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EDITORIAL COMMENT

Interventional Therapy for Acute Myocardial Infarction: Respect the Microvasculature*

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It is widely accepted that improved perfusion of viable myocardium preserves cardiac function and conveys long-term survival benefits after myocardial infarction (MI). Mechanical reperfusion for acute MI targets optimal revascularization of the epicardial artery but also aims at improved myocardial salvage. Intracoronary thrombus (especially large amounts) makes both of these goals difficult to achieve because attempts to maximize lesion-related outcomes may lead to embolization of thrombus distally with occlusion of the microvasculature and with actual prevention of myocardial salvage.

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A variety of interventional approaches have been targeted to acute MI interventions, but useful clinical investigation in this area has been hampered by: 1) the delayed recognition of adequate devices to treat the target lesion most optimally (e.g., balloon angioplasty only recently was proven beyond any doubt to be inferior to stent implantation) (1); 2) the confusion regarding the optimal combination antithrombotic regimen (e.g., limitations of intracoronary fibrinolytic therapy, the necessity of antithrombotic and antiplatelet therapy shortly after successful reperfusion, the importance of residual mural thrombus) (2); 3) "competition" between pharmacologic and mechanical approaches for primary reperfusion (e.g., angioplasty only recently has been understood as superior to fibrinolytic therapy and "worth the wait") (3,4); 4) the lack of appropriately designed studies with thrombectomy devices in acute MI (e.g., early experience largely was exhausted on thrombotic lesion and vein graft registries rather than proper acute MI) (5); 5) the rather-recent development of distal embolic protection devices and their potential acute MI applications; and 6) the difficulty to properly assess important differences among different strategies without "major" (large in size and cost) mortality trials.

This field is profoundly complex because of the interrelationship of all the above concepts, the acuity of the clinical situation (and hence the necessity for rapid treatment and also rapid enrollment in relevant clinical trials) (6), and the potential risk to underestimate a potentially important tool if tried along other inappropriate choices, for example, the role of thrombectomy might be underestimated if one were to study even a perfect catheter along with intracoronary fibrinolytics and balloon angioplasty alone. Moreover, the end points of "reperfusion" and "thrombus resolution" have been traditionally difficult to accurately define and measure objectively, thus making the evaluation of thrombectomy devices problematic.

The choice of an appropriate study end point is also very important; for example, the administration of abciximab in acute MI interventions appears to be very beneficial with respect to early outcomes (lower subacute closure, improved 30-day outcome) (7,8), especially when given very early (8), but it does not offer any benefit over a placebo if a six-month restenosis-related outcome is examined (7) or if given late (1).

Regardless of all these issues, the demonstration of the importance of microvascular integrity for myocardial salvage (9) focused the interventional goals not only to the target lesion but to the prevention of distal embolization of thrombus as well. Distal emboli not only mechanically "plug" the microvasculature by themselves but also produce spasm and local inflammatory reaction that may further complicate recovery. In its extreme cases, this can be manifested as reduced Thrombolysis In Myocardial Infarction (TIMI) trial grade flow in the epicardial artery ("no-reflow" phenomenon). There are many cases, however, where this process is still present but it is undetected by the classic TIMI grade flow classification. Inadequate myocardial perfusion in the presence of ("normal") epicardial TIMI-3 flow could be detected as delayed resolution of ST-segment elevation but until recently was difficult to document angiographically. In acute MI cases with large epicardial artery thrombus load, one would be unreasonable to expect that all thrombotic particles would dissolve with pharmacologic therapy; the difficulty for proving the need for thrombectomy (or distal embolic protection) would be: 1) to have the proper device, and 2) be able to measure a parameter that acknowledges the importance of microvascular function and myocardial perfusion above and beyond epicardial artery patency.

Evaluation of the Myocardial Blush Grade (MBG) filled this particularly important gap and allowed further stratification of TIMI-3 flow according to this parameter (10–12). Normal MBG should characterize excellent microvascular function and myocardial perfusion, but decrements of MBG would indicate suboptimal microvascular flow despite epicardial TIMI-3 flow.

In this context, Napodano et al. (13) report in this issue of the *Journal* their single-center randomized study of intracoronary thrombectomy in acute ST-segment elevation

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MI and report on TIMI flow, MBG, and ST-segment resolution. Inclusion was limited to 12 h after onset of pain, thus studying the treatment of "fresh clot." Randomization to the use or not of thrombectomy (with the new X-sizer catheter, ev3, White Bear Lake, Minnesota) was performed right after the baseline angiogram and before wire cross. Pretreatment with aspirin and weight-adjusted unfractionated heparin was used, clopidogrel was not used, and abciximab was initiated after angiography in 41% to 43% of cases in both groups according to operator preference. Although not by an independent core laboratory, the angiographic analysis was painstaking and included measurements at baseline, after wire cross, after thrombectomy (only in the study group), and at final views. The study was appropriately powered to detect an absolute difference of 30% in MBG-3 ("normal" MBG) between the groups based on their earlier pilot study and published reports on MBG without thrombectomy (12,13).

