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:

- initially submitted by fax +44 171 388 0323 or e-mail 100536.2733@compuserve.com (where practicable). Always follow this up by posting the paper copy to us
 - 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.

Squatting revisited: comparison of haemodynamic responses in normal individuals and heart transplant recipients

SIR—We read with interest the investigation by Hanson *et al* into the haemodynamic effects of squatting after heart transplantation¹ and were impressed with the elegant demonstration that the effects of a squat on blood pressure and stroke volume are similar in heart transplant recipients and in normal subjects.

We are surprised that Hanson *et al* consider the transplanted heart to be denervated at a mean of 16 months after operation. There is clear evidence that at least sympathetic efferent reinnervation of the transplanted human heart occurs. Using injection of tyramine we and others showed sympathetic efferent reinnervation.^{2,3} We and others have failed to demonstrate parasympathetic reinnervation using autonomic function testing⁴ and intracoronary injection of contrast.⁵

Hanson *et al* conclude that the differences between normal controls and transplant recipients are due to denervation. While this may be true, there are alternative explanations for their findings. Cardiac transplant recipients are survivors of cardiac failure, and the absence of bradycardia in response to hypertension may be partly explained by persisting reduced central baroreflex sensitivity.⁶ The response of forearm vascular resistance in the transplant recipients is consistent with this. Thus the absence of bradycardia cannot be taken as evidence of vagal denervation.

The small increase in heart rate of the transplant recipients is also consistent with sympathetic reinnervation in the absence of parasympathetic innervation, and this increase may be stimulated by the effort of squatting, in a similar manner to the effect of sustained handgrip, rather than by a volume reflex. Most cardiac sensory nerves lie in the atria, and thus a significant number remain in the recipient atrial cuff. It cannot therefore be concluded that any effect of

atrial volume change on heart rate is direct.

We would also like to suggest that this manoeuvre might be an excellent non-invasive measure of sino-aortic baroreflex sensitivity, because of the rapid change observed in systolic blood pressure, akin to that observed after the strain phase of a Valsalva manoeuvre.⁷ We suggest that the haemodynamic effects of squatting provide opportunities for the investigation of baroreflexes in other groups of subjects, and may also be useful in measuring reinnervation after cardiac transplantation. All investigations of reflexes in cardiac transplant recipients should take the possibility of reinnervation into account.

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- 1 Hanson P, Slane PR, Rueckert PA, Clark SV. Squatting revisited: comparison of haemodynamic responses in normal individuals and heart transplantation recipients. *Br Heart J* 1995;74:154-8.
- 2 Wilson RF, Christensen BV, Olivari MT, Simon A, White CW, Laxon DD. Evidence for structural sympathetic reinnervation after orthotopic cardiac transplantation in humans. *Circulation* 1991;83:1210-20.
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- 4 Morgan-Hughes NJ, Kenny RA, Scott CD, Dark JH, McComb JM. Vasodepressor reactions after orthotopic cardiac transplantation: relationship to reinnervation status. *Clin Aut Res* 1994;4:1-5.
- 5 Arrowood JA, Goudreau E, Minisi AJ, Davis AB, Mohanty PK. Evidence against reinnervation of cardiac vagal afferents after human orthotopic cardiac transplantation. *Circulation* 1995;92:402-8.
- 6 Creager MA, Creager SJ. Arterial baroreflex regulation of blood pressure in patients with congestive heart failure. *J Am Coll Cardiol* 1994;23:401-5.
- 7 Airaksinen KEJ, Harttinen KEJ, Niemela MJ, Huikuri HV, Mussalo HM, Tahvanainen KUO. Valsalva manoeuvre in the assessment of baroreflex sensitivity in patients with coronary artery disease. *Eur Heart J* 1993;14:1519-23.

This letter was shown to the authors, one of whom replies as follows:

SIR—We are aware of recent reports of partial sympathetic reinnervation of the transplanted heart^{1,2} and initially we included a discussion of this issue in our paper. Subsequently we deleted that portion to shorten the text and because we did not have data to verify the presence or absence of sympathetic reinnervation in our patients.

It is unlikely that residual impairment of arterial baroreflex sensitivity was a factor in our study. Previous studies from our laboratory showed normal sinoaortic baroreflex control of sympathetic vasomotor tone in heart transplant recipients during orthostatic stress.³ In addition, baroreflex control of the innervated atrial remnant was also normal.³

The small increase in heart rate observed in the heart transplant recipients during squatting is difficult to explain. We agree that it is not possible to exclude an autonomic component, perhaps caused by sympathetic reinnervation.

Finally, we fully concur with the suggestion that the heart rate and blood pressure responses to the squatting manoeuvre may be used to evaluate baroreflex function in various groups of patients.

