LETTERS TO THE EDITOR

Scope
Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation
Letters should be:
- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors
They may contain short tables or a small figure. Please send a copy of your letter on disk. Full instructions to authors appear in the January 1999 issue of Heart (page 104).

Randomised trials of new surgical procedures are necessary

Sr,-It was with some dismay that we read the editorials on the problems and pitfalls of randomised controlled trials (RCTs) for evaluating new procedures in general and minimally invasive direct coronary artery bypass (MIDCAB) in particular. Many of the opinions offered in the articles arise from problems encountered as a result of poor design, planning, and execution of RCTs rather than as a result of the methodology itself. The timing of trials of new technologies is problematic. The ideal moment is between apples and oranges (that is, between different operations, different drug regimens (anti-arrhythmics in myocardial infarction and β-carotene to prevent lung cancer), or between different operations (laparoscopic versus open surgery for cholecystectomy)). The RCT they propose, minimally invasive coronary bypass (MIDCAB) versus angioplasty of the left anterior descending coronary artery, is a comparison between two procedures that have not been sufficiently described, not between two products to be compared in the same way. It is more likely that the MIDCAB will certainly be necessary at some stage.

We agree that meta-analysis of large clinical series can substitute for RCTs. In fact, the summary of my editorial defined the specific circumstances in which I felt that RCTs are likely to help and those in which they are not, after which I said “meta-analysis of large clinical series can substitute for those randomised studies that are unlikely to be helpful.” Actually, Sharples et al inadvertently substantiate my assertions. Their examples of useful RCTs were invariably comparisons between different drug regimens (anti-arrhythmics in myocardial infarction and β-carotene to prevent lung cancer), or between different operations (laparoscopic versus open surgery for cholecystectomy). The RCT they propose, minimally invasive coronary bypass (MIDCAB) versus angioplasty of the left anterior descending coronary artery, is a comparison between two procedures, a circumstance in which I agree that RCTs can be informative if they adhere to certain design criteria that I was careful to specify. I made no reference to the MIDCAB in my editorial, and was unaware of the editorial by Izzat et al until it was published, but their point of view seems unexceptional to me, as it merely advises proceeding deliberately.

Dr Sharples and colleagues for their interest in our editorial. However, they seem to have misunderstood the purpose of our commentary. We are not against the concept of RCTs but if these are to be useful to clinicians rather than to statisticians then they have to be generally applicable. The differences between a drug trial and those surgical procedures were clearly highlighted and discussed by Bonchek. It is obvious that the technicalities of the MIDCAB procedure are evolving rapidly and if a trial is done in the very early stages before the many technical problems have been overcome then the procedure is likely to fail badly and be
condemned. This is not the way to make progress. Surgeons and interventional cardiologists need time to develop procedures and to overcome the learning curve before submitting their technique to an RCT especially if the comparison is with drug therapy. While an RCT will have to be done with the MIDCAB procedure at some time but the most important question is when. Although Sharples et al feel that the time is right to conduct the first MIDCAB trial, the only reason for this appears to be the indications for MIDCAB are agreed on. However, they admit that the technique is still evolving. We all agree on the indications for MIDCAB, that is not difficult, but deciding when the technique has developed sufficiently to be subjected to a trial is another, more difficult question. We agree with their other comments about multidisciplinary and multicentre trials but they do not provide an answer on whether any technique ready to be subjected to an RCT? It cannot be in the early stages of development.

Cell adhesion molecules in cardiovascular disease: what can soluble levels tell us?

SrR—Considerable research energy is being directed towards cell adhesion molecules, and the recent review by Hills and Flapan provides a useful introduction. As they allude to, blockade of the interaction between leucocytes and the endothelium by agents that mimic or inhibit these adhesion molecules may become a new class of therapeutic agent. However, Hills and Flapan only briefly draw our attention to the presence of some contradictory results. For example, Frijs et al have reported raised concentrations of soluble E selectin in ischaemic stroke and carotid atherosclerosis, whereas we have been unable to find differences in the plasma of patients with angina or coronary artery disease: nor do concentrations predict adverse outcome. However, concentrations do rise slowly (reaching a peak at 3 days) after an acute myocardial infarction, and are moderately raised in some forms of peripheral atherosclerosis, with some correlation with the extent of disease. Soluble platelet endothelial cell adhesion molecule (sPECAM-1) may also arise from many cells, including endothelial cells, platelets, and leucocytes. We have however been unable to find differences in the plasma of patients with coronary artery disease or peripheral artery disease compared to controls. Despite the above, a firm consensus about the significance and value of concentrations of soluble adhesion molecules in cardiovascular disease has yet to emerge, mainly due to some contradictory results. For example, Frijs et al have reported raised concentrations of soluble E selectin in ischaemic stroke and carotid atherosclerosis, whereas we have been unable to find increased concentrations in patients with peripheral atherosclerosis; conversely, unlike us, they failed to find raised sICAM-1. De Caterina and colleagues reported increased levels of soluble ICAM-1 in peripheral atherosclerosis, whereas our group and Frijs et al have been unable to do so. It would be easy to jump to the conclusion that these inconsistencies are due to differences such as the stage and degree of disease of the subjects, and/or laboratory methods, although most of the latter are commonly used commercial reagents. However, by and large, none of these essentially cross sectional studies have recruited particularly large (>100) numbers of subjects, so that this may be one source of the inequalities. Until several large, hopefully prospective, studies are published, it seems likely that the simple in vitro demonstration of cell adhesion molecules or the measurement of soluble adhesion molecules has little to offer current practising cardiologists in their quest for improved patient care. Nevertheless, it is clear that cell adhesion molecules do at least play some important role(s) in cardiovascular pathology is a small step forward in the complex field of vascular biology and pathophysiology.

