heart disease.¹ One of their principal findings was that adrenaline produced ischaemia at a lower rate-pressure product than exercise. This raises many important questions about the mechanisms through which catecholamines produce ischaemia and about how such ischaemia can be prevented.

McCance and Forfar postulate that redistribution of coronary flow is the mechanism underlying the greater ischaemic effect of adrenaline, but recent biochemical data suggest an alternative explanation. Adrenaline (released from the adrenal medulla during stress) is a more potent stimulator of the β -2 subtype of adrenoceptor than noradrenaline (released from the sympathetic nerve endings during exercise). Stimulation of cardiac β -2 adrenoceptors, like β -1 adrenoceptors, has positive inotropic and chronotropic effects.^{2,3} However, biochemical studies have shown important differences in the linkage of β adrenoceptor subtypes to cardiac adenylate cyclase, with a higher proportion being linked to β -2 adrenoceptors than to β -1 adrenoceptors.⁴ Not all adenylate cyclase when activated leads to increased contractility; therefore, adrenaline activation of adenylate cyclase not linked to contraction (possibly linked to metabolic pathways) may lead to a further increase in oxygen consumption. This differential coupling to adenylate cyclase may explain why adrenaline infusions produce greater ischaemia than exercise for a given rate-pressure product.

Whatever the underlying mechanism, this study has important therapeutic implications. By failing to block β -2 adrenoceptors selective β -1 blockade will be inferior to non-selective β -blockade at antagonising the effects of adrenaline. Additionally selective β -1 blockade may actually lead to an enhancement of the ischaemic and arrhythmogenic effects of adrenaline because β -1 blocker treatment leads to a selective enhancement of the sensitivity of the heart to β -2 adrenoceptor stimulation.⁵⁻⁷ This may have enhanced the differences between exercise and adrenaline infusion seen in McCance and Forfar's study since 13/14 patients were taking a β -1 selective blocker (atenolol, metoprolol, and bisoprolol) until a few days before the study. Therefore this study adds further weight to the argument that non-selective β blockade may have advantages over β -1 selective blockade during stress—for example, myocardial infarction.

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

SIR,—We thank Hall and Ferro for their interesting comments on our paper. The mechanism of our observation that adrenaline produced ischaemia at a lower rate-pressure product than exercise must remain speculative, but we agree that the mechanism proposed by Hall and Ferro is also consistent with our data.

It is interesting to consider the ideal properties for a β blocker in the setting of acute myocardial infarction. The beta-1 selective agent atenolol was shown in ISIS-1 to reduce mortality when used early in acute myocardial infarction, a benefit largely due to a decrease in cardiac rupture. No other β blocker has been shown to decrease mortality when given acutely. But both propranolol² and metoprolol³ have been shown to reduce ventricular fibrillation in acute myocardial infarction. In animal studies timolol, pindolol, propranolol, metoprolol, and labetalol all increased the ventricular fibrillation threshold to a similar extent.⁴

Adrenaline is unlikely to be of direct relevance in causing late mortality after acute myocardial infarction but the question of which β blocker to use orally after acute myocardial infarction is as important as the question of which β blocker to use acutely. Propranolol, timolol, and metoprolol are all reported to reduce mortality and particularly sudden death after acute infarction.⁵ The mechanisms of benefit may be many and are probably different from those when β blockers are used acutely.⁶ It may be that here lipid solubility is more important than β -1 selectivity. An overview of the long-term β blocker trials has not suggested any difference between the β -1 selective and non-selective β blockers,⁷ though it seems that β blockers that do not have partial agonist activity may be more effective than those that do. There are insufficient data to be certain whether lipid solubility is important in this respect but all the drugs known to be efficacious are lipid soluble. Given the uncertainty about the importance of the ancillary properties of β blockers it seems reasonable to suggest that only β blockers with proven effects should be used for postinfarction prophylaxis⁵ and, despite the theoretical advantages of non-selective β blockade advanced by Hall and Ferro, the same is probably true of the use of intravenous β blockade in acute infarction. Thus we believe that, in the absence of proof of the relative benefits of non-selective and selective β blockers, atenolol and possibly metoprolol should remain for the present the first line intravenous β blockers in acute myocardial infarction.

