NOTES 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) vs 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 in tachycardia. How many patients received aminophylline 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 ischaemia1 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.1 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 intraserver 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.1 Transmitral flow was uninterpretable in four 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 conclusions1 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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This letter was shown to the authors, who reply as follows:

SIR,—Dr Mazeika and Dr Oakley quite rightly have brought to our attention some apparent contradictions between transmitral filling velocities and age and heart rate. We have sought to be very explicit about these variables. Neither is it known how heart rate affects subjects of different ages or how heart rate affects patients with different coronary artery disease. Despite these unknown variables we feel as though useful information can be derived from studying filling velocities during dipyridamole 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 this study but their importance as a more sensitive marker of ischaemia was discussed in the discussion section (p 270).

Regarding age 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 transmural 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 ischaemia.

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 J 1991;66:177-8). 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. 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 shows a clear peak between 8 am and 10 am on weekdays which is much sharper than 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 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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This letter was shown to the authors, who reply as follows:

STIR—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

STIR—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 (FHPPT) is the "gold standard" of hyperventilation testing; but that provocation by personally relevant stresses is at least as important. Indeed, in the context of cardiac patients, the latter stresses, which can in some cases activate the energetic vasoconstrictive pathways 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 depletion) it is likely that it is the neuroendocrine setting that can determine whether or not a given episode of hyperventilation has vasoconstrictive consequences.

It is a commonplace finding that many patients with recurrent hyperventilation illness 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.

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 (PET CO2) for their controls, we also note that their PET CO2 values of 38 mm Hg at 50% of maximum exercise and 37 mm Hg at maximum exercise are well below expected normal values.

The demonstration of increased minute ventilation for given minute carbon dioxide (VE/VECO2) is quite consistent with chronic hyperventilation. It is due either to reduced respiratory centre buffering or a flywheel effect which results from altered central pathways promote breathing, or both. The observation of a raised VE/VECO2 may well be the key indicator of a longer term tendency to hyperventilation, because as stated above, the FHPPT is a single act of hyperventilation and is dependent upon the patient's starting point in terms of other influences upon vasoconstrictive mechanisms, peripheral arousal and depletion of the body's buffering systems.

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

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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3 Lewis B. Chronic hyperventilation syndrome. JAMA 1964;189:404-8.

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

STIR—We appreciate the interest shown by Dr Nixon and colleagues in our paper. Our study refers of course to a carefully characterised patient group—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." Dr Nixon makes a pertinent point on the cases 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, in fact, 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 agreed, provided no evidence either for or against a diagnosis of hyperventilation. Chronic hyperventilation may indeed increase the VE/VECO2 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 is in general in deadspace ventilation. 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 spotlight continues to grow...