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