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Cyclosporin treatment and nitric oxide release in human coronary arteries

SIR,—We read with interest the report by Dr O'Neil and colleagues (*British Heart Journal* 1991;66:212-6) of the lack of effect of cyclosporin on nitric oxide release in human coronary arteries.¹ The data they presented are most valuable because they were obtained from human studies. However, we feel that the conclusion of the paper should be re-examined in the light of their results.

To assess the effect of cyclosporin *in vitro*, O'Neil *et al* applied the protocol that we have previously described.² After three hours of incubation with cyclosporin, the maximal relaxation (mean (SEM)) to substance P was reduced from 76.6 (7.4)% in control coronary artery rings to 63.0 (11.5)% and 62.2 (11.1)% in rings pretreated with cyclosporin 1000 and 2000 ng/ml, respectively. This difference was not statistically significant. However, at lower concentrations (10^{-10} and 10^{-9} mol/l) of substance P, the relaxant responses were significantly reduced in coronary artery rings incubated with cyclosporin compared with control rings (shown by O'Neil *et al* in fig 1). Substance P is known as an endothelium-dependent vasodilator³ and has already been used by O'Neil *et al* to test the ability of the coronary circulation to release nitric oxide *in vitro* in humans.⁴ As with other human vascular diseases,^{5,6} the mechanisms for relaxation of the underlying vascular smooth muscle in response to nitrovasodilators were not affected by cyclosporin (shown by O'Neil *et al* in fig 2). We therefore cannot see any other interpretation than the one suggesting that nitric oxide release is indeed impaired in rings incubated with cyclosporin when tested with low concentrations (10^{-10} and 10^{-9} mol/l) of substance P. Usually when they find no statistical difference between the maximal responses of the rings workers calculate the dose of agonist eliciting 50% of the full response (EC_{50}). This universally accepted method allows the detection of any shift of the dose-response curves. Inspection of fig 1 indicates that there is indeed a rightward shift of the dose-response curves obtained from rings treated with cyclosporin *in vitro*.

O'Neil *et al* found no significant correlation between the *in vivo* and *in vitro* coronary vasodilatory responses to substance P with either blood concentration of cyclosporin (fig

4) or the duration of treatment (fig 3). However, the correlation made from the in vitro study was for data in only three patients.

No information was given as to the clinical status of the 12 patients studied in vivo, especially their vasodilator regimens, the frequency of episodes of rejection, the use of other immunosuppressive agents, etc. . . . In patients with transplanted hearts the reactivity of any particular vascular bed is likely to be influenced by several interconnected factors. Therefore, the influence of a single factor, in this case cyclosporin treatment, cannot be assessed by simple linear regression. Furthermore, the study of the effect of cyclosporin on nitric oxide release after stimulation by substance P needs a control group. There was a control group in the in vitro study but not in the in vivo study.

In conclusion, we applaud O'Neill *et al* for their effort to address the important issue of vascular toxicity of cyclosporin in patients with transplants. However, we feel that both the design and the results of the study do not quite support the clear cut conclusion they made.

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

SIR,—We used three distinct models to assess the effect of cyclosporin on endothelial function in the human coronary circulation: none of them showed that cyclosporin was capable of compromising the ability of the vascular endothelium to release nitric oxide in response to an endothelium dependent vasodilator.

