Primary angioplasty for acute myocardial infarction: is the balloon half full or half empty?

Reperfusion therapy has become the cornerstone of the early treatment of acute transmural myocardial infarction. Both modern thrombolytic therapy and primary coronary angioplasty have been shown to restore early adequate flow in the infarct-related coronary artery in most patients with acute transmural myocardial infarction. A thrombolytic agent can be given intravenously in any hospital and even in an ambulance. Primary angioplasty is possible only in tertiary centres with angioplasty facilities, preferably with surgical standby. Small studies directly comparing primary angioplasty with thrombolytic therapy in patients eligible for thrombolysis indicate clinical superiority of angioplasty over thrombolytic therapy. In about 1200 patients in seven trials (only two containing more than 300 patients) mortality from acute myocardial infarction was 40% lower in the primary angioplasty than in the thrombolysis group (4% versus 7%, respectively). However, the trials differed in design, thrombolytic agents used, and patient-selection criteria, and they were conducted in a small number of centres, where staff were skilled in coronary angioplasty. A larger trial, following a single protocol, directly comparing primary angioplasty with the most efficient thrombolytic regimen (front-loaded tPA), and conducted in a larger number of centres around the world has been much needed.

The preliminary results of the large primary angioplasty versus thrombolysis substudy of GUSTO-II were presented at the 45th Annual Scientific Session of the American College of Cardiology in March, 1996. Over 1000 patients with acute myocardial infarction eligible for thrombolysis were randomised within 6 h of symptom onset to primary angioplasty or front-loaded tPA in angioplasty centres around the world. The primary endpoints were mortality, reinfarction, or disabling stroke at 30 days. From the preliminary findings (table) the reduction in morbidity and mortality from acute transmural myocardial infarction with primary angioplasty is less prominent than previously observed. The data for tPA are comparable to those found in other studies. The somewhat disappointing results with primary angioplasty do not reveal a group especially likely to benefit from either angioplasty or thrombolysis.  

From the results so far one cannot conclude that primary angioplasty is better than thrombolysis for patients with acute myocardial infarction. The primary angioplasty aficionados will state that it takes only 100 primary angioplasty procedures in acute myocardial infarction to prevent one death, one cerebral bleed, and two reinfarctions at the cost of one major non-cerebral bleed. But is it worthwhile? Costs will rise if primary angioplasty becomes the treatment of choice. The number of angioplasty sites, together with round-the-clock standby angioplasty teams, will have to be increased considerably. Emergency referral to existing centres may be an alternative—whether the time lost in the transfer limits the benefits of the strategy is being investigated.

For the moment, one can only conclude that primary angioplasty is at least an excellent and probably safe alternative to modern thrombolysis. Which of the two treatments is the superior cannot be assessed yet. The technique of coronary angioplasty is evolving rapidly, and stent implantation at time of primary angioplasty for acute myocardial infarction is not uncommon anymore. Safer thrombolytic strategies with higher early reperfusion rates will be available in the near future. Because of the logistic restrictions of primary angioplasty, thrombolytic therapy is still the gold standard for early treatment of acute transmural myocardial infarction.

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Table: Preliminary results of GUSTO-II substudy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Primary angioplasty</th>
<th>tPA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death*</td>
<td>6%</td>
<td>7%</td>
<td>0.57</td>
</tr>
<tr>
<td>Reinfarction*</td>
<td>4%</td>
<td>6%</td>
<td>0.24</td>
</tr>
<tr>
<td>Disabling stroke*</td>
<td>0%</td>
<td>1%</td>
<td>0.10</td>
</tr>
<tr>
<td>Death/reinfarction/disabling stroke*</td>
<td>10%</td>
<td>13%</td>
<td>0.06</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>0%</td>
<td>1%</td>
<td>0.02</td>
</tr>
<tr>
<td>Major non-cerebral bleeding</td>
<td>3%</td>
<td>2%</td>
<td>0.83</td>
</tr>
</tbody>
</table>

