EDITORIAL COMMENT

Circadian Variations in Acute Myocardial Infarction

Patients or Health Care Delivery?*

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Prompt restoration of coronary arterial blood flow has been the cornerstone of successful therapy for acute ST-segment elevation myocardial infarction (MI) for the past two decades. Data from randomized clinical trials (1) coupled with parallel angiographic studies have provided unequivocal proof that achievement of myocardial reperfusion is largely responsible for the observed health benefits (2,3). In addition, the “time-dependent” impact of fibrinolytic therapy (4) has been demonstrated consistently and provides incontrovertible support for increased patient survival, decreased infarct size, and improved left ventricular performance with early successful reperfusion. Accordingly, the National Heart Attack Alert Program and other broad-based health care initiatives were developed to rapidly identify and treat patients with acute MI (5).

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During the past decade, primary angioplasty has emerged as an attractive means to restore coronary arterial blood flow and myocardial perfusion among patients with ST-segment elevation MI. Clinical trials comparing pharmacologic and mechanical modalities of reperfusion have convincingly demonstrated that the latter more effectively achieves the objectives of treatment with a lower risk of major hemorrhage (6,7). This advantage translates to improvements in clinical outcomes, at least in the clinical trial setting. Patients undergoing primary angioplasty in the Primary Angioplasty in Myocardial Infarction (PAMI) trial were less likely to die or experience re-infarction than those receiving fibrinolytic therapy (5.1% vs. 12.0%) (6). Similarly, in Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO-IIb), patients undergoing primary angioplasty had a lower risk of death, MI, or stroke at 30 days than those receiving alteplase (9.6% vs. 13.6%) (7). Although these data have generated considerable enthusiasm for the use of primary angioplasty for ST-elevation MI, the question has been raised whether the results achieved by the high-volume centers offering round-the-clock services and employing experienced staff can be replicated in day-to-day practice. For example, in-hospital death rates for patients enrolled in the National Registry of Myocardial Infarction (NRMI) were similar for each reperfusion modality (primary angioplasty 5.2%, fibrinolytics 5.4%) (8). Other registries have made similar observations.

The contrasting outcomes for patients treated in large tertiary medical centers within the carefully defined construct of a clinical trial and daily practice in community hospitals are likely due to several factors. Catheterization laboratory volume, operator experience, and differing use of adjunctive therapies have each been shown to impact patient outcome (9,10). In addition, most observational studies suggest that the efficacy of primary angioplasty, as with fibrinolytic therapy, is time-dependent. In a study of 1,352 patients undergoing primary angioplasty at a single center, those in whom reperfusion was achieved in <2 h from symptom onset had markedly decreased 30-day mortality rates compared to those in whom reperfusion occurred beyond 2 h (4.3% vs. 9.2%) (11). Data from the NRMI-2 suggest a 40% to 60% increase in hospital mortality with door-to-balloon times in excess of 2 h (12).

Unfortunately delays in reperfusion are not unexpected, particularly for patients presenting to the hospital at night. In the NRMI-2, median time to first balloon inflation was 111 min, compared with 42 min for initiation of fibrinolytic treatment (door-to-needle) (13). Data from the same registry identified non-daytime presentation as one of the strongest predictors of door-to-balloon times >2 h. These data serve as the basis for current American College of Cardiology/American Heart Association (ACC/AHA) guidelines (14) that recommend door-to-balloon times of ≤90 min for primary angioplasty and encourage a concerted effort by institutions to ensure prompt treatment of patients with MI regardless of time of presentation.

In this issue of the Journal, the study by Henriques et al. (15) is of particular interest and relevance for national and international health care directives. Using data from 1,702 consecutive patients referred to a single center with acute ST-elevation MI, the investigators identified a difference in angioplasty success rates based on times of treatment. This was associated with a two-fold increase in 30-day mortality for patients admitted “off hours” (4.2% vs. 1.9%). Interestingly, and reflective of this center’s dedication to “round-the-clock” primary angioplasty, time to first balloon inflation was not significantly different by time of presentation (8:00 AM to 6:00 PM, 64 min vs. 6:00 PM to 8:00 AM, 69 min). These data suggest that the “time of treatment” is independent of “time to treatment” and collectively determines the benefit of mechanical reperfusion.

An explanation for the observed “circadian variation” in efficacy for primary angioplasty is not readily apparent. As suggested by the investigators, differing outcomes based on time of treatment may be linked to circadian variations in

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the pathobiology of atheromatous plaque rupture and localized thrombosis. Platelet aggregation in response to epinephrine, adenosine diphosphate, and thrombin is heightened during the early morning hours, particularly after arising from sleep (16,17). The plasma level of fibrinogen increases steadily between 6 AM and 12 PM, whereas anti-

thrombin levels decline (16). Similarly, several investigators have described a circadian variation or periodicity in fibrinolytic activity and thrombus lysability. Andreotti et al. (18) reported major circadian fluctuations in fibrinolytic factors, with a marked peak in plasminogen activator inhibitor activity during the early morning hours. Consistent with platelet biology and coagulation protease activity, a “prothrombotic period” exists between 6 AM and 12 PM and is independent of physical activity, work schedule, and/or sleep patterns. Epidemiologic data provide further support of periodicity, with an early morning peak in the occurrence of angina, MI, and sudden death (19,20).

