Haemodynamic effects of intravenous amrinone in patients with impaired left ventricular function

Sir,

The recent paper by Wilmshurst *et al.*¹ concluded that the beneficial haemodynamic effects of amrinone in patients with left ventricular impairment were attributable to vasodilatation, the drug having no demonstrable positive inotropic properties. This conclusion—which is at variance with a considerable body of experimental and clinical data—was based on the failure of amrinone to influence indices of left ventricular contractility. In two previous clinical studies, however, significant increments in left ventricular dp/dt max in excess of 40% were observed after amrinone therapy.^{2,3} Wilmshurst *et al.* proposed that simultaneous increments in heart rate were sufficient to account for this finding, apparently ignoring the fact that a similar increase in heart rate during their own study was associated with no change at all in left ventricular dp/dt max. Moreover, the paper by Benotti *et al.*² reported pronounced increments in left ventricular dp/dt max even in patients in whom heart rate remained unchanged.

Thus, the apparent absence of a positive inotropic response to amrinone in the patients studied by Wilmshurst *et al.* demands an alternative explanation which probably relates to the design of their study. When haemodynamic measurements are made directly after routine coronary angiography a stable baseline—essential in studies of this type—cannot be guaranteed. Atropine premedication, for example, ensures a changing vagal influence during the period of investigation.

Of added concern is the large though unspecified quantity of contrast material these patients must have received during the coronary and (duplicate) left ventricular angiograms. The profound haemodynamic effects of contrast material are particularly unpredictable in the presence of left ventricular disease and persist for at least 15 minutes after a single injection.⁴⁻⁷ Myocardial metabolism remains disturbed for considerably longer.⁸ In a study involving multiple contrast injections a 20 minute delay before data collection is unlikely, therefore, to be adequate. Moreover, the end-systolic pressure/volume measurements—collected of necessity at the time of angiography—are particularly difficult to interpret since any positive inotropic response to amrinone would be overwhelmed by the depressant effects of

contrast material which are maximal at this time. Analysis of these data is further complicated since no attempt was made to control heart rate by atrial pacing before and after drug intervention.

The failure of Wilmshurst *et al.* to show an inotropic response to amrinone is likely, therefore, to reflect the design of their study rather than the pharmacological activity of the drug.

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References

- 1 Wilmshurst PT, Thompson DS, Jenkins BS, Coltart DJ, Webb-Peploe MM. Haemodynamic effects of intravenous amrinone in patients with impaired left ventricular function. *Br Heart J* 1983; 49: 77-82.
- 2 Benotti JR, Grossman W, Braunwald E, Davalos DD, Alousi AA. Hemodynamic assessment of amrinone: a new inotropic agent. *N Engl J Med* 1978; 299: 1373-7.
- 3 Cardenas LM, Vidaurri A. Estudio de los efectos hemodinámicos de diferentes dosis de un nuevo inotrópico: la amrinona. *Arch Inst Cardiol Mex* 1979; 49: 961-8.
- 4 Rahimtoola SH, Duffy JP, Swan HJC. Ventricular performance after angiocardiology. *Circulation* 1967; 35: 70-8.
- 5 Brown AK, Epstein EJ, Coulshed N, Clarke JM, Doukas NG. Haemodynamic changes after angiocardiology. *Br Heart J* 1969; 31: 233-45.
- 6 Mullins CB, Leshin SJ, Mierzwiak DS, Alsobrook HD, Mitchell JH. Changes in left ventricular function produced by the injection of contrast media. *Am Heart J* 1972; 83: 373-81.
- 7 Hamby RI, Aintablian A, Wisoff BG, Hartstein ML. Effects of contrast medium on left ventricular pressure and volume with emphasis on coronary artery disease. *Am Heart J* 1977; 93: 9-18.
- 8 Wisneski JA, Gertz EW, Neese R, *et al.* Myocardial metabolic alterations after contrast angiography. *Am J Cardiol* 1982; 50: 239-45.

