LETTERS TO THE EDITOR

- The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.
- All letters must be typed with double spacing and signed by all authors.
- No letter should be more than 600 words.
- In general, no letter should contain more than six references (also typed with double spacing).

Left ventricular filling dynamics during dipyridamole induced myocardial ischaemia

SIR,—Shahi *et al* (*British Heart Journal* 1991;65:265-70) found altered pulsed Doppler transmitral flow profiles during myocardial ischaemia provoked by dipyridamole stress compared with controls and patients with coronary disease in whom ischaemia was not so induced. The interpretative difficulties and limitations of this approach in relation to the method used merit further comment.

Patient age, which importantly influences the filling pattern,¹ was lower in controls than in patients with coronary disease (45 (12) v 58 (6) years, $p = 0.002$). The consequences of dipyridamole induced haemodynamic changes on transmitral flow are therefore also likely to be affected by age. Age data are not given for the various groups and subgroups of the study population. Nor are we told whether all the subjects were in sinus rhythm.

Numerous factors can confound the evaluation of filling dynamics after dipyridamole infusion including the administration of aminophylline, which has positive inotropic and vasodilator properties, and fusion of early and atrial waves with tachycardia. How many patients received aminophylline and at what time in relation to the collection of Doppler data and how many developed a single filling wave? In addition, new transient mitral regurgitation is a well recognised consequence of dipyridamole induced ischaemia² and profoundly affects the filling pattern but was not sought by these investigators.

Chest pain and electrocardiographic changes were used as markers of ischaemia but are generally believed to be insensitive for this purpose.³ Transient regional asynergy on cross sectional echocardiography is best but no data on wall motion are given. Furthermore, Shahi *et al* attribute the altered filling response seen in group 3B to more pronounced ischaemia without any supporting evidence. A more likely explanation is the substantially different pre-infusion filling pattern in this subgroup.

The determination of baseline (temporal) variability is fundamental in studies of serial measures. Shahi *et al* have overlooked this and quote only intraobserver variability which takes no account of variation in Doppler indices owing to physiological and technical factors.

We studied 34 patients in sinus rhythm during dipyridamole stress and compared age matched coronary disease patients who developed ischaemia, detected by echocardiographic and electrocardiographic criteria, with those who did not.⁴ Transmitral flow was uninterpretable in three (9%) patients owing to fusion of the early and atrial waves. Doppler filling variables were insensitive in identifying patients with ischaemia induction even when this was severe. Our data strongly suggested that changes in ventricular loading and heart rate induced by dipyridamole masked the expected effects of myocardial ischaemia on the filling profile. Other workers have reached similar negative conclusions⁵ indicating that this approach cannot supplement wall motion analysis for the evaluation of patients with coronary artery disease. Despite reservations on interpretability, the data from Shahi *et al* are consistent with these observations and highlight the ease with which spurious differences between groups may emerge when numerous confounding variables are operative and group size is small.

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- 1 Bryg RJ, Williams GA, Labovitz AJ. Effect of aging on left ventricular diastolic filling in normal subjects. *Am J Cardiol* 1987;59:971-4.
- 2 Tomimoto S, Takeuchi M, Fukuzaki H. Non-invasive assessment of left ventricular diastolic filling in coronary artery disease by Doppler dipyridamole-stress testing. *Jpn Heart J* 1989;30:765-78.
- 3 Picano E. Dipyridamole-echocardiography test: historical background and physiologic basis. *Eur Heart J* 1989;10:365-76.
- 4 Mazeika P, Nihoyannopoulos P, Joshi J, Oakley CM. Evaluation of dipyridamole-Doppler echocardiography for detection of myocardial ischaemia and coronary artery disease. *Am J Cardiol* (in press).
- 5 Grayburn PA, Popma JJ, Pryor SL, Walker BS, Simon TR, Smitherman TC. Comparison of dipyridamole-Doppler echocardiography to thallium-201 imaging and quantitative coronary arteriography in the assessment of coronary artery disease. *Am J Cardiol* 1989;63:1315-20.

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

SIR,—Dr Mazeika and Dr Oakley quite rightly have brought attention to the differences in age between the control and study group which may have had an effect on our results. Both age and heart rate are well known to be major determinants of transmitral Doppler filling velocities and as yet no correction factors are known to allow for these variables. Neither is it known how heart rate affects subjects of different ages or how heart rate affects patients with abnormal filling velocities in different age groups. Despite these unknown variables we feel that useful information can be derived from studying filling velocities during myocardial ischaemia.

All patients studied were in sinus rhythm and remained in sinus rhythm during the study period.

Aminophylline was given to two patients in group 3A and one patient in group 3B. In two of these patients it was given at the end of the study period and therefore would not have affected the filling velocities.

