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 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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- 1 O'Neil GS, Chester AH, Kushwaka S, Rose M, Tadjkarimi S, Yacoub MH. Cyclosporin treatment does not impair the release of nitric oxide in human coronary arteries. *Br Heart J* 1991;66:212-6.
- 2 Dinh-Xuan AT, Fan TPD, Higenbottam TW, Wallwork J. Cyclosporine in vitro reduces endothelium-dependent relaxation to acetylcholine but does not affect relaxation to nitrovasodilators. *Transplant Proc* 1990;22:1723-5.
- 3 Dinh-Xuan AT, Higenbottam TW. Non-prostanoid endothelium-derived vasoactive factors. *J Int Med Res* 1989;17:305-15.
- 4 Chester AH, O'Neil GS, Moncada S, Tadjkarimi S, Yacoub MH. Low basal and stimulated release of nitric oxide in atherosclerotic epicardial coronary arteries. *Lancet* 1990;336:897-900.
- 5 Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Engl J Med* 1990;323:22-7.
- 6 Dinh-Xuan AT, Higenbottam TW, Clelland CA, *et al*. Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. *N Engl J Med* 1991;324:1539-47.

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 the difference in the response to low concentrations of substance P. Calculation of the EC₅₀ 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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- 1 O'Neil GS, Chester AH, Rose M, Tadjkarimi S, Yacoub MH. The effect of cyclosporine on the release of endothelium-derived relaxing factor from isolated human epicardial coronary arteries. *Transplantation* 1991;51:736-8.
- 2 Crossman DC, Larkin SW, Fuller RW, Davies GJ, Maseri A. Substance P dilates epicardial coronary arteries and increases blood flow in humans. *Circulation* 1989;80:475-84.
- 3 Dinh-Xuan AT, Fan TPD, Higenbottam TW, Wallwork J. Cyclosporine in vitro reduces endothelium-dependent relaxation to acetylcholine but does not affect relaxation to nitrovasodilators. *Transplant Proc* 1990;22:1723-5.
- 4 Chan BBK, Kern JA, Flanagan TL, Tribble CG, Kron IL. Effects of cyclosporine A (CSA) on vascular endothelial function and morphology. *Circulation* 1991;(suppl II):84:492.

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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- 1 The CAPPP Group. The Captopril Prevention Project: a prospective intervention trial of angiotensin converting enzyme inhibition in the treatment of hypertension. *J Hypertens* 1990;8:985-90.
- 2 Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Blood Pressure* (in press).

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

response. However, rather more important was the finding that whatever the length of the nitrate free interval the therapeutic effects became somewhat attenuated within eight hours of the start of treatment and appreciably so after 12 hours: there was therefore no point in testing a shorter nitrate free interval because important therapeutic effects do not seem to last for over 12 hours of continuous therapy. Waters *et al* were also unable to show therapeutic benefit during intermittent treatment when they tested 12 and 16 hours after patch application³ and though Schaer *et al*⁴ showed significant effects at four and eight hours it was clear from inspecting their data that the results at eight hours were rather less statistically significant than those at four hours. It thus seems likely that tolerance develops so quickly during transdermal therapy that it limits its efficacy as a day long prophylactic agent.

The study reported by Fox *et al* rather supports our findings because treatment had very little influence on the circadian pattern of silent ischaemia—as one would expect if treatment had only been effective during the first few hours.

It is certainly not justified to conclude that the significant treatment effects demonstrated between three and five hours after patch application indicate that tolerance has been "avoided". Our results supported by data from other studies suggest that while the effects measured at 3–5 hours may have remained significantly better than those seen during placebo treatment, they are likely to be significantly worse than those seen after only 30–60 minutes of treatment and significantly better than those measured after eight hours or more. In other words, it seems likely that tolerance is a gradual but continuous process beginning from the moment that treatment is initiated.

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- 1 James MA, Papouchado M, Jones JV. Tolerance to nitrates: does it occur and how long a nitrate free period is required to prevent it? [abstract]. *Br Heart J* 1988;59:125.
- 2 James MA, Papouchado M, Jones JV. Attenuation of nitrate effect during an intermittent treatment regimen and the time course of nitrate tolerance. *Eur Heart J* 1991;12:1266–72.
- 3 Waters DD, Juneau M, Gossard D, Choquette G, Brien M. Limited usefulness of intermittent nitroglycerin patches in stable angina. *J Am Coll Cardiol* 1989;13:421–5.
- 4 Schaer DH, Buff LA, Katz RJ. Sustained anti-anginal efficacy of trans-dermal nitroglycerin patches using an overnight 10 hour nitrate free interval. *Am J Cardiol* 1988;61:46–50.

Novel exercise protocol suitable for use on a treadmill or a bicycle ergometer

SIR,—In their letter Dr Essamri and colleagues correctly state that the standardisation of exercise tests is now a major issue (*British Heart Journal* 1991;66:405–6) but they criticise the standardised exponential exercise protocol (STEEP) devised by Dr Northridge and colleagues (*British Heart Journal* 1990;64:313–6). In this useful protocol the exponential increase in work rate tends to keep exercise duration within the "ideal" range of 5–15 minutes even if exercise capacity in terms of peak external work rate differs widely. Detailed tables are provided for cycle ergometry work rates adjusted for the subject's weight so that their STEEP will be

similar on a cycle ergometer and on a treadmill.

