Commentary

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

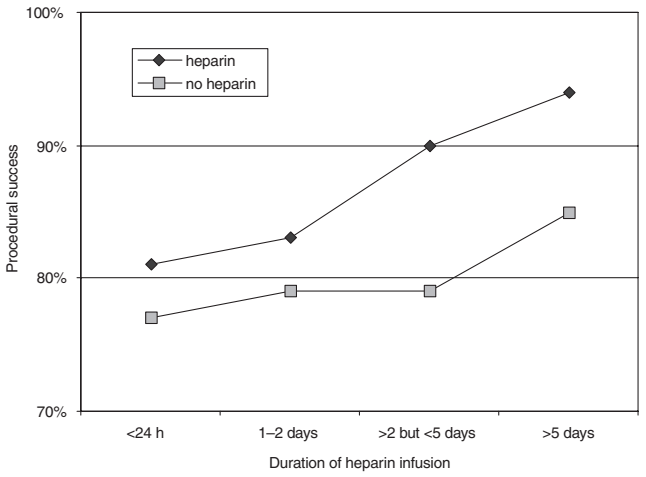
The natural history of acute coronary syndromes (ACS), formerly referred to as unstable angina, is characterized by an early, high-risk period followed by a longer period of diminishing risk, which ultimately is statistically indistinguishable from clinically stable coronary heart disease [1,2]. Classic 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

ACS = acute coronary syndrome; MACE = major adverse coronary events; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty.

Figure 1



Procedural success rates were significantly ($P < 0.05$) improved with a preprocedural infusion of heparin for at least 48 h. Adapted from [19].

recommended by many prior to PCI [9]. This period was in no way tantamount to benign neglect. The 'cooling off' period was defined, at that time, by state of the art anticoagulant, antiplatelet and anti-ischemic therapy. We have clearly learned much since these early studies. We now know that 'hot' patients truly have an underlying pathophysiology that has a strong inflammatory component [10]. Moreover, the 'hot' plaque in these patients is characterized by increased fragility [11], enhanced thrombogenicity [12,13], and cellular and molecular markers of inflammation [14]. It is, in fact, the presence of these inflammatory markers in the sera of these patients that appears to correlate best with both short-term and long-term clinical outcome [15,16]. Treatment programs directed towards 'cooling off' these patients must thus take into account this pathophysiology. The lessons learned from prior studies of PCI in patients with ACS have clearly provided a strong rationale for the current use of potent antiplatelet and antithrombotic agents. It is notable, however, that while specific anti-inflammatory therapy (in contrast to anti-infection therapy) may not be available at present, treatment programs that include an aggressive approach to lipid lowering may confer significant benefit [17]. The 'anti-inflammatory' sequelae of antioxidant and lipid lowering therapies are not, in fact, to be underestimated in their importance [18].

The past

Early studies, as has already been noted, reported higher rates of adverse clinical events during PCI in patients with ACS. Although subject to considerable bias as a consequence of their retrospective nature, several studies did suggest that a period of 'stabilization' resulted in improved clinical outcomes [9]. Given the presence of angiographically evident thrombus within the culprit vessel in such 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).

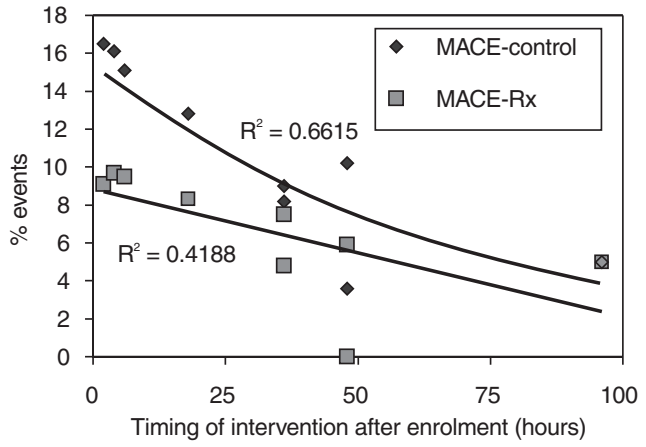
The present

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 CPK-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], VANQWISH [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

Figure 2



A significant inverse relationship exists between MACE rates and the timing of PCI irrespective of the nature of the study. See text for details.

versus deferred PCI is common to all. It can be seen that there is a statistically significant (inverse) relationship between short-term major adverse coronary events (MACE) rates as reported in the individual trials and the timing of intervention. Furthermore, it is of note that there is a 50% reduction of this MACE rate when intervention is deferred until at least 48 h following randomization.

