heart disease. 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 than exercise. 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 potent inotropic and chronotropic effects. However, biochemical studies have shown important differences in the linkage of β adrenoceptor subtypes to cardiac adenylyl cyclase, with a higher proportion being β-2 adrenoceptors than β-1 adrenoceptors. Not all adenylyl cyclase when activated leads to increased contractility; therefore, adrenaline activation of adenylyl cyclase not linked to contractility (possibly via a metabolic pathway) may lead to a further increase in oxygen consumption. This differential coupling to adenylyl 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 selectively, 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. 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.

JA HALL
Cardiac Unit, Papworth Hospital
Papworth Everard, Cambridge CB3 8RE
A FERRO
Clinical Pharmacology Unit,
Addenbrooke's Hospital,
Cambridge CB2 2QQ

2 Kaumann AJ, Lemon H. β-2 adrenoceptor mediated positive inotropic effect of adrenaline in human ventricular myocardium. Naunyn-
5 Hall JA, Kaumann AJ, Brown MJ. Selective β-1

Cyclopisoparin treatment and nitric oxide release in human coronary arteries

SR—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 cyclopisoparin on nitric oxide release in human coronary arteries. 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 cyclopisoparin in vitro, O'Neil et al. applied the protocol that we have previously described. After three hours of incubation with cyclopisoparin, the maximal relaxation (mean SEM) to substance P was reduced from 76.6 (7.4)% to 63.0 (11.5)% and 62.2 (11.3)% in rings pretreated with cyclopisoparin 1000 and 2000 ng/ml, respectively. This difference was not statistically significant. However, at lower concentrations (10^-10 and 10^-8 mol/l) of substance P, the relaxant responses were significantly reduced in coronary arteries incubated with cyclopisoparin compared with control rings (shown by O'Neil et al in fig 1). Substance P is known as an endothelium-dependent vasodilator 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. As with other human vascular diseases, the mechanisms for relaxation of the underlying vascular smooth muscle response to nitricodilatation were not affected by cyclopisoparin (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 cyclopisoparin compared with low concentrations (10^-10 and 10^-8 mol/ l) of substance P. Usually when they find no statistical difference between the maximal responses of the rings without and with cyclopisoparin, they can consider 50% of the full response (EC50). 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 shift of the dose-response curves obtained from rings treated with cyclopisoparin in vitro. O'Neil et al. found no significant correlation between the inhibition of calcium entry into platelets and vasodilator responses to substance P with either blood concentration of cyclopisoparin (fig
Letters to the Editor

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 vitro. Especially their vasodilator regiments, the frequency of episodes of rejection, the use of other immunosuppressive agents, etc... In patients with transplanted hearts the variability of the 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 demonstrated 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 trauma, especially because we feel that both the design and the results of the study do not quite support the clear cut conclusion they made.

T. Dinh-Xuan, T. Timothé W. Higenbottam
Department of Respiratory Physiology,
Papworth Hospital,
Cambridge CB3 8RE


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 EC50 values in comparing threedrug hearts to those to low concentrations of substance P. Calculation of the EC50 values shows minimal dose ratio shift of <3, but the maximum dilatary response was preserved. In our discussion, we pointed out the difficulty 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 in 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 clinical and histologic features. 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 al3 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 aorta 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 clinical 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.

GREGORY S’ O’NEILL
ADRIAN H CHESTER
SUDHIR KUSHWAHA
MARLENE ROSE
SAMAD TADIKARIMI
MASAHITO YACOUB
HORSEFIELD HOSPITAL,
HORSEFIELD,
Middlesbrough TS9 6EH


Please refer to page 421 for the reply of the authors to this letter.
Cyclosporin treatment and nitric oxide release in human coronary arteries.

A T Dinh-Xuan and T W Higenbottam

Br Heart J 1992 67: 420-421
doi: 10.1136/hrt.67.5.420

Updated information and services can be found at:
http://heart.bmj.com/content/67/5/420.citation

Email alerting service

These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/