Editorial

From Primary to Secondary Percutaneous Coronary Intervention: The Emerging Concept of Early Mechanical Reperfusion With Delayed Facilitated Stenting—When Earlier May Not Be Better

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(See article by Tang et al. on pages 541-547 in this issue.)

With the rise of percutaneous coronary intervention (PCI) and the availability of new anticoagulants, many revascularization strategies have been described for patients with ST-segment elevation myocardial infarction (STEMI) (Table 1). These strategies aim at 3 simple targets: to accelerate reperfusion, to minimize thrombus burden, and to promptly stabilize the infarct-related lesion.

The rush to stabilize the infarct-related lesion originates from the early days of fibrinolytic therapy, when 10% to 15% of patients experienced an acute coronary reocclusion after successful reperfusion. At that time, reocclusions were associated with a near tripling of mortality. Before the widespread use of primary PCI, coronary interventions were rarely performed after fibrinolytic drug administration because they increased bleeding complications but provided no obvious benefit. In the early days of primary PCI, balloon angioplasty was preferred to stenting because of concerns about acute stent thrombosis. It was only after thienopyridines became available that acute stenting gained wide acceptance, as thienopyridines provided no obvious benefit. Nevertheless, the mortality benefits of primary stenting are far from compelling. In at least 2 major contemporary primary PCI trials, a greater number of deaths were seen among patients treated with stents compared with those treated with balloon angioplasty alone. Stents implanted in a thrombotic environment can paradoxically compromise coronary blood flow by causing distal emboli and no-reflow phenomena. In the recent Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) trial, for instance, only half the patients treated by primary stenting left the catheterization laboratory with normal myocardial perfusion, despite the use of thrombectomy and maximal anticoagu-

Distal embolization after primary stenting has been associated with larger enzymatic infarct size, lower left ventricular ejection fraction, and increased mortality. With the widespread use of dual antiplatelet therapy, glycoprotein IIb/IIIa blockade, and adjunctive anticoagulation, the rate of coronary artery reocclusion after myocardial infarction has dropped significantly. However, primary stenting continues to cause distal embolization and no reflow. One solution could be to delay stent implantation in successfully reperfused STEMI patients. This, at least, is what Tang et al. suggest in this month’s issue of the Canadian Journal of Cardiology.

The study by Tang et al. and related concepts hold the promise of a possible revolution in the way we treat myocardial infarction. Tang et al. compared immediate vs delayed stent implantation in patients with a first STEMI successfully reperfused by thrombectomy. Patients with low residual thrombus burden were assigned to immediate stenting, whereas patients with larger thrombus burden were assigned to delayed stenting after 7 days of adjunctive anticoagulation and antiplatelet therapy. Delayed stenting was associated with a significant reduction in poststenting coronary embolism and no-reflow phenomena (19% vs 3%). While the difference was not statistically significant, delayed stenting translated into a trend toward fewer major cardiac events at 6 months (23% vs 10%). Of note, the extent of myocardial damage measured by regional contraction abnormalities was significantly lower among patients managed with delayed stenting. The rates of bleeding remained similar between groups. While many consider that STEMI care has reached a plateau, the emerging concept of delayed stenting may well be the next step that breaks this plateau and further improves patient outcomes. For that, the authors are to be congratulated.

The study presents limitations that require mention. While less than a third of the consecutively presenting patients were enrolled in the study, the exclusion criteria are not clearly identified in the paper. Without clear knowledge of these criteria, it is difficult to obtain a clear representation of the inception cohort used in the study. Notably, the proportion of patients not eligible for the study because of small vessel size or imprac-
ticable anatomy is not indicated. The authors do not mention whether coronary flow had to be normalized (thrombolysis in myocardial infarction flow, grade 3 [TIMI 3]) before patients could be enrolled in the study. Arguably, this information is important since TIMI flow is an important predictor of acute reocclusion after reperfusion. Methodologically, the interobserver variability for the quantitative coronary analysis was not disclosed. The finding that delayed stenting likely prevents congestive heart failure could have been substantiated with disclosed. The finding that delayed stenting likely prevents server variability for the quantitative coronary analysis was not yields a power of 37%.

In this case, the authors seem to have assumed that 1 specified group (the delayed stenting) would have the best outcome. This assumption is not appropriate if one believes that delayed stenting could cause harm. Understandably, this pilot study was not based on a prespecified hypothesis; the many unadjusted statistical comparisons should raise concern around the possible false-positive and -negative findings. For example, Tang et al. observed a trend in favour of a reduction in congestive heart failure (5% vs 19%). Assuming an alpha value of .05 and equal variance between groups, the study had a post hoc statistical power of 52% to detect a statistically significant difference in the rates of congestive heart failure. The same calculation performed at the prespecified combined endpoint yields a power of 37%.