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-term 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.

References

1. Braunwald E, Mark DB, Jones RH, Cheitlin MD, Fuster V, McCauley KM: **Clinical Practice Guideline No. 10. Unstable angina: diagnosis and management**. *AHCPR Publication No. 94-0602*, March 1994.
2. van Domburg RT, van Zijl AJ, Veerhoek RJ, Simoons ML: **Unstable angina: good long-term outcome after a complicated early course.** *J Am Coll Cardiol* 1998, **31**:1534–1539.
3. Lewis HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE, Schnaper HW, Lewinter MM, Linares E, Pouget JM, Sabharwal SC, Chester E, Demots H: **Protective effects of aspirin against myocardial infarction and death in men with unstable angina**. *N Engl J Med* 1983, **309**:396–403.
4. Theroux P, Ouimet H, McCans J, Lator JG, Joly P, Levy G, Pelletier E, Juneau M, Stasiak J, deGuise P: **Aspirin, heparin or both to treat acute unstable angina**. *N Engl J Med* 1988, **319**:1105–1111.
5. Fragmin and Fast Revascularization During Instability in Coronary Artery Disease Investigators: **Invasive compared with non-invasive treatment in unstable coronary artery disease: FRISC II prospective randomized multicenter study**. *Lancet* 1999, **354**:708–715.
6. Wallentin L, Lagerqrest B, Husted S, Kontay F, Stahle E, Swahn E, for the FRISC II Investigators: **Outcomes at 1 year after an invasive compared with a non-invasive strategy in unstable coronary artery disease: the FRISC II invasive randomized trial.** *Lancet* 2000, **356**: 9–16.
7. Anderson HV, Cannon CP, Stone PH, Williams DO, McCabe CH, Knatterud GL, Thompson B, Willerson JT, Braunwald E: **One year results of the TIMI IIIB clinical trial: a randomized comparison of tissue-type plasminogen activator vs. placebo and early invasive vs. conservative strategies in unstable angina and non-Q wave myocardial infarction.** *J Am Coll Cardiol* 1995, **26**:1643–1650.
8. Ouyang P, Brinker JA, Mellits ED, Weisfeldt ML, Gerstenblith G: **Variables predictive of successful medical therapy in patients with unstable angina**. *Circulation* 1984, **70**:367–376.
9. DeFeyter PJ, Serruys PW: **Percutaneous transluminal coronary angioplasty for unstable angina**. In *Textbook of Interventional Cardiology*, Vol. 1, 2nd edn. Edited by Topol EJ. Philadelphia, PA: WB Saunders, 1993:274–291.
10. Ross R: **Atherosclerosis — an inflammatory disease**. *N Engl J Med* 1990, **340**:115–126.
11. Shah PK, Falk E, Badimon JJ, Fernandez-Ortiz A, Mailhac A, Villareal-Levy G, Fallon JT, Regnstrom J, Fuster V: **Human monocyte-derived macrophages induce collagen breakdown in fibrous caps of atherosclerotic plaques. Potential role of matrix-degrading metelloproteinases and implications for plaque rupture**. *Circulation* 1995, **92**:1565–1569.
12. Topol EJ: **Toward a new frontier in myocardial reperfusion therapy: emerging platelet preeminence**. *Circulation* 1998, **97**:21–28.
13. Theroux P, Fuster V: **Acute coronary syndromes — unstable angina and non-Q wave myocardial infarction**. *Circulation* 1998, **97**:1195–1206.
14. Kinlay S, Selwyn AP, Libby P, Ganz P: **Inflammation, the endothelium and the acute coronary syndromes**. *J Cardiovasc Pharm* 1998, **32(Suppl 3)**:S62–S66.
15. Liuzzo G, Brasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A: **The prognostic value of C-reactive protein and serum amyloid — a protein in severe unstable angina.** *N Engl J Med* 1994, **331**:417–424.
16. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, Braunwald E: **C-Reactive protein is a potent predictor of mortality independent of and in combination with troponin T in acute coronary syndromes: a TIMI 11A sub-study**. *J Am Coll Cardiol* 1998, **31**:1460–1465.
17. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S, Flaker GC, Braunwald E, for the Cholesterol and Recurrent Events (CARE) Investigators: **Inflammation, pravastatin and the risk of coronary events after myocardial infarction in patients with average cholesterol levels**. *Circulation* 1998, **98**:839–844.
18. Rosenson RS, Tangney CC, Casey CL: **Inhibition of pro-inflammatory cytokine production by pravastatin**. *Lancet* 1999, **353**:983–984.
19. Lukas-Laskey MA, Deutsch E, Barnathan E, Laskey WK: **Influence of heparin therapy on percutaneous transluminal coronary angioplasty outcome in unstable angina pectoris**. *Am J Cardiol* 1990, **65**:1425–1429.
20. EPIC Investigators: **Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high risk coronary angioplasty**. *N Engl J Med* 1994, **330**:956–961.
21. Liuzzo G, Buffon A, Biasucci LM, Gallimore R, Caligiuri G, Vitelli A, Altamura S, Ciliberto G, Rebuzzi AG, Crea F, Pepys MB, Maseri A: **Enhanced inflammatory response to coronary angioplasty in patients with severe unstable angina**. *Circulation* 1998, **98**:2370–2376.

