Debate: When should we intervene in unstable angina?
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Abstract

Current treatment modalities for patients with acute coronary syndromes center on early diagnosis, risk stratification and, increasingly, early treatment including invasive approaches. The appropriate timing of these invasive modalities in the context of the overall treatment program remains an area of controversy. Specifically, studies in the past recommended a period of medical ‘stabilization’ while current approaches are considerably more aggressive. The potential hazard of early intervention, in particular, has not properly been weighed against the benefit. This article hopes to provide a framework for examining the appropriate timing of intervention, specifically percutaneous coronary intervention, in acute coronary syndromes.

Keywords: acute coronary syndromes, early intervention, percutaneous coronary intervention

Introduction

The natural history of acute coronary syndromes (ACS), formerly referred to as unstable angina, is characterized by an early, high-risk period followed by a longer period of diminishing risk, which ultimately is statistically indistinguishable from clinically stable coronary heart disease [1,2]. Classic studies have now demonstrated important effects of specific pharmacologic treatments for these patients [3,4]. However, a disturbingly persistent rate of death or myocardial infarction of 12.1% at 6 months [5], and of 14.1% [6] and 12.2% [7] at 1 year, in conjunction with an increasingly aggressive approach to patient management, has led to the present controversy over the appropriate treatment of these patients. Specifically, the widespread availability of invasive services (at least in the USA) has accelerated the timing of invasive approaches to patient management. While some of this compressed care has been driven by third-party payors, a significant component of what to do and when is at the discretion of the physician. Therefore, a careful look at the time-honored approach defined as ‘cooling off’ and the current approach of ‘do-it-now’ is in order.

What is ‘cooling off’?

Our earlier concept of clinical quiescence was based on eliminating the frequency of anginal episodes [8]. In the early days of percutaneous transluminal coronary angioplasty (PTCA), now referred to as percutaneous coronary intervention (PCI), ‘hot’ patients appeared to fare less well with our efforts [9]. A period of ‘cooling off’ was therefore
patients, algorithms were developed that included an extended period of anticoagulation prior to PCI. Our group reported improved procedural outcomes in patients with unstable angina who received an extended period of intravenous heparin [19]. Importantly, a relatively well-defined ‘cut point’ was seen at 72 h [19]. It is also of note that this time dependence of procedural success was seen in both groups of patients (Fig. 1).

The present
The advent of potent pharmacologic adjuncts, for example platelet glycoprotein IIb/IIIa receptor antagonists, and the enhanced procedural safety offered by stents have dramatically changed the current landscape. In lieu of any period of ‘cooling down’, patients are now referred for invasive coronary procedures with alacrity. The latter, coupled with an ever-increasing trend in the performance of combined diagnostic and interventional procedures, has resulted in PCI being performed at a very early stage in the natural history of ACS. It is during this early period that the hazard of intervention is greatest [5,20]. Specifically, the marked inflammatory response and liberation of cytokines [21], the generation of free radicals [22], the enhanced activity of both intrinsic and extrinsic pathways of coagulation [23], and the perturbations in endothelial function that characterize both the active lesion and the response to mechanical disruption [14] all contribute to this potential hazard.

Another issue, however, is now upon us: PCI itself is associated with myocardial damage as reflected in postprocedural increases in myocardial-specific enzymes [24,25]. These measures of myocardial necrosis following PCI are in fact found more frequently in the setting of ACS than in more clinically stable populations [25]. While the etiology of the postprocedural enzyme release remains speculative, the possibility of distal thrombo-embolization consequent to plaque disruption is strongly supported by the mitigation of these events with the use of platelet glycoprotein IIb/IIIa receptor antagonists [26]. In virtually every recent trial of PCI in the setting of ACS, the increase in postprocedural CKP-MB fraction is several-fold greater than the control (prePCI) rate [26]. A second hazard is thus apparent, but whether this second hazard is disproportionately increased in patients undergoing ‘early’ PCI compared with a delayed procedure is unclear. An examination of the outcomes following PCI in clinical trials in which patients were randomized to either an ‘aggressive’ approach versus a ‘conservative’ approach (TIMI III [7], VANNOWISH [27], FRISC-II [5]) or pharmacologic trials in which PCI was deferred as a consequence of the duration of infusion of the study drug (EPIC [20], CAPTURE [28], PURSUIT [29], PRISM-PLUS [30]) provides some interesting insights (Fig. 2).

Although these trials differed substantially in design, primary end-points and pharmacologic adjuncts, the theme of early
Another look

It is important to point out that these opinions are neither an indictment of the invasive approach to ACS nor support for the conservative approach. They rather argue for a period of ‘stabilization’ with appropriate treatment and a treatment algorithm that emphasizes the appropriate time for intervention. There is little question that ‘earlier is better’ with respect to intervention in the setting of acute myocardial infarction. However, important differences in clinical, pathophysiologic, coronary anatomic and hemodynamic features distinguish patients with non-ST-elevation myocardial infarction from their more dramatic counterparts. It is suggested, in this article, that the ‘appropriate’ timing for PCI in the setting of ACS must consider the early hazard of procedural-related myonecrosis, the short- and long-term consequences of procedural-related increases in inflammatory markers and markers of the thrombotic state, and, finally, the increasingly cogent evidence in support of aggressive treatment of modifiable risk factors. The only answer to this question is, as always, a prospective randomized trial stratified by the timing of PCI.

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