This letter was shown to the authors, Dr Wilmshurst and colleagues, who reply as follows:

Sir,

We thank Timmis *et al.* for their letter and interest in our research, but disagree that our conclusions are "at variance with a considerable body of experimental and clinical data". Amrinone has positive inotropic properties in normal animals,¹ animals with acutely induced experimental cardiac failure,¹ and normal human myocardium.² This property, in contrast to the direct vasodilator effects,^{1,2} is not detectable at therapeutic concentrations.² In both animals³ and man² the in vitro inotropic effects disappear with chronicity and severity of cardiac failure. Intracoronary infusion of amrinone in patients produces no change in haemodynamics despite therapeutic concentrations of the drug in the coronary sinus blood.⁴ In the presence of vasodilatation, it is doubtful that a positive inotropic effect can be shown in man without invasive measurements of indices of contractility. Three studies⁵⁻⁷ have measured such indices, but only ours⁷ has attempted to demonstrate a dose response relation. In the two smaller series^{5,6} use of a haemodynamic end-point⁵ and peak effect⁶ cast doubt upon the demonstration of a positive inotropic effect. Use of peak effects allow one to filter random haemodynamic variables and accept changes that occur only if they are in the direction of a preconceived notion. Use of a haemodynamic end-point, for example specified fall in filling pressure, may affect interrelated haemodynamic variables measured simultaneously.

In our paper⁷ we stated that "at least part of the increase in max dp/dt is the result of the increase in heart rate" not that "the increments in heart rate were sufficient to account for this" as stated by Timmis *et al.* The heart rate increase (30%) reported by Cardenas *et al.*⁶ was not similar to that (9%) seen in our study.⁷ Timmis *et al.* cite the findings of Wisneski *et al.*⁸; but this paper could not have shown that "myocardial metabolism remains disturbed for considerably longer" (than 20 minutes after angiography) since the authors⁸ made no measurements after this interval. Furthermore one of their own references⁹ is counter to their argument that the maximum depressant effect of contrast medium occurs simultaneously with ventricular contrast injection; instead the depressant effect was detected only after the twelfth beat⁹ by which time contrast would have disappeared from the ventricle.

Atropine was given to patients with impaired left ventricular function, and hence reduced vagal activity, to prevent sudden increases in vagal tone which may accompany cardiac catheterisation. If anything it is likely to accentuate any inotropic effects of amrinone by shifting the dose response curve to the left.¹⁰ During the approximately 45 minutes between control and final measurements the pharmacodynamic effects

of atropine on the cardiovascular system are unlikely to have changed much. Atropine, a highly selective muscarinic blocker, seems preferable to diphenhydramine used by Benotti *et al.*,⁵ which, as well as powerful anticholinergic effects, has H₁ blocking and quinidine-like actions, can cause both vasoconstriction and vasodilatation, and is reported to cause sudden changes in blood pressure. Cardenas *et al.*⁶ make no mention of giving any drugs (including local anaesthetics). Benotti *et al.*⁵ also performed cineangiography at the time of their study in six patients but they do not say when.

The use of angiography does present problems, but the combination of diagnostic and research procedures makes this necessary. The alternative is two separate catheterisations. We were initially worried about giving an "inotropic" agent to patients with coronary artery disease and so elected to perform coronary angiography first. We used biplane cineangiography and the minimum number of injections (five to six injections, 5 to 8 ml 76% Urografin). The interval between coronary angiography and the subsequent research procedure always exceeded 45 minutes. We do not believe this is contrary to standard practice. As we stated⁷ the interval between the first left ventricular cineangiogram and subsequent interventions/measurements exceeded 20 minutes and no measurements were made after the second left ventricular cineangiogram. Our study was a haemodynamic study and 20 minutes after angiography is adequate for return to haemodynamic baseline, as Timmis *et al.* point out. The metabolic effects of contrast are of some relevance. Unlike the majority of our patients, all those in the series by Wisneski *et al.*⁸ had coronary artery disease, and in these the metabolic effects of angiography are exaggerated.¹¹ In the paper by Wisneski *et al.*⁸ at 20 minutes after left ventricular cineangiography all the metabolic effects were of small and decreasing magnitude, with the exception of arterial concentration and myocardial extraction of free fatty acid. We feel that the time of heparinisation may be in part responsible for the reduction in arterial free fatty acid at 20 minutes.¹² We find it interesting that in this paper⁸ 10 ml contrast injected into the venous system should alter myocardial metabolism as much as a similar intracoronary bolus or larger left ventricular injection. This suggests that multiple doses of contrast may not have an additive effect upon myocardial metabolism, as suggested by Timmis *et al.* It is obvious that all invasive procedures affect variables measured, but we hope, like others, to design our experiments to keep this to a minimum. We are sure that the differences between our conclusions⁷ and those of others^{5,6} are based partly on differences in experimental design. We believe our design is more likely to offer an under-