22. Buffon A, Santini SA, Ramazzotti V, Rigattieri S, Liuzzo G, Biasucci LM, Crea F, Biardina B, Maseri A: **Large, sustained cardiac lipid peroxidation and reduced antioxidant capacity in the coronary circulation after brief episodes of myocardial ischemia**. *J Am Coll Cardiol* 2000, **35**:633–639.
23. Fuster V, Fayad Z, Badimon J: **Acute coronary syndromes: biology**. *Lancet* 1999, **353(Suppl II)**:5–9.
24. Abdelmeguid AE, Topol EJ, Whitlow PL, Sapp, SK, Ellis SG: **Significance of mild transient release of creatine kinase – MB fraction after percutaneous coronary intervention**. *Circulation* 1996, **94**: 1528–1536.
25. Califf RM, Abdelmeguid AE, Kuntz RE, Popma JJ, Davidson CJ. Cohen EA, Kleiman NS, Mahaffey KW, Topol EJ, Pepine CJ, Lipicky RJ, Granger CB, Harrington RA, Tardiff BE, Crenshaw BS, Bauman RP, Zuckerman BD, Chaitman BR, Bittl JA, Ohman M**: Myonecrosis after revascularization procedures.** *J Am Coll Cardiol* 1998, **31**:241–251.
26. Kong DF, Califf RM, Miller DP, Moliterno DJ, White HD, Harrington RA, Tcheng JE, Lincoff AM, Hasselblad V, Topol EJ: **Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease**. *Circulation* 1998, **98**:2829–2835.
27. Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, Wexler LF, Kleiger RE, Pepine CJ, Ferry DR, Chow BK, Lavori PW, for the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators: **Outcomes in patients with acute non-Q-wave myocardial infarction randomly asigned to an invasive as compared with a conservative management approach**. *N Engl J Med* 1998, **38**:1785–1792.
28. The CAPTURE Investigators: **Randomized, placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study.** *Lancet* 1997, **349**:1429–1435.
29. The PURSUIT Trial Investigators: **Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes.** *N Engl J Med* 1998, **339**:436–443.
30. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Visible Signs and Symptoms (PRISM-PLUS) Study Investigators: **Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction**. *N Engl J Med* 1998, **338**:1488–1497.

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