Angioplasty for the treatment of acute myocardial infarction

K J Beatt, F Fath-Ordoubadi

In principle, any innovative treatment that is to be accepted into clinical practice should be justified on the basis of the following criteria: a sound pathophysiological mechanism for its beneficial effect, safety and efficacy in the clinical setting, a financial cost that justifies the benefit to the targeted patient population, and the ability to apply the treatment in a practical manner. The first of these, encompassing the concept of early and sustained patency, provides the basis for understanding why primary angioplasty is so effective at treating acute myocardial infarction.

Early patency

The global utilisation of streptokinase and tissue plasminogen activator (t-PA) for occluded coronary arteries (GUSTO I trial¹ has shown the regimen of accelerated t-PA to be superior to other tested thrombolytic strategies in terms of achieving higher early patency and lower mortality. Perhaps more importantly the study demonstrated that suboptimal reperfusion with compromised flow is little better than an artery that remains occluded.² The early (90 minute), complete (TIMI grade 3 flow), and sustained reperfusion of the infarct related artery are the most crucial factors in preventing death and impairment of cardiac function following an acute myocardial infarction.³ Even with optimal thrombolytic therapy only 54% of the patients eligible for thrombolytic treatment in the GUSTO I trial achieved early high grade patency. In contrast, current primary angioplasty studies show that reperfusion rates are generally greater than 90%, and in some studies as high as 98%.⁴ Whereas improvements in time to thrombolytic treatment and new thrombolytic agents may significantly improve patency, it is unlikely to approach that achieved by primary angioplasty and may increase the risk of fatal or disabling strokes. The aggressive use of anticoagulants and antiplatelet agents has led to only a modest increase in arterial patency at the expense of an exponential increase in intracranial bleeds.⁵ There are now several clinical trials assessing treatments with new thrombolytics, antithrombins, and antiplatelet agents for acute myocardial infarction that have been prematurely terminated because of excessive bleeding. There is hope that newer agents will provide higher patency rates with an acceptable risk profile, but the use of these agents remains speculative, whereas the risk profile as well as the benefits for angioplasty are well documented.

Sustained patency

Having demonstrated a superior early patency rate, is the advantage of primary PTCA sustained? The reductions in recurrent ischaemia

and the need for further hospital admissions have been striking and provide the basis for an effective one stop strategy for treating acute ischaemia (fig 1). The ability to assess the extent of the disease and to treat effectively on day 1 reduces the need for the traditional non-invasive investigations that may be repetitive, unreliable or frankly misleading in an appreciable number of patients.

Again the mechanism of benefit is through the maintenance of arterial patency. Repeat angiography has demonstrated that patients having primary angioplasty maintain patency better than those receiving thrombolysis and this is reflected in clinical outcome. In the Zwolle trial arterial patency at 20-80 days was 68% in the thrombolytic group and 91% in the angioplasty group ($P = 0.001$) with corresponding reinfarction rates of 19% and 3%. ($P = 0.001$).^{4,6} The figures for the combined endpoint of nonfatal myocardial infarction and death was 28% and 7%, respectively, giving a relative risk for thrombolysis compared with angioplasty of 4.3 (95% confidence interval (CI) 2.2 to 8.3). The ability to discharge patients from hospital secure in the knowledge that a further unheralded event is unlikely is reassuring for both the patient and the physician.

Current status of primary angioplasty

The stimulus for the current interest in primary angioplasty came in 1993 from the landmark publications of the three prospective randomised trials, two from the United States^{7,8} and one from the Netherlands.⁴ More recently, the results of the GUSTO IIb angioplasty substudy have been reported.⁹ This is by far the largest of the completed trials recruiting 1138 patients from centres around the world representing a variety of experience and varying clinical practice. The study was powered to show a difference in the primary composite end point of death, non-fatal reinfarction, and disabling stroke at 30 days. The results show that this end point was reached in 9.6% of the angioplasty group and 13.7% of the accelerated t-PA group ($P = 0.033$). Mortality was 5.7% and 7%, respectively (NS). Eighty two per cent of those randomised to angioplasty received this treatment 3.8 hours following the onset of pain and 1.3 hours following randomisation. However, the success rate in terms of TIMI-3 flow was only 73%. This was significantly lower than the 90% plus TIMI-3 flow achieved in other contemporary randomised trials and is highly relevant as mortality in the patients with TIMI-3 flow in the GUSTO IIb study was 1.6%, while those with TIMI-0, 1, and 2 flows had a mortality increase of more than 10-fold to 21%, 14%, and 20%, respectively.⁹ This is, perhaps, the