standing of the actual pharmacological effects of the drug.

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References

- 1 Alousi AA, Edelson J. Amrinone. In: Goldberg ME, ed. *Pharmacological and biochemical properties of drug substances*. Vol 3. Washington DC: American Pharmaceutical Association, 1981: 120-46.
- 2 Wilmshurst PT, Walker JM, Fry CH, *et al.* The inotropic and vasodilator properties of amrinone on isolated human tissue. *Clin Sci* 1983; **64**: 7P.
- 3 Gaide MS, Fitterman WS, Wiggins JR, Myerburg RJ, Cameron JS, Bassett AL. Amrinone relaxes potassium-induced contracture of failing right ventricular muscle of cats. *J Cardiovasc Pharmacol* 1983; **5**: 335-40.
- 4 Wilmshurst PT, Thompson DS, Dittrich HC, *et al.* Effects of intravenous and intracoronary amrinone in congestive cardiac failure [Abstract]. *Circulation* 1982; **66** (suppl 2):137.
- 5 Benotti JR, Grossman W, Braunwald E, Davolos DD, Alousi AA. Hemodynamic assessment of amrinone: a new inotropic agent. *N Engl J Med* 1978; **299**: 1373-7.
- 6 Cardenas LM, Vidaurri A. Estudio de los efectos haemodinámicos de diferentes dosis de un nuevo inotrópico: la amrinona. *Arch Inst Cardiol Mex* 1979; **49**: 961-8.
- 7 Wilmshurst PT, Thompson DS, Jenkins BS, Coltart DJ, Webb-Peploe MM. Haemodynamic effects of intravenous amrinone in patients with impaired left ventricular function. *Br Heart J* 1983; **49**: 77-82.
- 8 Wisneski JA, Gertz EW, Neese R, *et al.* Myocardial metabolic alterations after contrast angiography. *Am J Cardiol* 1982; **50**: 239-45.
- 9 Mullins CB, Leshin SJ, Mierzwiak DS, Alsobrook HD, Mitchell JH. Changes in left ventricular function produced by the injection of contrast media. *Am Heart J* 1972; **83**: 373-81.
- 10 Endoh M, Yamashita S, Taira N. Positive inotropic effect of amrinone in relation to cyclic nucleotide metabolism in the canine ventricular muscle. *J Pharmacol Exp Ther* 1982; **221**: 775-83.
- 11 Visioli O, Cucchini F, Bongrani S, Ferrari R. Lactate production after left ventricular angiography in coronary artery disease [Letter]. *Am Heart J* 1978; **96**: 835-6.
- 12 Thompson DS, Naqvi N, Juul SM, Coltart DJ, Jenkins BS, Webb-Peploe MM. Haemodynamic and metabolic effects of atenolol in patients with angina pectoris. *Br Heart J* 1980; **43**: 668-79.

Notice

British Cardiac Society

The Autumn Meeting will be held at Wembley on 21 and 22 November 1983, and the closing date for abstracts was 26 July 1983.

The Annual General Meeting for 1984 will take place in Leicester on 11 and 12 April 1984, and the closing date for receipt of abstracts will be 3 January 1984.

The Autumn Meeting in 1984 will be held on 3 and 4 December 1984, and the closing date for receipt of abstracts will be 15 August 1984.