EDITORIAL

Time delay in primary angioplasty: how relevant is it?

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Heart 2007;**93**:1164–1166. doi: 10.1136/hrt.2006.112805

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Many clinical trials have shown that primary percutaneous coronary intervention (PPCI) is more effective than thrombolysis for the treatment of ST-segment elevation myocardial infarction (STEMI).[1] According to current guidelines, PPCI is the preferred form of reperfusion treatment for patients with STEMI. However, advantages of an invasive approach over fibrinolytic treatment may be blunted by several factors. Most important include low availability of experienced institutions offering 24 hour/7 day PPCI service and delay to invasive treatment due to prolonged transport. The delayed initiation of reperfusion treatment and its effect on clinical outcomes in STEMI and long-term mortality as well as logistic problems of the organisation of cardiac care have been extensively discussed.

In this issue of *Heart*, Asseburg *et al* present a meta-analysis of randomised studies comparing PPCI and fibrinolytic treatment for patients with STEMI (***see article on page 1244***).[2] Of special interest is the application of Bayesian statistical methods for analysis of treatment efficacy with respect to PPCI-related delay. It is noteworthy that the analysis included 30-day and 6-month end points. The investigators demonstrated that the advantage of PPCI over fibrinolytic treatment was lost with increasing PPCI-related delay. Loss of the 6-month mortality advantage of PPCI over fibrinolytic treatment was observed for PPCI-related delay >90 minutes.

Occlusion of the infarct-related artery produces acute ischaemia, leading to progression of myocardial necrosis within several hours. A number of factors may affect progression of myocardial necrosis (completeness of coronary occlusion, presence of collaterals, preconditioning or an individual demand for myocardial oxygen). Despite the variability related to the factors mentioned above, duration of ischaemia remains the most important determinant of infarct size and myocardial damage.

TIME TO REPERFUSION AND CLINICAL OUTCOMES

Clinical trials of fibrinolytic agents have shown a significant relationship between symptom onset to reperfusion time and mortality. Earlier studies evaluating PPCI did not show such a relationship, which was accounted for by the superiority of PCI over fibrinolysis in restoring blood flow in the infarct-related artery that was independent of ischaemia duration. Zijlstra *et al* demonstrated a relationship between time delay and mortality at 30 days and 6 months in the fibrinolysis group and no such relationship in the PPCI group.[3] Cannon *et al* found that mortality when PPCI is used is related to door-to-balloon time but not to symptom onset-to-balloon time.[4] However, the inclusion of patients with low-risk profiles might be the reason for the lack of the relationship between the time delay and clinical outcomes. Antoniucci *et al* studied over 1300 patients and showed a relationship between time to treatment and mortality in ''not low-risk patients'' but not in low-risk patients.[5] Similarly, Brodie *et al* demonstrated a significant relationship between time to treatment and mortality only in patients with cardiogenic shock—that is, with the highest risk profile.[6] Finally, De Luca *et al* found that there was a definite relationship between time delay to treatment and 1-year mortality. Each 30 minutes of delay was associated with a relative risk increase of 7.5% at the 1-year follow-up.[7]

Door-to-balloon time is another factor that must be considered when assessing the effect of ischaemia on clinical outcomes. Liem *et al* demonstrated that additional time delay due to transport was associated with a more extensive enzymatic infarct size and a lower left ventricular ejection fraction at 6-month follow-up as compared with non-transferred patients.[8] The GUSTO-IIb trial showed a significant relationship of time from study enrolment to first balloon inflation with 30-day mortality. Finally, Brodie *et al* in a recent analysis of over 2300 patients showed a relationship between door-to-balloon time and late mortality (median 83 months) only in high-risk patients.[9] Door-to-balloon time was also analysed in randomised studies where long-distance transport for primary angioplasty was required. Such studies as PRAGUE, PRAGUE-2, DANAMI-2 or AIR-PAMI did not provide definite answers as door-to-balloon time was relatively short. Furthermore, these studies may be biased owing to preselection of suitable patients, in this case exclusion of patients for whom transport would be too risky and who in clinical practice are transferred for PPCI because of contraindications to fibrinolysis. There is still no clear answer as to how long the initiation of reperfusion can be delayed to maintain the superiority of PPCI over fibrinolysis.

In the past few years, several meta-analyses have been carried out to compare PPCI and fibrinolysis with respect to time delay. Kent *et al* demonstrated that the survival benefit of PPCI

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Abbreviations: NRMI, National Registry of Myocardial Infarction; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction

(30-day mortality) decreased with increasing PPCI-related delay. However, a delay of 50 minutes yielded equivalent reductions in mortality.[10] Similarly, Nallamothu and Bates showed that the mortality benefit associated with PPCI was lost if PPCI-related delay exceeded 60 minutes.[11] Combined analysis of the National Registry of Myocardial Infarction (NRMI)-2, -3 and -4 by Pinto *et al* showed that PPCI-related delay was much longer—that is, 114 minutes, and varied considerably depending on various factors like duration of symptoms, age, infarction location.[12] Conversely, results from the RIKS-HIA Registry suggest that fibrinolysis should be considered as an alternative to PPCI only when PPCI-related delay exceeds 4 hours, which would extend access to PPCI to markedly more patients.[13] A major limitation of the Registry may be that patients referred for PPCI were at low risk and that the number of patients with prehospital fibrinolysis undergoing rescue PCI or planned angiography/revascularisation during hospitalisation was small, which could bias the final results in favour of PPCI. Also, Boersma in his meta-analysis demonstrated that invasive treatment was better than fibrinolysis regardless of PPCI-related delay, with the 30-day mortality reduction being significantly higher when the PCI-related delay was <35 minutes.[14] It is important to note that the analysis included only patients with time delay <120 minutes (median PPCI delay 55 minutes).