Department of Cardiology, and Royal Postgraduate Medical School Hammersmith Hospital, London, UK

Correspondence to: Dr Beatt, Department of Cardiology, Hammersmith Hospital, London W12 0HS, UK; email: kbeatt@rpgms.ac.uk

Figure 1 Incidence of recurrent ischaemia in three of the randomised trials comparing primary angioplasty with thrombolysis.^{4,7,8}

most important message from this trial—in order for primary angioplasty to be an effective alternative to more conventional therapy a high early rate of TIMI-3 flow must be achieved.

An updated meta-analysis including this and nine other studies with a total of 2606 patients showed that patients undergoing PTCA had a mortality of 4.4% compared with 6.5% of patients receiving thrombolysis (34% reduction, $P = 0.02$), a death and non-fatal myocardial infarction rate of 7.2% *v* 11.9% (40% reduction, $P = 0.0001$), and for the important complication of haemorrhagic stroke, a rate of 0.1% *v* 1.1% (65% reduction, $P = 0.0005$).¹⁰ Figures from this analysis are combined with other studies to estimate the number of lives saved using a variety of contemporary treatments for acute myocardial infarction in fig 2. However, the use of these figures, although compelling in themselves, considerably underestimates the true benefit

Figure 2 Comparison of number of lives saved per 1000 patients treated at 30 days following acute myocardial infarction (MI) for different reperfusion strategies and aspirin. Acc-tPA, accelerated tPA; SK, streptokinase; Asp, aspirin. The figures have been derived by taking the overall mortality rate in control patients as 11.5% for all MIs and 16.9% for anterior MIs (taken from FTT's collaborators study²¹). Mortality rate for primary angioplasty for the overall population and for anterior MIs was taken as 4.4% (from meta-analysis of primary PTCA⁸) and 7.1% (taken from GUSTO IIb⁹), respectively; for accelerated tPA as 6.3% and 8.6%, respectively (taken from GUSTO I⁹); for streptokinase with aspirin as 8% and 10%, respectively; for streptokinase alone 10.4% and 11.3%; and for aspirin as 10.7% and 12.8%, respectively (taken from ISIS-2 study²²).

of primary angioplasty in the total patient population, something that becomes apparent with a more critical analysis of the randomised trial in acute ischaemia.

Limitations of randomised trials in acute myocardial infarction

The results of well conducted randomised clinical trials are widely accepted as the most appropriate method of evaluating clinical practice. An important and overriding principle in the conduction and interpretation of these trials is that the recruited trial population should be a true sample population reflecting the characteristics of the population of interest, and ideally all patients should receive the treatment allocated at randomisation. Most recent studies assessing the effect of invasive investigation fall well short of meeting these criteria. Obtaining representative populations becomes particularly difficult once there is the perception, by either physician or patient, that one or other of the treatment arms is superior. In particular, those at highest risk are preferentially offered the "optimal" treatment and are therefore not recruited for the trial. This concept, which is self evident to those recruiting patients for trials, is often not appreciated by statisticians and non-involved commentators. Studies assessing the effects of thrombolytics in acute myocardial infarction have consistently selected a population at lower risk than the true myocardial infarction population; an observation that is confirmed by the comparatively low mortalities recorded in both treatment arms.^{11,12} Recent intervention studies where records have been kept of the total population show that the sample population may be as low as 4% of recruitable population. Most studies do not document this important detail, which has major implications in the way the results are interpreted.

The problem is compounded by crossover from one treatment arm to another, which may be as high as 50% in some trials, and again will occur more frequently in the patients at highest risk.^{13,14} In a recent study concluding that primary angioplasty offered no additional benefit compared to thrombolytic therapy, 30% of those receiving thrombolysis underwent angioplasty in the first 24 hours.¹⁵ This subgroup may influence the favourable outcome of the thrombolysis group, and a more appropriate conclusion from the dataset provided (which is also a selected dataset) would be to argue that the outcomes of patients receiving thrombolysis are similar to those having primary angioplasty if, and only if, immediate angioplasty is available to the thrombolytic group who most need it.