Two patients in the control group developed a single filling velocity during the study period but only for a maximum of two readings. In these patients the filling velocity of the early filling wave just before merging of the waves was taken to represent the filling velocity.

To allow for baseline temporal variability the mean value of five one minute recordings was taken to represent baseline value.

Regional wall motion abnormalities were not specifically assessed in our study but their importance as a more sensitive marker of ischaemia was discussed in the discussion section (p 270).

Reference 5 quoted by Dr Mazeika and Dr Oakley was cited in our paper together with its limitations. We cannot comment on reference 4 at present.

Although it was not possible for technical reasons to assess the presence of mitral regurgitation during myocardial ischaemia in our study, Dr Mazeika and Dr Oakley are correct to state that this may have affected our results. Ischaemia-induced mitral regurgitation would increase left atrial pressure and therefore decrease the isovolumic relaxation period and subsequently increase the transmitral pressure gradient with a resulting increase in the early filling velocity and a possible decrease in the atrial filling velocity. It is therefore possible that this may be the reason for the difference in left ventricular filling velocities in groups 3A and 3B. Both at the end of the abstract and in the discussion section we stated that our observations could be attributable either to the degree of myocardial ischaemia or to different haemodynamic changes occurring during myocardial ischaemias.

Once again we would like to emphasise that the study was designed to observe the left ventricular filling characteristics during myocardial ischaemia and not to suggest that these changes in filling velocities could predict myocardial ischaemia in an individual patient (last paragraph p 269).

I hope these comments will help clarify the points made by Dr Mazeika and Dr Oakley.

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Circadian variation in the frequency of onset of chest pain in acute myocardial infarction

SIR,—Dr Thompson and colleagues make a convincing case in Leicester for a midnight peak in onset of myocardial infarction in addition to the well-known one at 8 am (*British Heart Journal* 1991;65:177-8). They try to persuade us that meta-analysis of other studies would confirm this. Unfortunately they have omitted from their references perhaps the largest study of all.¹ This was the collected data from the World Health Organisation Regional Office for Europe Heart Attack Registers of the 1970s covering some 10 000 events. The pooled data from these show a clear peak between 8 and 10 am on weekdays which is much sharper at 10 am on Saturdays and Sundays. There is also a bulge around 4-5 pm but no overall peak around midnight. The exception interestingly is a possible such peak on Saturday.

If the Leicester peak is not just a chance finding, and it is found in some cities but not others and may be related to Saturdays, one

wonders whether it is related to closing time in public bars.

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- 1 World Health Organisation Regional Office for Europe. Myocardial Infarction Community Registers. Public Health in Europe 5. Copenhagen, 1979.

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

SIR,—We thank Professor Tunstall-Pedoe for his interesting comments on our paper. The confirmation of the finding of a secondary midnight peak in the onset of chest pain in acute myocardial infarction in a five year retrospective analysis of a five year prospective study makes it unlikely that the peak is a chance finding. Our discussion reaches no conclusion about its possible cause but our data do not exclude the possibility that the midnight peak is a local phenomenon whose explanation might lie in local circumstances. We find the explanation in terms of public house closing times intriguing but unlikely to be correct. Our data, which have also been analysed for the frequency of acute myocardial infarction on days of the week (unpublished), do not provide significant support for the Saturday hypothesis. Moreover, a change of licensing hours applied to Leicester which liberalised weekday public house opening, occurred during the prospective data collection and did not result in a measurably stronger trend in support of the midnight peak during the later stages of the study.

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Syndrome X and hyperventilation

SIR,—Syndrome X and hyperventilation have long been associated, and Lewis and colleagues (*British Heart Journal* 1991; 165:94–6) are to be congratulated for their discriminating contribution to the field and for raising several important questions. A central issue is whether hyperventilation can be dismissed on the basis of a rather limited schedule of testing. For example, it is no longer thought that the forced hyperventilation provocation test (FHPT) is the “gold standard” of hyperventilation testing,^{1,2} but that provocation by personally relevant stressors^{3,4} is at least as important. Indeed, in the context of cardiological patients, the latter stressors, which can also activate the adrenergic vasoconstrictive pathways⁵ are probably the triggers most relevant in everyday life. Furthermore, besides the interplay between hyperventilation and sympathetic nervous system activation (with consequences such as magnesium depletion⁶) it seems likely that it is the neuroendocrine setting that can determine whether or not a given episode of hyperventilation has vasoconstrictive consequences.⁷

It is a commonplace finding that many patients with recurrent hyperventilation illnesses do not hyperventilate during an exercise test, but readily overbreathe in response to an emotional challenge, particularly when

the challenge involves the recall of feelings of being trapped or of anger.^{4,7}