Dr Dinh-Xuan and Dr Higenbottam are correct in pointing out the importance of EC_{50} values in comparing the difference in the response to low concentrations of substance P. Calculation of the EC_{50} values shows minimal dose ratio shift of <3, but the maximum dilatory response was preserved. In our discussion we pointed out the loss in sensitivity at low concentrations of substance P, but we believe that in light of the evidence from the retransplanted patients and the in vivo study this effect is not clinically relevant. This view accords with the results from our

previously published data where therapeutic concentrations of cyclosporin had no effect on any part of the dose response curve for substance P in human coronary arteries.¹

We stated both in the abstract and the methods section that the patients in the in vivo study were clinically well and free of rejection at the time of assessment. Admittedly, these patients do form a complex group in terms of medication and clinical history. However, irrespective of "interconnected factors" the fact remains that patients who receive cyclosporin after transplantation, retain a response to substance P and isosorbide dinitrate that resembles that reported in healthy volunteers.²

Data from human studies are important in that a previous report by Dinh-Xuan *et al*³ suggests that inhibition of the release of endothelium dependent relaxing factor (EDRF) in a rat model may contribute to the underlying mechanisms of cyclosporin associated hypertension in humans. We attribute this to a genuine species difference, however, it seems that from the most recent reports the cyclosporin associated vascular dysfunction in rat aortae may also be due to an increased response to vasoconstrictors rather than to a reduction in EDRF release.⁴

The mechanisms underlying the vascular effects of cyclosporin in humans that precipitate clinically relevant hypertension and renal damage remain to be elucidated. Our findings indicate that direct inhibition of nitric oxide is unlikely to be the mechanism responsible.

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Antihypertensive drugs and plasma lipids

SIR,—In his editorial (*British Heart Journal* 1991;66:409-10) Professor Swales commented that a trial comparing diuretics or β blockers with one of the new classes of agents would be desirable. He also writes that "such an end point trial has not been set up and it is unlikely to be set up in the near future. . . ." The Captopril Prevention Project (CAPPP), which is now in its second year and conducted with the endorsement of the European Society of Hypertension, is precisely such a trial. Its aims and design have been reported.¹ In brief, hypertensive men and women aged

25-66 are randomised to captopril based treatment or diuretic β blocker based treatment (ACE inhibitors excluded); the aim is to detect a 20% difference in cardiovascular mortality with a power of 80% at the 5% significance level (two sided).

The study is being conducted at 275 health care centres in Sweden and Finland and the PROBE (prospective, randomised, open, blinded end point evaluation) design is used.² In September 1991 more than 6000 patients had been recruited to CAPPP. It is hoped that by 1996 enough end points will have accumulated for the study to be ended (with a significant outcome).

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Avoidance of tolerance and lack of rebound with intermittent dose titrated transdermal glyceryl trinitrate

SIR,—The study by Fox *et al* (*British Heart Journal* 1991;66:151-5) addressed an important question concerning nitrate tolerance and "rebound angina" during nitrate free periods. However, the main conclusions of the study are neither new nor entirely accurate, and leave many questions unanswered. How long do the patches remain effective? Do they last all day? When does tolerance start to develop and how long a nitrate free period is required to prevent the development of tolerance? "Rebound" might not be such a problem if the patches only need to be left off for an hour or two.

At least five previous studies have now shown that nitrate patches remain effective shortly after being re-applied after a nocturnal nitrate free period. What remains unclear, however, is how quickly tolerance develops after a patch has been applied, and therefore what is the duration of daytime efficacy during an intermittent treatment regimen. It is also not known how long a nitrate free period is required to reverse tolerance; this study does nothing to address these points.

We examined many of these questions in a previous study (the results of which were presented to the British Cardiac Society in 1987).¹ Using three active or dummy patches applied consecutively for 32-36 hours and conduction of four exercise tests over this period we assessed the effects of continuous treatment for three, eight, 12, 15, and 24 hours, and of intermittent treatment on two consecutive days using two different nitrate free periods of 12 or 16 hours. Our results showed the now familiar finding that the patches remained effective three hours after treatment was restarted.² They also showed that the length of nitrate free interval (12 hours or 16 hours) did not influence this