Andrew D Blann and Gary Y H Lip

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Drs Blann and Lip provide an excellent appraisal of the current state of research into the role of soluble adhesion molecules in cardiovascular disease. Although this is an area that was only mentioned briefly in our overview we agree that it is of interest and importance.

And note, soluble adhesion molecules may affect the activity of leukocytes in vivo. Certainly, this has been demonstrated in vitro, where soluble E selectin is capable of increasing neutrophil f2 integrin expression and motility.9 This may facilitate their adhesion to damaged arterial endothelium or, potentially, encourage their sequestration in capillary beds that would, in turn, reduce the number of leukocytes that contribute to the atherogenic process. Alternatively, if the functions of each molecule is better understood, therapeutically use systemic adhesion receptor analogues is some way off—local administration may be a more realistic approach in any case. Since leukocytes may become possible within the next few years, improving vascular imaging with adhesion receptor labelled vehicles that are capable of binding to, and thus identifying, diseased and activated endothelium,9

While soluble adhesion molecules may complicate efforts to manipulate leukocyte-endothelial cell interactions serum concentrations could provide a useful insight into the health of vascular endothelium. Raised concentrations could provide a useful insight as to endothelial cell interactions serum concentrations rise further in unstable coronary artery disease and possible outcome.10-12

An alternative possibility is that soluble adhesion molecules might reduce leucocyte adhesion and/or diapedesis by competing for binding sites or by less direct mechanisms.9 Until such issues are resolved, and the precise contribution of each molecule is better understood, therapeutic use of systemic adhesion receptor analogues is some way off—local administration may be a more realistic approach in any case. Since leukocytes may become possible within the next few years, improving vascular imaging with adhesion receptor labelled vehicles that are capable of binding to, and thus identifying, diseased and activated endothelium.

In addition to the increase of sICAM-1 in stable coronary artery disease, concentrations rise further in unstable disease13—presumably reflecting endothelial damage and activation. These early data exhibit a striking similarity to previous reports linking raised C reactive protein (CRP) to atherosclerosis and cardiovascular risk.14 This suggests that sICAM-1 may serve as a more specific indicator of endothelial dysfunction and inflammation. However, while raised CRP is associated with adverse outcome in acute coronary syndrome, there have been no large trials assessing the predictive value of sICAM in this setting.

Concentrations of angiotensin II, endothelin-1, and BNP in the coronary sinus and ascending aorta of patients with heart disease

SIR,—It has been well documented that neurohormonal mediators, such as the renin-angiotensin system,endothelin, and brain natriuretic peptide (BNP), are severely activated in patients with congestive heart failure, and that the circulating concentrations of these mediators are good predictors of the severity of congestive heart failure and mortality.2,3 It is not clear, however, whether the increase in plasma concentrations of angiotensin II and endothelin-1 is caused by increased expression and spillover from cardiac tissue in patients with heart disease. To address this question, we measured the plasma concentrations of angiotensin II, endothelin-1, and BNP in blood withdrawn from both coronary sinus and ascending aorta in five patients subject to cardiac catheterisation. All patients were studied in the morning and in a fasting state. Informed consent was obtained from each patient before the study. Coronary sinus blood was sampled using a 6 or 7 Fr catheter inserted via the right femoral vein. The position of the tip of the catheter was confirmed fluoroscopically and by blood oxygen saturation (mean (SD) 41 (3 %)). Arterial blood was withdrawn using a 6 Fr pigtail catheter positioned in the ascending aorta adjacent to the coronary ostia, which was inserted via the femoral artery. Care was taken to use the same amount of time for drawing arterial blood samples as for the coronary sinus blood sampling. The blood samples were transferred to tubes containing EDTA that were precooled with ice, and centrifuged immediately after at 1000 g for 10 minutes at 4°C. The plasma was stored at −20°C until analysis. The plasma concentrations of angiotensin II and endothelin-1 were measured by radioimmunoassay.

