing primary angioplasty continue, “low tech” strategies are needed to insure that primary angioplasty is performed in <90 minutes. I call on all providers of primary angioplasty to track and report the time from presentation at surrounding hospitals until the artery is open to assure that this 90-minute timeline is being met through a process of continuous quality improvement.

Much of the delay remains in getting the patient to come to the hospital. Why do people delay in seeking medical attention in the setting of acute myocardial infarction? The Rapid Early Action for Coronary Treatment (REACT) study sheds some light on the demographic, situational, and belief factors that impact the use of emergency medical services (EMS).9 This study was drawn from data in 20 communities across the country and, as a result, is less susceptible to bias that may arise in analyses emanating from individual communities. Although 89.4% of community survey respondents said they would use EMS services, only 23.2% of patients who actually had chest pain used EMS services.

The disconnect between what people seem to understand is the right course of action in a survey and actual patient behavior when faced with a cardiac emergency themselves points to certain potentially modifiable situational or belief factors. Denial of the cardiac origin of the pain may obviously play a critical role: if a patient thinks the discomfort is “due to a heart attack” then they are more likely to use EMS services. Those patients self-prescribing antacids or aspirin, who may have attributed the pain to another cause, were less likely to use EMS services. In contrast, those patients who were familiar with heart disease who were taking nitroglycerine were more likely to use EMS services. These data point to the potential role of patient education in improving delays in seeking medical care.
From a healthcare delivery perspective, the presence of a tax-based prepaid EMS system doubled the likelihood of using EMS services. Somewhat disappointingly, talking with a doctor was not associated with use of EMS services. One could argue that the physician was familiar with the patient and was acting prudently to prevent unneeded hospitalizations. However, 83% of patients who spoke with a doctor were subsequently admitted to the hospital. Although increasing age, white ethnicity, and living alone were associated with greater use of EMS services, these demographic variables cannot be impacted, and some (old age and living alone) may simply reflect reduced access.

**Time to Act**

To improve these delays, the National Heart, Lung, and Blood Institute (NHLBI), through its National Heart Attack Alert Program and Act in Time to Heart Attack Signs campaign, and the American Heart Association, through its Operation Heartbeat, the Red Cross, and National Council on Aging have joined forces to reduce the time between the onset of symptoms and treatment. The goals of these programs are to increase the awareness of cardiac warning signs by 20% by 2003; to increase by 15% the awareness of the need to call 9-1-1 first when experiencing symptoms of a heart attack; to talk to patients about their risk of heart attack, how to recognize symptoms of acute myocardial infarction, and the proper action to take if they think they are having a heart attack; to encourage patients that “When in Doubt, Check It Out” and “better safe than sorry”; and to remind patients that coronary heart disease is still the top killer of both men and women.

These data add to the growing body of literature supporting the hypothesis that “time is myocardium,” and perhaps we should also say that “time is outcomes.” Now is the time to act to move this effort out of the laboratory and out of clinical trials and into the hands of agencies, providers, and patients in the arena of public health policy.

**References**

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