When assessing the true benefit of primary angioplasty, care should be taken to avoid using selected data from unrepresentative sample populations that fail to adhere to their randomised treatments. In this respect the Zwolle study deserves special consideration. Conducted at a time when there was genuine doubt concerning the benefit of primary angioplasty, it is unusual in that virtually all eligible patients admitted to hospital were

recruited, irrespective of their underlying risk. A 50% reduction in mortality was demonstrated with primary angioplasty at a mean follow up of 30 months; a reduction considerably greater than the meta-analysis has determined.⁴

The point is further illustrated by analysing the subset of patients with the highest mortality. In the Primary angioplasty in myocardial infarction (PAMI) trial patients older than 70 years with an anterior myocardial infarction and a heart rate faster than 100 beats/min treated with thrombolysis had a mortality of 10.4% compared to 2.0% with angioplasty.

The current meta-analysis shows that although the *relative* mortality reductions are impressive they translate into only a modest *absolute* benefit because of low mortalities inherent in preferentially recruiting low risk patients into randomised clinical trials. However, critical analysis of the data available suggests that these relative reductions also apply to high risk patients, where the benefit becomes far more substantial than the figures that are quoted in fig 2. The difficulties of performing randomised trials where interventional procedures are involved have forced trials designs that are impractical and difficult to implement according to protocol and may therefore not answer the relevant questions. In this situation more attention should be paid to the mechanisms of benefit and the surrogates of favourable clinical outcomes, avoiding the often heard cry for additional randomised trials, without full understanding of the limitations of their predecessors.

Practical and cost issues

As the data on the benefit of primary angioplasty has become favourable the arguments opposing the use of the procedure have centred on the costs and the difficulty of providing access for most if not all patients. The two most comprehensive primary angioplasty studies have shown that primary angioplasty is no more expensive than thrombolysis particularly if costs are adjusted for survivors and the expenses are considered over one year.^{16 17} The higher initial cost of primary angioplasty is offset by the increased costs of re-admissions for recurrent ischaemia in the patients treated with thrombolysis. Further cost savings can be achieved by concentrating expertise so that more patients are admitted to fewer, more experienced units. The recognition that many of the traditional non-invasive tests become redundant following the initial determination of coronary anatomy and LV function will allow further refinement of postmyocardial infarction management with further efficiency and cost savings.

Most of the data on primary angioplasty comes from centres experienced in invasive procedures. Performing primary angioplasty is more demanding than the elective use of the procedure. It should be recognised that experience, expertise, and an adequate throughput of patients are essential components for achieving acceptable standards in primary angioplasty, as is the case for elective angio-

plasty. A recent registry documenting primary angioplasty in 4625 patients showed that units performing more than 40 angioplasties annually for acute myocardial infarction demonstrated significantly better outcomes,¹⁸ while the GUSTO II trial showed improved results in centres performing more than 625 angioplasty procedures a year.⁷

Implications for current practice

Over the past 20 years angioplasty has developed from a crude technique limited in its application to the most common revascularisation procedure for coronary artery disease. It is broadly most effective at treating acute ischaemia, and the greatest mortality benefit is achieved treating acute myocardial infarction. There can no longer be disagreement that for many high risk patients, primary angioplasty offers a cost effective mortality benefit many times greater than conventional treatment. Even more compelling is the use of the procedure for treating patients in situations where there is no effective alternative—where thrombolysis is contraindicated or where complications develop as a result of failed thrombolysis. Units that are able to offer this treatment will achieve substantially better results than those that are only able to offer treatment with intravenous thrombolysis.

In 1971 the benefits of thrombolysis were demonstrated in a controlled randomised trial¹⁹ and in 1985 an overview established the message beyond doubt.²⁰ Yet it took many more years for the treatment to become established practice for all patients. There is now a need to evaluate a further change in treatment and to establish how this can be made available for those who most stand to benefit. The indicators are that with a willingness to change and an appropriate reallocation of current resources the necessary progress can be made.