The differences between the cycle ergometer STEEP and treadmill STEEP protocols reported by Dr Essamri are relatively small—approximately a 13–19% difference in $\dot{V}O_2$ over the last six minutes of exercise. Such differences are expected because the cardiopulmonary responses to exercise vary according to the mass of active muscle: at a given submaximal work rate, heart rate and $\dot{V}O_2$ tend to be higher with cycle ergometry, whereas peak heart rate and $\dot{V}O_{2max}$ tend to be higher on treadmill exercise.^{1,2} Standardisation of work rate according to lean body mass rather than total body weight might further reduce these differences,^{3,4} but to expect cycle ergometry and a motorised treadmill to be equivalent is unrealistic.

Dr Essamri and colleagues also suggest that the relatively slow rise in $\dot{V}O_2$ over the first minutes of the STEEP makes it an unsuitable basis for the prediction of $\dot{V}O_{2max}$ from $\dot{V}O_2$ at submaximal work rates. However, such extrapolations are always subject to large errors^{5,6} and maximal tests are preferred when $\dot{V}O_{2max}$ is to be determined.⁷

However, in the graphs presented by Dr Northridge and Dr Essamri we note that $\dot{V}O_2$ continues to increase steeply as a function of time over the last few minutes of exercise, whereas in many other protocols $\dot{V}O_2$ tends towards a plateau—it rarely if ever attains a plateau but at least becomes less steep, with a negative second derivative $d^2\dot{V}O_2/d(\text{time})^2$.² If subjects perform maximal symptom limited exercise then the effect of the continued steep rise in $\dot{V}O_2$ may be to amplify the effects on measured $\dot{V}O_{2peak}$ of small changes in exercise duration due to variations in motivation and encouragement.

The debate between proponents of the cycle ergometer and proponents of the motorised treadmill is likely to continue for many years—the advantages and disadvantages of each are balanced and preferences often differ on a geographical basis.^{8,9} As it is unlikely that cardiologists in all countries will agree to standardise on one or other form of exercise testing, the STEEP is a useful attempt to bridge this divide.

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- 1 Astrand P-O, Rodahl K. Textbook of work physiology, 3rd ed. New York: McGraw-Hill, 1986;311–4 and 355–8.
- 2 Martin WH III, Berman WI, Buckley JC, Snell PG, Blomqvist G. Effects of active muscle mass size on cardiopulmonary responses to exercise in congestive heart failure. *J Am Coll Cardiol* 1989;14:683–94.
- 3 Jones NL. Clinical exercise testing, 3rd ed. Philadelphia: W B Saunders, 1988:160–1.
- 4 Sparling PB, Cureton KJ. Biological determinants of the sex difference in 12-minute run performance. *Med Sci Sports Exer* 1983;15:218–23.
- 5 Astrand P-O, Rodahl K. Textbook of work physiology, 3rd ed. New York: McGraw-Hill, 1986:376.
- 6 Legge BJ, Banister EW. The Astrand-Ryhmung nomogram revisited. *J Appl Physiol* 1986;61:1203–9.
- 7 Jones NL. Clinical exercise testing, 3rd ed. Philadelphia: W B Saunders, 1988:127–8.
- 8 Atterhog J-H, Jonsson B, Samuelsson R. Exercise testing in Sweden: a survey of procedures. *Scand J Clin Lab Invest* 1979;39:87–92.
- 9 Stuart RJJ, Ellestad MH. National survey of exercise stress testing facilities. *Chest* 1980;77:94–7.

BOOK REVIEW

Cardiac Electrophysiology and Arrhythmias. Eds Charles Fisch, Borys Surawicz. (Pp 448; \$84) New York: Elsevier, 1991. ISBN 0-444-01601-5

This book is in many ways a testimony to the extraordinary progress in the subject over the past two or three decades. Indeed, 30 years ago there would have been little worth writing save for the six chapters on clinical arrhythmias, and each of these is in any case substantially influenced by the advent of clinical electrophysiological studies.

The editors, two leaders in the field, and respected because they have proved themselves in the classic tradition over the years, are to be commended for the fact that they have broadened the scope so considerably beyond Fisch's own recent book on the electrocardiographic diagnosis of arrhythmias. The first two major parts include chapters on mechanisms and on experimental arrhythmias which some might, unwisely, decide to gloss over. Difficult though some may be for the clinician, they are well worth reading for they form the scaffolding upon which the edifice of clinical arrhythmias, their diagnosis and management, depend. Over the past 20 years we have all become aware of the importance of the cardiac action potential and of ion movements, both in the genesis of normal and abnormal rhythms and in consideration of their treatment in some instances. But no longer can one divide arrhythmias in an apparently simple fashion into those dependent on automaticity and those that arise because of reentry; one can get deeper, by looking into the factors that promote such changes and also give rise to afterdepolarisations, the relevance of which are now becoming better appreciated.

Many will turn first, and justifiably, to the two excellent chapters on the differential diagnosis of tachycardias dependent on the width of the QRS, by Fisch and by Wellens; but there is important information in all the other chapters on clinical arrhythmias, and many who read these chapters will thereby be reminded of difficult cases that perhaps "got away". The use of exercise testing, signal averaged electrocardiography, and programmed electrical stimulation are all well discussed in separate chapters. The pharmacological sections offer relatively less new information and the chapter on sudden cardiac death, in particular, is somewhat out of place under pharmacology and not of the same high quality as most of the other contributions. The last part, dealing with non-pharmacological treatment, with emphasis on developments in pacing and ablative techniques (both electrically based and surgical) is of great interest because there are many developments in this area that are insufficiently widely known and where more patients could receive help.

Virtually all the chapters are well and relevantly referenced and the book not only has current usefulness but will continue to be a reliable and substantial source of information for some years to come. Many cardiologists will wish to acquire it themselves as well as to see it on departmental library shelves.

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