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- 1 Wilson RF, Christensen BV, Olivari MT, Simon A, White CW, Laxon DD. Evidence for structural reinnervation after orthotopic cardiac transplantation in humans. *Circulation* 1991;83:1210-20.
- 2 Wharton J, Polak JM, Gordon L, Bannar NR, Springdall DR, Rose DR, Khagani A, Wallwork J, Yacoub MH. Immunohistochemical demonstration of human cardiac innervation before and after transplantation. *Circ Res* 1990;66:900-22.
- 3 Jacobsen TN, Morgan BJ, Scherrer U, Vissing S, Lange R, Johnson N, *et al*. Relative contributions of cardiopulmonary and sinoaortic baroreflexes in causing sympathetic activation in human skeletal muscle circulation during orthostatic stress. *Circulation* 1993;73:367-78.

Serum lipids four weeks after acute myocardial infarction are a valid basis for lipid lowering intervention in patients receiving thrombolysis

SIR,—Carlsson *et al* suggested that serum lipids should be measured 4 weeks after acute myocardial infarction treated with thrombolysis because there were no significant differences between these values and those obtained within 24 hours of onset of symptoms.¹ This may in fact not be valid if the acute measurements were largely taken after and not before thrombolysis, because thrombolysis itself may be associated with a small but significant fall in total cholesterol² and concentrations may not return to basal values until several months later.³ The danger of course is that some patients with spuriously low concentrations may be overlooked. Given that the 4S study clearly supports active intervention for secondary prevention,⁴ each hospital should identify their best local practice of targeting patients for intervention. The previously recommended strategy² of routinely taking blood for lipid measurement when intravenous access is secured for thrombolysis is easily applied, yields accurate baseline results, and helps to ensure that no patient with hypercholesterolaemia is missed.

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- 1 Carlsson R, Lindberg G, Westin L, Israelsson B. Serum lipids four weeks after acute myocardial infarction are a valid basis for lipid lowering intervention in patients receiving thrombolysis. *Br Heart J* 1995;74:18-20.
- 2 Chua TP, Fry IDR, Frankell RJ, Lim R. Serum cholesterol concentration before and after streptokinase in acute myocardial infarction. *J Int Med* 1993;234:603-5.
- 3 Ryder REJ, Hayes TM, Mulligan IP, Kingswood JC, Williams S, Owens DR. How soon after myocardial infarction should plasma lipid values be assessed? *BMJ* 1984;289:1651-3.
- 4 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.

This letter was shown to the authors, one of whom replies as follows:

SIR,—Dr Bennie refers to a study from Chua *et al* including 26 male patients. Chua *et al* reported a 0.4 nmol/l fall in serum cholesterol concentration from a pre-streptokinase treatment concentration of 7.0 nmol/l. They concluded that serum cholesterol concentrations may be underestimated when they are measured after streptokinase treatment. However, the clinical importance of this underestimation of the lipid concentration is of less importance than the time lost when patients wait 3-6 months before start-

ing lipid lowering treatment. We fully agree that it is better to measure lipid concentrations before thrombolytic treatment. If such early lipid estimations are not available, values obtained within 24 hours after admission or 4 weeks later are a sufficiently valid basis for reaching a decision about early lipid intervention.

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Aortic distensibility measured by magnetic resonance imaging in patients with Marfan's syndrome

SIR,—Adams and colleagues¹ reported aortic distensibility measurements based on assessments by eye of magnetic resonance (MR) and echocardiographic images in 12 patients with Marfan's syndrome. They suggest that the measurements are reproducible. Without re-scanning their patients on a separate occasion and repeating their analyses we do not see how they can conclude this. They do not specify the oscillation frequency of the ultrasound probe used for echocardiography, but at 2.5–3.5 MHz, which is typical for such work, the maximum spatial resolution would be of the same order of magnitude as the change in aortic diameter being measured. Furthermore, the errors involved in the off-line measurement of dimensions from a scan are much less than those involved in actually performing the scan.² Therefore data on the repeatability of the analysis procedure—or mean $\pm$ SD values from repeat scans at the same visit—tell us very little, if anything, about the true reproducibility of the measurement techniques.

In any discussion of the validity of direct measurements of distensibility at a particular aortic cross-section it is important to consider the role of blood pressure. Adams *et al* measured the change in diameter (or area) at discrete cross-sections of the ascending and descending thoracic aorta but then applied blood pressure values recorded from the brachial artery to calculate aortic distensibility. Blood pressure varies along the arterial tree and amplification of the pressure pulse between central and peripheral arteries makes brachial pressure values an inaccurate measure of central aortic pressure.³ There can be absolute differences in systolic and pulse pressures of up to 20 mm Hg.³ This problem can be partly overcome by indirectly determining an average elastic property of the aortic wall based on pulse wave velocity (PWV) measurements.⁴ Such an approach does not require the blood pressure at a particular aortic cross-section to be known.⁵ This is especially pertinent because aortic distensibility indices determined from PWV measurements have good reproducibility (coefficient of variation < 10%).⁴ A transfer function can also be used to calculate central aortic systolic and pulse pressures based on non-invasively determined data on pressure waveforms in peripheral arteries.³