The control group had higher rate of occluded arteries at baseline (85% vs. 74%) but a lower rate of persistent occlusion after wire cross (50% vs. 57%). Restoration of antegrade flow occurred in almost one-third of originally occluded arteries, and even TIMI-3 flow was achieved in almost one third of the total cases within each group just by the wire (Fig. 2A in reference 13), a characteristic of truly "fresh clot." However, these remarkable improvements were not accompanied by improvements of similar magnitude in MBG (<20% improvement in occluded microvasculature, Fig. 2B in reference 13); this difference underlines how "strict" this new angiographic end point is compared with TIMI grade flow; less than one-half of epicardial arteries with TIMI-3 flow after wire cross had MBG-3. After thrombectomy, TIMI-3 and MBG-3 improved to 94% and 72%, respectively, at the final angiogram. In contrast, the control group had 96% TIMI-3 flow but only 37% MBG-3. In addition, there was significantly more "no-reflow" and distal embolization in the control group. These angiographic measures were accompanied by the more frequent resolution (at least 50% from pre-percutaneous coronary intervention) of ST-segment elevation with thrombectomy (83% vs. 52%). Although temporal changes in left ventricular ejection fraction were no different between the two treatment groups, significant improvement was noted in patients with normal final MBG score regardless of treatment allocation. The latter finding should indicate that there is room for improvement even in the thrombectomy arm.

Another interesting finding of this study was the significantly greater direct stenting approach after aspiration, which indicated that savings with respect to the cost of predilation balloon may subsidize the thrombectomy catheter cost.

These results generally support the favorable effect of thrombectomy in acute MI intervention but also underline that thrombectomy does not really work alone. Within the thrombectomy group, 78% had TIMI-3 flow and 52% had MBG-3 after aspiration (Figs. 2B and 3 of reference 13), and both of these parameters improved at the final angiogram. This was achieved because of the restoration of antegrade flow and appropriate pharmacotherapy. In fact, one would expect even better results in this study group if more aggressive pharmacologic therapy had been instituted. Emergency room administration of clopidogrel loading dose as well as abciximab should be expected to enhance angiographic outcomes and myocardial recovery in synergy with thrombectomy. Still unexplored is the role of low molecular weight heparins and direct thrombin inhibitors in this clinical context with or without abciximab.

Is it possible that one could expect similar results with aggressive pharmacotherapy alone without thrombectomy? Data from this study do not show any such trend (Fig. 4B of reference 13); neither did data of the multicenter X-TRACT trial (Stone GW, oral presentation, American Heart Association, 2002). However, an aggressive pharmacologic protocol as described above has not been formally studied as alternative to mechanical thrombectomy.

Another question would be whether distal embolic protection would be an alternative to thrombectomy. Although distal embolic protection has worked well in saphenous vein grafts that do not have any side branches, it is not logistically deciphered with respect to coronary application. This concept is currently being studied in a multicenter trial with the use of the distal balloon occlusion and aspiration system. I would think that ultimately both thrombectomy and distal embolic protection will be shown beneficial in thrombotic MI lesions, and their use could be dictated by specific anatomic scenarios until a head-to-head comparison is performed. Specific device characteristics (and shortcomings) would probably matter much in such comparisons. For example, Napodano et al. (13) had three persistent occlusions that were characterized by the inability of the aspiration catheter to reach or cross the lesion; potential use of a lower-profile distal protection device might have rendered these cases technically feasible. Even within each group of devices, there are potentially important differences that have not been explored in clinical trials, for example: 1) the principle of rheolytic thrombectomy while the Angiojet catheter (Possis Medical Inc., Minneapolis, Minnesota) is retracted versus aspiration thrombectomy while the X-sizer catheter is advanced forward; 2) the differential impact of more powerful aspiration with larger Angiojet catheters versus the delivery of smaller-size thrombectomy catheters to the distal vessel; and 3) distal embolic protection with a distal occlusion balloon and aspiration system versus a proximally positioned similar system versus a distal filter.

In summary, I think that our refined understanding of adjunct pharmacologic therapy during percutaneous coronary intervention of thrombotic lesions, device choice in acute MI intervention, and improvement in thrombectomy catheters (and the upcoming development of several distal protection devices for acute MI) indicate that significant

advances in this area should be expected in the near future, enabling not only epicardial artery revascularization but microvascular protection as well.

The development of the new angiographic end point of MBG enables a more detailed and strict efficacy analysis. However, we should move very cautiously in adopting it universally because there are certain questions regarding this new marker of microvascular performance, such as: 1) reproducibility, 2) investigational integrity, and 3) prognostic importance. Starting from the last issue, there are data that abnormal MBG correlates with more late adverse events just as powerfully as abnormal epicardial TIMI grade flow does (10–12). However, this has not been confirmed yet in specifically designed prospective trials. In addition, confusion still exists on how to properly evaluate this parameter. Studies have been reported thus far from specialized angiographic laboratories, with angiograms both performed and interpreted by experts in this field; would the detailed protocol for performance of angiograms "appropriate for MBG evaluation" be reproduced as accurately/reliably in multicenter trials in less specialized centers and how do potential flaws affect applicability of MBG score? Finally, how are bias-related issues resolved regarding this semiquantitative scoring system? This is easier said than done because thrombectomy (and distal embolic protection) devices under evaluation are not easily blinded, and proper MBG and TIMI score evaluations should be performed on spliced films so that only the pre- and final angiograms are evaluated without any availability of the interpreter to have access to visual or other information regarding the device used during the case. I am not sure this specific methodologic rigor has been followed thus far in the "proof-of-principle" MBG studies but should be specifically demanded from now on if this parameter is accepted as a major efficacy endpoint.

Meanwhile, ST-segment resolution is documented in many contemporary acute MI trials, and the emergence of cardiac magnetic resonance imaging allows for very detailed and reproducible quantification of MI size and temporal changes in microvascular perfusion and myocardial function after primary (direct), rescue, delayed, or "facilitated" reperfusion strategies. After a rather quiescent period that followed the investigation of intravenous fibrinolytic agents (14,15), acute MI is becoming again the "hot topic" of interventional cardiology research and cardiologists (and patients) should be excited about it.

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