- 1 The GUSTO Investigators. An international trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673–82.
- 2 The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase or both on coronary artery patency, ventricular function and survival after acute myocardial infarction. *N Engl J Med* 1993;329:1615–22.
- 3 Fath-Ordoubadi F, Huehns TY, Al-Mohammad A, Beatt KJ. Significance of the TIMI scoring system in assessing infarct-related artery reperfusion and mortality following acute myocardial infarction. *Am Heart J* 1997;133:60–6.
- 4 Zijlstra F, de Boer MJ, Hoorntje JCA, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;328:680–4.
- 5 The GUSTO II Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. The global use of strategies to open occluded coronary arteries (GUSTO) IIa investigators. *Circulation* 1994;90:1631–7.
- 6 Zijlstra F, de Boer MJ, Beukema, et al. Mortality, reinfarction, left ventricular ejection fraction and costs following reperfusion therapies for acute myocardial infarction. *Eur Heart J* 1996;17:382–7.
- 7 Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction (PAMI group). *N Engl J Med* 1993;328:673–9.
- 8 Gibbons RJ, Holmes DR, Reeder GS, et al, for the Mayo coronary care unit and catheterization laboratory groups. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. *N Engl J Med* 1993;328:685–91.
- 9 The GUSTO-IIb Angioplasty Subgroup Investigators. An international randomized trial of 1138 patients comparing primary coronary angioplasty versus tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997;336:1621–8.

- 10 Simes JR, Weaver DW, Ellis SG, Grines CL. Overview of the randomised trials of primary PTCA and thrombolysis in acute myocardial infarction [abstract]. *Circulation* 1997;**94**(suppl):1331.
- 11 ISIS-3 collaboration group. A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;**339**:753–70.
- 12 The GUSTO IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996;**335**:775–82.
- 13 RITA trial participants. Coronary angioplasty versus coronary artery bypass surgery: the randomised intervention treatment of angina (RITA) trial. *Lancet* 1993;**341**:573–80.
- 14 TIMI IIIB investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB trial. Thrombolysis in myocardial ischemia. *Circulation* 1994;**89**:1545–56.
- 15 Every NR, Parsons LS, Haltky M, et al. For the MITI investigators. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. *N Engl J Med* 1996;**335**:1253–60.
- 16 de Boer MJ, van Hout BA, Liem AL, Suryapranata H, Hoorntje JCA, Zijlstra F. A cost-effective analysis of primary coronary angioplasty versus thrombolysis for acute myocardial infarction. *Am J Cardiol* 1995;**76**:830–3.
- 17 Stone GW, Grines CL, Rothbaum D, et al. Analysis of the relative costs and effectiveness of primary angioplasty versus tissue-type plasminogen activator: the primary angioplasty in myocardial infarction (PAMI) trial. *J Am Coll Cardiol* 1997;**29**:901–7.
- 18 Zahn R, Vogt A, Neuhaus K-L, Schuster S, Senges J for the ALKK study group. Angioplasty in acute myocardial infarction in clinical practice: results in 4625 patients from the ALKK angioplasty registry [abstract]. *J Am Coll Cardiol* 1997;**29**(suppl A):15A.
- 19 European Working Party. Streptokinase in recent myocardial infarction: a controlled multicentre trial. *BMJ* 1971;**3**:325–31.
- 20 Yusuf S, Collins R, Peto R, et al. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side effects from 33 randomised controlled trials. *Eur Heart J* 1985;**6**:556–85.
- 21 Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indication for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;**343**:311–22.
- 22 ISIS-2 (Second International Study of Infarct Survival) collaboration group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17187 cases of acute myocardial infarction. *Lancet* 1988;**ii**:349–60.

Is primary angioplasty feasible or will we provide a two-tier service?

Pascal Chatelain, Philip Urban

Primary angioplasty for acute myocardial infarction has its fans, its doubters, and those (the majority) who belong to neither camp because they have no choice other than thrombolysis to achieve myocardial reperfusion in their institution. Should they feel inadequate and guilty not to be in a position to offer the "best" treatment? Should they all start a hard and long fight with their administration for an increased share of scarce resources? In other words, should the clinical superiority of primary angioplasty be used as an argument for the availability of catheterisation laboratories and interventionists in every hospital? A responsible answer to these questions should probably be negative.

To abandon thrombolysis as the treatment of choice for acute myocardial infarction would certainly be a mistake as it has several advantages over primary angioplasty. First, if appropriately prescribed, its administration by a general practitioner or a junior casualty doctor will be as effective as when given by the most experienced cardiologist. Second, thrombolysis can be administered out of hospital when geographical constraints make this necessary.¹ Third, new thrombolytic agents are under investigation with the common aim to achieve TIMI-3 flow more rapidly in a larger number of patients.²

On the other hand, several advantages of primary angioplasty remain. Overall analysis of more than 2000 patients randomised in eight studies so far demonstrates a significant mortality reduction of angioplasty compared with thrombolysis, and the rare but devastating occurrence of intracerebral bleeding is also avoided.³ Coronary anatomy and left ventricular function are assessed immediately, allowing better therapeutic decisions including early discharge.⁴ The efficacy of reperfusion can be monitored directly and eventually

modified by further mechanical and pharmaceutical interventions. Finally, this treatment allows the patient to be in expert hands during the acute phase of the disease.