As far as the data presented by Lewis *et al* are concerned, besides noting the absence of figures for end tidal pressure of carbon dioxide (CO₂ ET) for their controls, we also note that the CO₂ ET values of 38 mm Hg at 50% of maximum exercise and 37 mm Hg at maximum exercise are well below expected normal values.⁸

The demonstration of increased minute ventilation for given minute carbon dioxide (VE/VCO₂) is quite consistent with chronic hyperventilation. It is due either to reduced respiratory centre buffering⁹ or a flywheel effect when regularly over-activated pathways promote breathing,¹⁰ or both. The observation of a raised VE/VCO₂ may well be the key indicator of a longer term tendency to hyperventilation, because as stated above, the FHPT is a single act of hyperventilation and is dependent upon the patient's starting point in terms of other influences upon vasoconstriction such as emotional arousal and depletion of the body's buffering systems.

A basic question about syndrome X patients is whether their responsiveness to recognised vasoconstrictive influences is greater than average, just as Europeans in general are more responsive than the Japanese.¹¹

We suggest that Lewis *et al* have sharpened the definition of characters in the drama of syndrome X and hyperventilation but have not yet brought down the final curtain.

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- 1 King JC, Rosen SD, Nixon PGF. Failure of awareness of hypocapnia. *J R Soc Med* 1990;83:765–7.
- 2 Roll M, Zetterquist S. Acute chest pain without obvious organic cause before the age of 40 years. *J Intern Med* 1990;228:223–8.
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- 4 Nixon PGF, Freeman LJ. The “think test”: a further technique to elicit hyperventilation. *J R Soc Med* 1988;81:277–9.
- 5 Groen JJ. The measurement of emotion and arousal in the clinical physiological laboratory and in clinical practice. In: Levi L, ed. *Emotions: their parameters and measurement*. New York: Raven Press, 1975:727–46.
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- 9 Brown EB, Jr. Physiological effects of hyperventilation. *Physiol Rev* 1953;33:445–71.
- 10 Folgering H, Colla P. Some anomalies in the control of P_aCO₂ in patients with a hyperventilation syndrome. *Bull Eur Physiopathol Respir* 1978;14:503–12.
- 11 Maseri A, Kaski JC. Pathogenetic mechanisms of coronary artery spasm. *J Am Coll Cardiol* 1989;14:610–2.

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

SIR,—We appreciate the interest shown by Dr Nixon and colleagues in our paper. Our study refers of course to our carefully characterised patients—an important consideration given the widely differing patient groups

represented in published reports on patients with unexplained chest pain. Clearly the filing category of syndrome X is coming to the end of its useful life, particularly in view of the confusion now arising over a different “syndrome X”.¹

In specific comment on the points raised by Dr Nixon and colleagues—our patients with syndrome X all described typical angina and, in every case, exercise induced the same symptom. We would argue that an exercise test in such a group represents a “personally relevant stressor”. The finding of normal arterial PCO₂ values throughout exercise in our syndrome X patients formed the basis for our conclusion that they were not then hyperventilating inappropriately (which in common usage is the implication inherent in the term). Because we showed that end tidal PCO₂ correlated only poorly with arterial PCO₂ in these patients, their end tidal measurements, we agree, provided no evidence either for or against a diagnosis of hyperventilation. Chronic hyperventilation may indeed increase the VE/VCO₂ slope but only in the presence of low arterial PCO₂ (the modified alveolar gas equation states: VE = 863 VCO₂/Paco₂(1 – Vd/VT). The normal arterial PCO₂ in our patients implies an increase in deadspace ventilation.² We did not measure arterial PCO₂ in our control patients for ethical reasons.

We share the view that the final curtain is not yet drawn on the various players on this ill-lit stage, while our spotlights continue to weave. . .³

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- 1 Dean JD, Jones CJH, Hutchison SJ, Peters JR, Henderson AH. Syndrome(s) X. *Lancet* 1991;337:916.
- 2 Jones NL. *Clinical exercise testing*. 3rd ed. Philadelphia: W B Saunders, 1988:13–74.
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Alcohol ablation of atrioventricular conduction

SIR,—Dr Cunningham and Dr Rowland (*British Heart Journal* 1991;65:115) favour the use of “conventional” methods of ablation of atrioventricular conduction rather than the new method of ethanol ablation. “Conventional” methods include, according to them, radiofrequency ablation (with its known low success rate), higher energy shocks (with a known high complication rate), and low energy shocks (only three published reports of this—two abstracts and a small series). Long-term results with ethanol ablation remain excellent.¹ No deaths have been reported after alcohol ablation. Its success rate, even when analysed on the basis of intention to treat, is comparable to “conventional” methods. The results of “conventional” methods were never presented on an intention to treat basis.

It looks to me as if there are no “conventional” or “established” methods for the ablation of atrioventricular conduction. Only long-term results will show which method offers the best results at the lowest risk. Meanwhile, investigators and physicians