### Prior Experience With Delayed Stenting

The findings reported by Tang et al. are biologically plausible and are consistent with similar previously published work (Table 2). Cafri et al. originally studied the consequences of delaying primary PCI in a cohort of patients with angiographically visible coronary thrombus. In their series, delaying the stent implantation for 5 days reduced the occurrence of thrombus-related angiographic events from 27% to 4%. In the largest study to date, Di Pasquale et al. compared the efficacy of immediate (<2 hours after reperfusion) vs delayed facilitated PCI (12 to 72 hours after reperfusion) in a population of patients with STEMI reperfused with a pharmacologic combination of glycoprotein IIb/IIIa blockade plus half the conventional dose of recombinant tissue plasminogen activator (rtPA). Patients were treated with aspirin, heparin, and a thienopyridine. Vessel patency could be maintained in all patients randomized to the delayed PCI strategy. Stents implanted an average of 50 ± 22 hours after symptom onset were associated with fewer angiographic events and a significant reduction in death and myocardial infarction at 6 months. Interestingly, delayed stenting was also associated with less restenosis (22.6% vs 15%, \( P = 0.01 \)) at 6 months.

An interesting delayed stenting strategy is the minimalist immediate mechanical intervention (MIMI). This approach advocates that reperfusion should be attempted with the tools

### Table 1. Percutaneous coronary intervention (PCI) strategies used in ST-segment elevation myocardial infarction (STEMI)

<table>
<thead>
<tr>
<th>Study, year, design, average delay for PCI</th>
<th>Angiographic events</th>
<th>Significant bleeding</th>
<th>Adverse cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate PCI</td>
<td>Delayed PCI</td>
<td>Immediate PCI</td>
</tr>
<tr>
<td>Cafei et al.,12 2004, Prospective Cohort, 4.9 d ± 3.0 d</td>
<td>22/82 (27%)</td>
<td>1/24 (4%)</td>
<td>2/82 (3%)</td>
</tr>
<tr>
<td>Di Pasquale et al.,10 2006, RCT, 45.1 h ± 20.2 h</td>
<td>90/225 (40%)</td>
<td>37/226 (16%)</td>
<td>10/225 (4%)</td>
</tr>
<tr>
<td>Issa et al.,14 2006, Case-Series, &gt; 24 h</td>
<td>9/39 (23%)</td>
<td>2/39 (5%)</td>
<td>1/39 (3%)</td>
</tr>
<tr>
<td>Meneveau et al.,7 2009, Case-Control, 21.1 h ± 5.4 h</td>
<td>9/47 (19%)</td>
<td>1/40 (3%)</td>
<td>0/47 (0%)</td>
</tr>
</tbody>
</table>

Statistically significant differences are indicated in bold. Data presented as absolute number and percentage.

PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

* Defined as thrombus-related angiographic events resulting from the intervention, including coronary embolism, no-reflow phenomenon, and acute coronary closure.

1 Variable definitions used.

1 Variable composite endpoints used:

1 In-hospital occurrence of death, myocardial infarction, and urgent revascularization.

1 Death or myocardial infarction within 6 months.

1 Cardiac death, nonfatal infarction, recurrent ischemia, target lesion revascularization, or congestive heart failure within 6 months.

### Table 2. Clinical studies comparing immediate vs delayed stenting in successfully reperfused, thrombus-laden infarct-related arteries

<table>
<thead>
<tr>
<th>Study, year, design, average delay for PCI</th>
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**Figure 1.** Simplified strategy of delayed percutaneous coronary intervention (PCI). Gp, glycoprotein; PTCA, percutaneous transluminal coronary angioplasty; STEMI, ST-segment elevation myocardial infarction; TIMI 3, thrombolysis in myocardial infarction flow, grade 3.
least likely to injure the artery or cause distal emboli; with stents implanted only after the thrombus has significantly regressed, usually after many days of anticoagulation. Using the MIMI approach, Isaza et al., using a guidewire alone or a small-size (≥1.5 mm) balloon catheter (the study was performed before thrombectomy was available), successfully reperfused 77 of the 93 patients presenting with STEMI. Of the 77 patients, 84% had >50% resolution of their ST-segment elevation at 1 hour after the intervention. At 24 hours, all patients maintained patent infarct-related arteries. The association of aspirin, clopidogrel, abciximab, and heparin decreased the thrombus score from 2.1 ± 1.2 after the MIMI-approach to 0.9 ± 1.3 at 24 hours (P < 0.001). Only 2 patients assigned to delayed stenting experienced an angiographic event. Similar results were recently reported by Meneveau et al. in patients with recent STEMI showing a patent yet thrombus-laden coronary artery.9