Available evidence shows that PPCI-related delay is an important factor in selecting the best reperfusion strategy, whereas duration of ischaemia is one of the most important determinants of outcome for patients with STEMI. If PCI-related delay is expected to be >90–120 minutes, early reperfusion may be achieved with fibrinolysis, preferably in the prehospital setting, with transport for delayed elective angiography/PCI within <24 hours after pain onset (pharmacoinvasive strategy) or rescue PCI only if needed. The pharmacoinvasive strategy is currently recommended by the European Society of Cardiology for each patient treated with fibrinolysis and with or without demonstrable myocardial ischaemia. Facilitated PCI (immediate PCI after lytics) is not recommended after the ASSENT-4 PCI study results for patients with relatively short delay (104 minutes). There are no data from large randomised studies evaluating outcome for patients with PCI delay >120 minutes due to the need for transport to another hospital. The Krakow Registry shows that combined fibrinolysis using reduced-dose alteplase and abcximab during transport of about 150 minutes for combo-facilitated PCI may yield similar results as PPCI performed at <90 minutes; however, there is an increased risk of bleeding complications.[15] Large randomised studies (CARESS in AMI, FINESSE) will probably provide answers to questions about the efficacy and safety of combo-facilitated PCI. Results of the EUROTRANSFER Registry, an international study to evaluate the usefulness of glycoprotein IIb/IIIa facilitated PCI, will be presented soon.

FACING REALITY

Clinical trials have confirmed the superiority of PPCI over fibrinolysis.[1] It may be difficult to translate these results into clinical practice. The main reason is selection of patients with STEMI for trials conducted in a high volume centre. Clinical outcome after interventional treatment depends closely on the experience of both the operators and the PCI laboratory as a whole. The current guidelines unequivocally recommend that PPCI should be performed by skilled professionals within <90 minutes after first medical contact in a laboratory that performs at least 400 PCIs a year (including at least 36 procedures for STEMI). The NRMI-3 and -4 showed that only 4.2% of patients transferred for treatment actually undergo PPCI within the recommended 90 minutes (15% of patients within less than <2 hours). Longer door-to-balloon times were mainly due to comorbid conditions, absence of chest pain, delayed presentation after symptom onset, less specific ECG findings and hospital presentation during off-hours. Hospital presentation during off-hours, especially at night time may be the reason not only for reperfusion treatment delay but also for the reduced efficacy of PPCI and higher inhospital mortality.[16]

SUMMARY

Longer door-to-reperfusion time in patients with STEMI is associated with a worse long-term clinical outcome regardless of the type of reperfusion strategy used. Available data confirm the superiority of PPCI over fibrinolysis for patients with STEMI, with the early-term mortality benefit associated with PPCI being limited to patients with a relatively short PPCI-related delay. PPCI-related delay is much longer in clinical practice than recommended in the guidelines. It appears necessary to improve transport logistics, monitor the duration of delay and clinical outcome and implement standards for local management of patients with STEMI. It is also advisable to adjust treatment to the individual patient's needs (type of pharmacotherapy, transport for PPCI versus fibrinolysis) based on the risk of infarction (duration of symptoms at presentation, infarct location, signs of heart failure), risk of bleeding (age) and the possibility of transport for PPCI (expected delay). Fibrinolysis certainly should not be the end of the reperfusion therapy in STEMI. Facilitated PCI with fibrinolytic treatment and/or glycoprotein IIb/IIIa facilitated PPCI might be the option in selected patients to counteract the negative effects of expected PCI-related delay, and the year 2007 is likely to provide more data.

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Conflict of interest: None declared.

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IMAGES IN CARDIOLOGY

doi: 10.1136/hrt.2006.101022

Wolff–Parkinson–White syndrome and persistent azygous drainage of the inferior vena cava

A 33-year old man with a history of transient palpitations presented to casualty with sustained tachycardia. His ECG showed pre-excited atrial fibrillation, with a left-sided accessory pathway. He was cardioverted to sinus rhythm, and transferred for electrophysiological treatment. A quadrupolar lead was advanced from the right femoral vein under fluoroscopy, and it was noted that despite being wholly within the cardiac silhouette no electrogram was recordable. Contrast injected into the venous sheath demonstrated persistent azygous venous drainage of the inferior vena cava (panels A and B). An echocardiogram showed normal cardiac structure, drainage of the hepatic veins into the right atrium, and superior vena cava opacification with bubble injection into the femoral sheath. Electrodes were passed to the coronary sinus (CS) from the right subclavian vein, and to the right atrium (HRA) and ventricle (RV) from the femoral vein (panel C, left anterior oblique). A retrograde approach was used to advance the ablation electrode to the left ventricle from the femoral artery. The accessory pathway was mapped to the free wall at 3 o'clock on the mitral valve annulus, and successfully ablated. A subsequent cardiac magnetic resonance scan confirmed no other abnormality.

Though a number of developmental anomalies of the inferior vena cava are described, they are rare in isolation. Persistent azygous drainage of the inferior vena cava is associated with atrial isomerism. The transeptal approach has replaced the reterograde approach for ablating left-sided pathways as the preferred method. The reterograde approach is, however, a tested and invaluable technique if transeptal puncture is not possible.

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