Table 1 shows the clinical characteristics, haemodynamic and echocardiographic data, and plasma concentrations of angiotensin II, endothelin-1, and BNP in both the coronary sinus and ascending aorta. Patient 1, who had the most severe congestive heart failure among the five patients studied, had the highest plasma concentrations of angiotensin II, endothelin-1, and BNP in both the coronary sinus and ascending aorta. The plasma concentrations of angiotensin II and endothelin-1 in the coronary sinus were lower than or equal to those in the ascending aorta in all patients. In contrast, the plasma concentration of BNP was apparently higher in the coronary sinus than in the ascending aorta in all patients. The differences in BNP concentrations between the coronary sinus and ascending aorta were more prominent in

<table>
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<th>Patient</th>
<th>Age/sex</th>
<th>NYHA class</th>
<th>Diagnosis</th>
<th>Mean BP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>LVEDD (mm)</th>
<th>EF (%)</th>
<th>Angiotensin II (pg/ml)</th>
<th>Endothelin-1 (pg/ml)</th>
<th>BNP (pg/ml)</th>
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<td>III</td>
<td>Cardiac sarcoidosis</td>
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<tr>
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<td>Postanterior MI</td>
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<td>38</td>
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<td>3</td>
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</table>

NYHA class, New York Heart Association class; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; LVEDD, left ventricular end diastolic dimension; EF, ejection fraction determined by echocardiography; ASD, atrial septal defect; MI, myocardial infarction.


2Smith CW. Potential significance of circulat-


5Blann AD, Seiguer M, Steiner M, et al. Circulating sICAM-1, sVCAM-1, and E-selectin in carotid atheroscle-


7Blann AD, and TICAM CN. Circulating ICAM-1 in peripheralartery disease and hypercholesterolaemia: rela-
tionship to the levels of atherosclerotic disease, smoking, and in the prediction of adverse events. Thromb Haemost 1997;79:


10Shy KG, Chintag H, Lin CC, et al. Circulating interleukin-6 and sICAM-1 and E-selectin in patients with acute coronary syn-

11Ridker PM, Cushman M, Stamper MJ, et al. Inflammation, aspirin, and the risk of cardio-


patients with higher BNP concentrations in the ascending aorta with the exception of patient 2, who had remarkable pulmonary hypertension.

These results suggest that, even though all three neurohormonal mediators appear to be good predictors of the severity of heart failure, the circulating concentrations of angiotensin II and endothelin-1 do not predominantly derive from cardiac tissue (unlike BNP, which predominantly derives from myocardium). Further investigation with a larger number of patients is needed to confirm this conclusion.

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Stamps in cardiology: foxglove

Sir,—The beautifully illustrated “Stamps in cardiology” on digitalis was fascinating. Ever since my medical school days, I have been wondering about the reason behind the plant’s common name—the foxglove. While it was easy to understand the Latin digitus in allusion to the finger-like blossoms of the plant; none of the professors around the world where I travelled to lecture could give me an explanation for foxglove.


Anomalous origin of the left coronary artery from the pulmonary artery

Sin,—Case 2 from this report has subsequently been admitted with chest pain and polymorphic ventricular tachycardia (VT). This was initially treated with oral β blockers, but at electrophysiological testing the VT was still inducible. Coronary angiography showed no significant change from her previous angiogram. A myocardial perfusion scan with adenosine stress confirmed an anterior myocardial infarction with some flow reduction in the peri-infarct zone. There is difficulty in demonstrating reversible ischaemia in the presence of ALCAPA; however, she has been referred for surgical revascularisation and will be given an implantable cardioverter defibrillator if the VT remains inducible postoperatively.

A conservative strategy might be employed in this condition, however surgical intervention may still need to be considered for late complications.

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NOTICES

The fourth European forum on quality improvement in health care and the fourth Swedish QUL conference will be held in Stockholm, Sweden, 25–27 May 1999. For further information, contact Ms Marchella Mitchell, BMA Conference Unit, BMA House, Tavistock Square, London WC1H 9JP, UK; tel: +44 (0) 171 383 6478; fax: +44 (0) 171 383 6869; email: mmitchell@bma.org.uk.

The third international meeting on interventional cardiology: frontiers in interventional cardiology will be held at the ICC Jerusalem International Conventional Center, Jerusalem, Israel, 27 June to 1 July 1999. There will also be a satellite symposium Stenting and adjunctive pharmacological therapy, 1–4 July in Eliat, Israel. For further information please contact Secretariat, 3rd International Meeting on Interventional Cardiology: Frontiers in Interventional Cardiology, PO Box 50006, Tel Aviv 61500, Israel; tel: +972 3 5104000; fax: +972 3 5175674/ 5140077; email: intercard@kenes.com.

The fourth world stroke congress will be held 25–29 November 2000 in Melbourne, Australia. For further information please contact ICMS Pty Ltd, 84 Queensbridge Street, Southbank, Victoria 3006, Australia; tel: +61 3 9682 024; fax: +61 3 9682 0288; email: stroke@icms.com.au.
Randomised trials of new surgical procedures are necessary

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