The impact of pathobiologic periodicity on response to treatment in patients with MI has been studied. Using data from the Physician’s Health Study, Ridker et al. (20) noted a bimodal distribution of MI onset, with a primary peak in the morning hours in patients treated with placebo. This morning peak was decreased by 60% in patients receiving alternate-day aspirin, in essence eliminating any circadian variation in MI onset. Although the anticoagulant effects of a continuous heparin infusion appear to follow a circadian variation, the clinical significance of this has not been established (21). Finally, a diurnal variation in response to fibrinolytic therapy has also been documented. In a study of 244 patients with MI treated with either urokinase or tissue plasminogen activator, resistance to fibrinolysis was observed in the early morning and late evening hours (22).

Although it is an interesting hypothesis to consider, it seems unlikely that circadian variations in either thrombotic propensity or platelet behavior strongly contribute to the findings of Henriques et al. (15). The existence of circadian variation in a number of physiologic pathways, particularly platelet aggregation, cause thrombotic potential in the early morning hours. Accordingly, it is difficult to link heightened platelet activatability with the efficacy of angioplasty performed at night. Second, although intrinsic fibrinolytic capacity could be influenced by circadian variation in platelet or thrombotic activity, it is more challenging to postulate a link between these events and failure of initial mechanical revascularization. If either pathway were operational, one would have possibly expected recurrent thrombosis, MI, or sudden death following initial angioplasty; however, these outcomes were not reported. In addition, the administration of aspirin and heparin to all patients before their procedure would have minimized the impact of circadian variations in prothrombotic propensity.

On the basis of the available information, it seems much more likely that differences in outcomes observed in this study are accounted for by variations in patient characteristics, their care-seeking patterns, and/or the administered processes of care. Although baseline demographic and clinical characteristics stratified by time of presentation failed to reveal statistically significant differences in the variables measured, other nonreported factors may have been influential. Nearly one-half of the patients were referred from outside hospitals. It is possible that triage decisions varied by time of day and, as a result, more inherently ill or complex patients were transferred for angioplasty while others remained at community hospitals for fibrinolytic and/or medical treatment. The investigators acknowledge that patients presenting at night may have longer delay times from MI onset to presentation, even though symptom onset to admission did not differ significantly by time of day in their study (8:00 AM to 6 PM, 143 min vs. 6 PM to 8 AM, 146 min). Information derived from other observational studies suggests this may be the case. Data abstracted from the medical records of 1,255 patients with validated MI enrolled in the Worcester Heart Attack Study between 1995 and 1997 show marked differences in “pre-hospital” delay for patients presenting at different times of the day (23). Patients presenting from 12 AM to 6 AM delayed 1.4 h longer (mean pre-hospital delay 5.5 h) than those presenting from 6 AM to 12 PM. Onset of symptoms in the nighttime hours was significantly associated with delays of >2 h. These differences could certainly impact reperfusion success rates and clinical outcomes. Similarly, although the single site experience described in the current study employed 24-h services and achieved short time delays, the investigators appropriately acknowledge that other potentially important variables in patient care delivery could be impacted by time of day. Timely utilization of adjunctive therapies might also differ by time of day. Unfortunately, data on these and other treatment differences between groups in the current study are not provided.

An important consideration for “off-hours” primary angioplasty that is not commented on in the present study is whether the performance and characteristics of the health care team varies according to time of day. In most institutions the cardiac catheterization laboratory team, including the senior operators, work the daytime hours but take “call” at night for emergencies. On any given night the health care providers can be mildly to severely sleep deprived depending on their call schedule, daytime activities, and the length/intensity of prior shifts. The detrimental impacts of short-term and/or chronic sleep deprivation on cognitive performance and motor function are recognized and have been studied in a variety of subjects including healthy volunteers, truck drivers, and airline pilots. It has been estimated that wakefulness for 24 h is equivalent to a blood alcohol level of 0.1% with respect to effect on cognitive performance (24). As reviewed by Veasey et al. (25) in a recent issue of JAMA, the effects of sleep deprivation have been particularly well studied in medical residents in training. In one retrospective review of 6,371 surgical cases in which residents participated, 351 postoperative complications were identified (26). Although there were no differences in outcome by call
schedule type, complication rates were 45% higher for residents on call the previous night. In another study of 14 surgical residents, speed and accuracy for simulated laparoscopic procedures suffered greatly after 17 h on call (average sleep time 1.5 h) (27). These and other data suggest that even brief periods of sleep deprivation can impair procedure-related performance. A study of emergency department physicians found that night-shift physicians performed poorly on simulated intubation and clinical triage when compared with physicians working during the day (28). Performance further deteriorated with continued night shift duty. As residents on the night shift were documented to have inadequate sleep during the day, it was suggested that their worsening performance was due to sleep deprivation as well as circadian variations in cognitive function and manual dexterity. Surprisingly little if any attention has been paid to the impact of sleep deprivation and/or circadian variations on performance in other health care providers (staff physicians, fellows, nurses, technicians). One should consider strongly whether one or more of these factors contributed to the current study’s findings. Although current ACC/AHA guidelines stipulate that primary angioplasty must be performed by experienced operators (>75 cases/year), in high-volume institutions (>400 cases/year), and in a timely fashion (door-to-balloon time <90 min), there are no specific recommendations regarding nighttime staffing, work schedules, or hours on call (14). Given that many practicing interventionalists completed their training before currently existing reforms for residency training, they may feel that guidelines are unnecessary or perhaps even obstructive, yet they would likely agree that the cognitive and technical demands for performing primary angioplasty are substantial.

Given the burden of coronary heart disease worldwide, and the exponential growth in the use of mechanical revascularization, the data presented in the study by Henriques et al. (15) warrant careful consideration. If, in fact, procedural success rates and associated outcomes are influenced by time of day, the investigators have brought to light an important issue with substantial health care policy implications. Further studies designed to evaluate circadian variations in care-seeking behavior among patients with MI, as well as the performance of the health care team treating them, must be undertaken.

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