* at 30 days

(which were obtained in the angioplasty-treated patients and were read in a core laboratory). Coronary reperfusion (TIMI flow grades 2 and 3) occurs in only 83% of patients who have undergone angioplasty, with 74% of the patients having TIMI-3 flow, which is the level of reperfusion associated with the best survival. In earlier studies adequate reperfusion with front-loaded tPA occurred in 54% of patients. Since the time to reperfusion is probably similar in both arms of the GUSTO-II angioplasty substudy, the small absolute gain of 20% adequate reperfusion with angioplasty is likely to explain why the benefit of primary angioplasty over thrombolysis was only moderate. Subgroup analysis did not reveal a group especially likely to benefit from either angioplasty or thrombolysis.)
Genetic abnormalities, male infertility, and ICSI

See page 1290

Intracytoplasmic sperm injection (ICSI) has revolutionised the management of severe male-factor infertility. In 1992 Palermo and colleagues demonstrated that the insertion of a single sperm into the cytoplasm of a mature oocyte will result in fertilisation and an apparently normal embryo. Since that initial report, successful fertilisation has been achieved for nearly every spermatozoal abnormality or combination of abnormalities. Even men thought to have azoospermia due to gonadal failure can now become fathers, a possibility considered remote only 3 years ago. In recent years, however, it became apparent that many men with severe male-factor infertility also harbour genetic mutations that not only can be the cause of their reproductive abnormalities but also may affect other somatic functions. For example, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene can be associated with congenital absence of the vas deferens and with the clinical expression of cystic fibrosis. In contrast, non-obstructive azoospermia should prompt karyotype analysis since chromosomal abnormalities such as Klintelber’s syndrome will often be found. In this week’s issue Reijo and colleagues expand the association between severe male-factor infertility and underlying genetic abnormalities by demonstrating that some men with non-obstructive azoospermia or oligospermia carry deletions of the azoospermia factor on the long arm of the Y chromosome. De-novo mutations seem to be the cause of the infertility, and they are carried in the semen of affected individuals.

Concern has been expressed that ICSI may contribute to an expansion of mutations in the general gene pool, on the assumption that ICSI helps to overcome a previous inefficiency of transmission. A similar concern arose after the introduction of insulin. Previously, women with diabetes rarely conceived, either because of severe illness or because of anovulation with amenorrhea. Just as the treatment of diabetic women was not halted to prevent the conception of potentially diabetic children, it would seem unreasonable to withhold ICSI to prevent the birth of potentially infertile or subfertile sons.

Genetically related male infertility can occur even without ICSI. For example, paternity with mosaic Klintelber’s syndrome and congenital absence of the vas deferens have been reported. Reijo’s report also suggests that some azoospermia factor deletions result in less severe forms of oligospermia than do others. It is quite likely that these “milder” defects will not prevent pregnancies from occurring. Nor does the transmission of a gene (or genes) always result in the transmission of specific phenotypes. Mercier et al have described brothers with identical CFTR gene mutations but differing phenotype; only one expressed congenital absence of the vas deferens. This similar observations suggest that the phenotypic expression of genetic mutations may be determined by other genetic or by environmental factors. Finally, we must remember that the fertilisation and developmental potential of sperm harbouring genetic mutations is unknown. In one case, ICSI for a mosaic Klintelber’s patient produced high rates of fertilisation but embryo cleavage was uncharacteristically slow and pregnancy potential uncertain at best.

Thus ICSI may not have much impact on existing dissemination patterns for infertility-associated gene mutations in the male, though some increase in prevalence or in severity cannot be ruled out. ICSI still needs to be viewed with caution because long-term follow-up data on offspring are not available. Advances in preimplantation genetics may provide us with the tools needed to ensure that embryos created through ICSI are genotypically normal, at least in respect of mutations associated with male infertility. Until then, our concerns should be shared with patients as part of an informed consent process that precedes assisted reproduction via ICSI.

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