Papers that describe the application of MRI or echocardiography for directly measuring the change in aortic diameter (or area) between diastole and systole by eye are increasing. But not many papers report the reproducibility of such methods for non-invasively assessing aortic distensibility. Kupari *et al* reported a mean (SD) reproducibility for their MR measurements in the

ascending and descending aorta of 26.3 (23.3)% and 34.5 (32.1)%, respectively.⁶ Isnard *et al* using echocardiography reported reproducibility values of up to 23% in the ascending aorta.⁷ Dart *et al* also used echocardiography and, taking special care to obtain images exactly perpendicular to the aortic arch (to avoid measuring the change in diameter of an ellipse), obtained a mean reproducibility (SEM) in young, healthy, athletic men of 9.4 (2.9)%.⁸ Unfortunately, these latter data tell us very little, if anything, about the reproducibility of the technique in older patients with stiffer arteries in whom the change in aortic diameter during the cardiac cycle would be much reduced (as would the measurement reproducibility). In view of these data we do not find it surprising that Adams *et al* found that individual values for aortic distensibility varied by up to a factor of five depending on whether MR or echocardiographic data were used.

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- 1 Adams JN, Brooks M, Redpath TW, Smith FW, Dean J, Gray J, *et al*. Aortic distensibility and stiffness index measured by magnetic resonance imaging in patients with Marfan's syndrome. *Br Heart J* 1995;73:265–9.
- 2 Lehmann ED, Hopkins KD, Gosling RG. Direct aortic distensibility measurements and their reproducibility. *Eur Heart J* 1994;15:1141–2.
- 3 Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J* 1993;14:160–7.
- 4 Hopkins KD, Lehmann ED, Gosling RG. Aortic compliance measurements: a non-invasive indicator of atherosclerosis? *Lancet* 1994;343:1447.
- 5 Lehmann ED. Biophysical properties of the aorta. *Lancet* 1994;344:1763.
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- 7 Isnard RN, Pannier BM, Laurent S, London GM, Diebold B, Safar ME. Pulsatile diameter and elastic modulus of the aortic arch in essential hypertension: a noninvasive study. *JACC* 1989;13:399–405.
- 8 Dart A, Silagy C, Dewar E, Jennings G, McNeil J, Cameron J. Direct aortic distensibility measurements and their reproducibility. *Eur Heart J* 1994;15:1142–3.

This letter was shown to the authors, two of whom reply as follows:

SIR,—Magnetic resonance imaging is an established non-invasive method of assessing anatomical structure and dimensions. We have shown in our study that aortic images obtained by this technique can be produced quickly and simply in patients with Marfan's syndrome and in healthy controls. Measurements made on these images can be reproducibly assessed by independent observers. We did not perform further scans on a second occasion and therefore cannot comment further on the reproducibility of this technique.

We agree that brachial pressure is lower than that measured directly. However, as Stefanadis *et al* have shown, the underestimation is similar in patients with coronary disease and healthy men and the pulse pressure measured indirectly by sphygmomanome-

ter correlates well with the pressure measured directly by catheterisation of the ascending aorta. Aortic distensibility determined non-invasively is closely related to that obtained using direct measurements.¹ We chose to use brachial pressure rather than pulse wave velocity because brachial pressure is more widely available and easier to use.

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- 1 Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. *Eur Heart J* 1990;11:990–6.

Is aspirin safe for patients with heart failure?

SIR—The prophylactic benefit of aspirin may have been overstated not only in coronary heart disease, as Cleland *et al* suggest,¹ but also in thromboembolism related to non-valvular atrial fibrillation (NVAF). In NVAF, this overstatement may be the result of failure to recognise that warfarin cannot prevent all thromboembolic events in all patients all the time,² and that aspirin may sometimes be perceived to have a prophylactic benefit because some NVAF patients have non-cardiac mechanisms of thromboembolism that are more amenable to risk modification by aspirin than by warfarin.^{3,4}

Furthermore, the risk/benefit profile of antithrombotic treatment might be more favourably disposed towards aspirin than towards warfarin in high-intensity⁵ than in low-intensity⁶ anticoagulant regimens. For thromboembolic prophylaxis, the principal disadvantage of aspirin is the unpredictability of its dose dependence with time⁷: this confounds comparisons between antithrombotic drugs and between subgroups receiving the same drug.

The seemingly intractable dilemmas of antithrombotic therapy can only be resolved by a complex trial simultaneously posing the questions "which patient?", "which drug?", "what dose?", and "what duration?"

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- 1 Cleland JGF, Bulpitt CJ, Falk RH, Findlay IN, Oakley CM, Murray G, *et al*. Is aspirin safe for patients with heart failure? *Br Heart J* 1995;74:215–9.
- 2 Archer SL, James KE, Kvernem LR, *et al*. Role of transoesophageal echocardiography in the detection of left atrial thrombus in patients with chronic nonrheumatic atrial fibrillation. *Am Heart J* 1995;130:287–95.
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- 5 Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: stroke prevention in atrial fibrillation II Study. *Lancet* 1994;343:687–91.
- 6 Ezekowitz MD, Bridgers SL, James KE, *et al*. Warfarin in the prevention of stroke associated with non-rheumatic atrial fibrillation. *N Engl J Med* 1992;327:1406–12.
- 7 Helgason CM, Bolin KM, Hoff JA, *et al*. Development of aspirin resistance in persons with previous ischemic stroke. *Stroke* 1994;25:2331–6.