However, recent multicentre data from the GUSTO IIb trial⁵ suggest that the overall differences between primary angioplasty and accelerated tissue plasminogen activator (t-PA) are rather small, and point to the need for subgroup analysis. High risk patients, and probably patients with a contraindication to thrombolysis, are emerging as those with the best indications for primary angioplasty.

After a rather unequal competition between both strategies during the first 10 years of the reperfusion era, an unpleasant and unjustified feeling of revenge has been perceptible behind several affirmations favouring primary angioplasty. We should stop competing and concentrate on the real issues. These include making primary angioplasty available for the subset of patients most likely to benefit from the procedure, and organising adequate referral networks. It must then be the responsibility of every physician to make the best decision after a thorough (but swift) evaluation of the individual patient's situation.

- 1 GREAT Group. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian region early anistreplase trial. *BMJ* 1992;**305**:548–3.
- 2 Fuster V. Coronary thrombolysis—a perspective for the practicing physician. *N Engl J Med* 1993;**329**:723–5.
- 3 Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and reinfarction rates? A quantitative overview (meta-analysis) of the randomized clinical trials. *Circulation* 1995;**91**:476–85.
- 4 Brodie B, Grines CL, Spain M, Griffin J, Balestrini C, Stone GW, et al. A prospective, randomized trial evaluating early discharge (day 3) without non-invasive risk stratification in low risk patients with acute myocardial infarction: PAMI-2 [abstract]. *J Am Coll Cardiol* 1995; (suppl):5A.
- 5 The GUSTO-IIb Angioplasty Subgroup Investigators. An international randomized trial of 1138 patients comparing primary coronary angioplasty versus tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997;**336**:1621–8.

Cardiology Center,
University Hospital,
1211 Geneva 14,
Switzerland

Correspondence to:
Dr Urban.

vascular disease, risk factors, interventions, and prognosis, fulfilling criteria for a suitable non-invasive assessment of endothelial function. Furthermore, several groups have targeted this molecule as a means of intervening in the thrombotic process.¹⁶ The next five years will tell if this approach is successful.

The non-invasive approach outlined by Mullen and colleagues has provided invaluable opportunities to dissect the pharmacology of the endothelium. However, by its very nature such an approach is unlikely to provide epidemiological data or even data to compare groups with large numbers of subjects. We submit that plasma markers such as von Willebrand factor and soluble thrombomodulin are likely candidates for providing data of this nature.

ANDREW BLANN
GREGORY LIP

*Haemostasis, Thrombosis and Vascular Biology Unit,
University Department of Medicine,
The City Hospital, Dudley Road,
Birmingham B18 7QH, UK*

- 1 Mullen MJ, Thorne SA, Deanfield JE, Jones CJH. Non-invasive assessment of endothelial function. *Heart* 1997;77:297-8.
- 2 Lip GYH, Blann AD. Von Willebrand factor and its relevance to cardiovascular disease. *Br Heart J* 1995;74:580-3.
- 3 Blann AD, Taberner DA. A reliable marker of endothelial cell dysfunction: does it exist? *Br J Haematol* 1995;90:244-8.
- 4 Badimon L, Badimon JJ, Chesebro JH, Fuster V. von Willebrand factor and cardiovascular disease. *Thromb Haemostas* 1993;70:111-18.
- 5 Greaves M, Pickering C, Knight G, Boulton ALM, Ball J, Ward JD, et al. Changes in the factor VIII complex in diabetic ketoacidosis: evidence of endothelial cell damage? *Diabetologia* 1987;30:160-5.
- 6 Van den Berg M, Boers GHJ, Franken DG, Blom HJ, van Kamp GJ, Jakobs C, et al. Hyperhomocysteinaemia and endothelial dysfunction in young patients with peripheral arterial occlusive disease. *Eur J Clin Invest* 1995;25:176-81.
- 7 Thompson SG, Kienast J, Pyke SDM, Haverkate F. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N Engl J Med* 1995;332:635-41.
- 8 Blann AD, Miller JP, McCollum CN. Von Willebrand factor and soluble E-selectin in the prediction of cardiovascular disease progression in hyperlipidaemia. *Atherosclerosis* 1997;132:151-6.
- 9 Boffa MC. Considering cellular thrombomodulin distribution and its modulating factors

can facilitate the use of plasma thrombomodulin as a reliable endothelial marker. *Haemostasis* 1996;26(Suppl 4):233-43.