An overview of the previous studies (Table 2) allows 4 comments. First, untoward ischemic events are infrequent in the interval between index reperfusion and actual stent implantation. In the reported series, 2 patients experienced recurrent angina, but none experienced acute coronary artery reocclusion. This observation suggests that adjunctive anticoagulation and enhanced antiplatelet therapy may adequately stabilize the infarct-related lesion subjected to stenting. Second, delayed stenting is consistently associated with fewer procedure-related coronary events. The rates of postprocedural TIMI 3 flow observed with delayed PCI (ranging from 83% to 100%)9,12 compare favourably with the rates associated with fibrinolytic served with delayed PCI (ranging from 83% to 100%)9,12 coronary events. The rates of postprocedural TIMI 3 flow obstenting is consistently associated with fewer procedure-related infarct-related lesion subjected to stenting. Second, delayed PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

**Table 3. Potential advantages and disadvantages of delayed PCI**

<table>
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<tr>
<th>Advantages of delayed PCI</th>
<th>Disadvantages of delayed PCI</th>
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<tr>
<td>• Decreased rates of angiographic events (distal emboli, no-reflow) with reduced infarct size</td>
<td>• Increased bleeding hazard</td>
</tr>
<tr>
<td>• Time to assign the most appropriate treatment strategy (stent vs coronary artery bypass grafting vs medical therapy alone)</td>
<td>• Possible acute coronary reocclusion</td>
</tr>
<tr>
<td>• No stent or PTCA needed in 10% of patients9,14</td>
<td>• Repeated cardiac catheterization required</td>
</tr>
<tr>
<td>• Allows statin preloading before angioplasty13</td>
<td>• Prolonged hospital stay and increased immediate costs (cost-effectiveness unknown)</td>
</tr>
<tr>
<td>• Stent selectively implanted during routine duty hours18</td>
<td></td>
</tr>
<tr>
<td>• Possible reduction in congestive heart failure,10 reinfection, and death16</td>
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</tr>
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</table>

**Future Directions**

Data from the available studies of delayed PCI converge toward a few key principles (Fig. 1). Once flow has been emergently re-established (preferably by mechanical means such as thrombectomy or small-size balloon catheter deployment), a stent should be implanted in the immediate STEMI-PCI setting only when no residual thrombus is visible. In the face of significant residual thrombus burden, stents should be withheld until adjunctive anticoagulation and antiplatelet therapies have been administered. Once significant thrombus meltdown is confirmed by angiography, the most appropriate treatment, whether stenting, coronary artery bypass grafting, or medical therapy, should be offered to the patient.

Table 3 summarizes some of the advantages and disadvantages potentially associated with delayed stenting. The delay between reperfusion and stent implantation allows for time-sensitive selection of the most appropriate treatment strategy. In the study by Isaza et al., for instance, 19 of the 77 patients initially reperfused with the MIMI therapy ended requiring coronary artery bypass grafting instead of stenting.14 Six patients (8%) without residual lesions on the follow-up angio-gram did not require stents. In Meneveau et al., this proportion reached 10%. Concerns about bleeding risks may be partially offset by the growing use of transradial intervention.15 What remains unknown is whether the increased costs associated with adjunctive anticoagulation, repeated catheterization, and extended hospital stay will be offset by the potential cardiovascular events prevented by delayed stenting.

Delaying stent implantation contradicts many of the dogmas of contemporary cardiology and calls into question decades-old paradigms. The most appropriate next step is a randomized controlled trial. The available evidence suggests that in hemodynamically stable STEMI patients with a patent infarct-related artery and a reperfused myocardium, it is reasonable to test whether a strategy that combines adjunctive anti-thrombin and antiplatelet therapies with late stenting is superior to primary PCI. The delayed PCI strategy merits particular consideration when the infarct-related artery shows evidence of high thrombus burden after the initial reperfusion. If this strategy of delayed PCI does prove to be advantageous, several questions will arise, such as the optimal delay before stent implantation and the most appropriate adjunctive therapy. Because of these various possibilities, cost-effectiveness studies would become important.

The strategy of delayed stenting capitalizes on the best of what interventional cardiology has to offer for patients with STEMI—thrombectomy and enhanced antiplatelet therapy. In this era of fast and furious cardiology, it also capitalizes on the best healing nature can offer: time.

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**Disclosures**

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**References**