- 10 Blann AD, Amiral J, McCollum CN. Circulating endothelial cell/leucocyte adhesion molecules in ischaemic heart disease. *Br J Haematol* 1996;95:263-5.
- 11 Seigneur M, Dufourcq P, Gin H, Delafaye C, Amiral J, Pruvost A, Boisseau MR. Plasma thrombomodulin levels increase with the severity of diabetic retinopathy. *Blood Coag Fibrinolys* 1994;5:845-6.
- 12 Blann AD, Amiral J, McCollum CN. Prognostic value of increased soluble thrombomodulin and increased E-selectin in ischaemic heart disease. *Eur J Haem.* [In press.]
- 13 Gearing AJH, Newman W. Circulating adhesion molecules in disease. *Immunol Today* 1993;14:506-12.
- 14 Blann AD, Seigneur M, Steiner M, Boisseau MR, McCollum CN. Circulating endothelial cell markers in peripheral vascular disease: relationship to the location and extent of atherosclerotic disease. *Eur J Clin Invest.* [In press.]
- 15 Belch JFF, Shaw JW, Kirk G, McLaren M, Robb R, Maple C, Morse P. The white blood cell adhesion molecule E-selectin predicts restenosis in patients with intermittent claudication undergoing percutaneous transluminal angioplasty. *Circulation* 1997;95:2027-31.
- 16 Ruggeri ZM. Inhibition of platelet vessel wall interaction. Platelet receptors, monoclonal antibodies, and synthetic peptides. *Circulation* 1990;81(Suppl 1):135-9.

This letter was shown to the authors, who reply as follows:

We read with interest the letter from Drs Blann and Lip regarding the advantages and limitations of plasma markers of endothelial cell function. We share their interest in this area of research and its potential clinical application. We feel, however, that evaluation of nitric oxide mediated arterial physiology in large conduit arteries using the non-invasive techniques described¹ may provide insight into the pathophysiology of vascular disease, be an early marker of endothelial injury, and a means of evaluating interventions early in the natural history of atherogenesis.

The value of these measures in predicting disease development and outcome is not known and is central to current research efforts. Our published data, however, indicate that this technique can be used to study

endothelial function in large groups of subjects from early in childhood, to provide epidemiological data, compare groups of subjects with risk factors, and demonstrate beneficial response to interventions.²⁻⁵

M J MULLEN
M E DEANFIELD
*Great Ormond Street Hospital for
Children NHS Trust,
Great Ormond Street,
London WC1N 3JH, UK*

- 1 Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;340:1111-15.
- 2 Leeson CPM, Whincup PH, Cook DG, Donald AE, Papacosta O, Lucas A, et al. Flow mediated dilatation in 9-11 year old children: the influence of intrauterine and childhood factors. *Circulation.* [In press.]
- 3 Celermajer DS, Sorensen KE, Bull C, Robinson J, Deanfield JE. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *J Am Coll Cardiol* 1994;24:1468-74.
- 4 Sorensen KE, Celermajer DS, Georgakopoulos D, Hatcher G, Betteridge DJ, Deanfield JE. Impairment of endothelium-dependent dilation is an early event in children with familial hypercholesterolemia and is related to the lipoprotein (a) level. *J Clin Invest* 1994;93:50-5.
- 5 Clarkson P, Adams MR, Powe AJ, Donald AE, McCredie R, Robinson J, et al. Oral L-arginine improves endothelium-dependent dilation in hypercholesterolemic young adults. *J Clin Invest* 1996;97:1989-94.

CORRECTION

Pregnancy and congenital heart disease
C M Oakley Heart 1997;78:12-14.

The first sentence of the section **Atrial septal defects** should have read:

"The only frailty of patients with unrepaired atrial septal defects is intolerance of blood loss that can force left to right shunting, to the sudden detriment of left ventricular and coronary flow."

And not as published. The error is regretted.