



Title	Responses of plasma concentrations of A type natriuretic peptide and B type natriuretic peptide to alacepril, an angiotensin-converting enzyme inhibitor, in patients with congestive heart failure [4]
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Insulin resistance, high prevalence of diabetes, and cardiovascular risk in immigrant Asians

SIR,—We read with interest the findings of Dhawan *et al.*¹ who highlighted the importance of hyperinsulinaemia, central obesity, and physical inactivity as risk factors in Asians with angiographically significant coronary artery disease. Both British and Indian Asians were found to share a predisposition to insulin resistance and its associated metabolic abnormalities—and hence a high cardiovascular risk. They conclude that this finding is likely to favour a genetic rather than environmental basis for the recognised high mortality in this ethnic group. However, migrants are not a random sample of the original population,² and their “selection” is likely to be determined by several health and socioeconomic factors, which are likely to influence their morbidity and mortality. If this environmental effect were a significant determinant of cardiovascular risk, one would not expect to see the high mortality from ischaemic heart disease (IHD) that has been recorded in Asians in South Africa,³ Trinidad,⁴ and Singapore,⁵ who emigrated over a century ago.

We recently reported a survey in which we studied the cardiovascular risk factor profile of all Asian men admitted with acute myocardial infarction during 8 weeks to our city centre district general hospital in Birmingham, England, and to the San Fernando General Hospital, in Trinidad⁶: 74 patients were studied (55 patients (mean (SEM) age 58.1 (1.4)) in Trinidad (Trinidad group) and 19 in Birmingham (62.1 (2.6)) (UK Group) (table).

We also found that mean systolic and diastolic blood pressures were higher in those with hypertension in the Trinidad group (146.6 (16.9)/93.4 (11.4) mm Hg than in the UK group (120.8 (25.4)/75.0 (13.4) mm Hg, $P < 0.05$).⁶ Though Asians in Trinidad have in many ways adapted to the lifestyle of the host population, this does not appear to have reduced their cardiovascular risk profile, because those admitted with acute myocardial infarction had, in fact, a greater prevalence of central obesity, smoking, and higher blood pressures than a similar group in England.⁶

Central obesity and physical inactivity were common to both communities in England and Trinidad and their relation to insulin resistance may be particularly important in Asians with IHD. Our data support the hypothesis of a genetic predisposition to central obesity and diabetes in Asians that seems to have been retained by

third generation Asian immigrants in Trinidad. This may explain the persistently high mortality from IHD in Asians.

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- 1 Dhawan J, Bray CL, Warburton R, Ghambhir DS, Morris J. Insulin resistance, high prevalence of diabetes, and cardiovascular risk in immigrant Asians. Genetic or environmental effect? *Br Heart J* 1994;72:413–21.
- 2 Marmot MG, Adelstein AM, Bulusu L. Lessons from the study of immigrant mortality. *Lancet* 1984;i:1455–8.
- 3 Walker ARP. The epidemiology of ischaemic heart disease in the different ethnic populations in Johannesburg. *S Afr Med J* 1980; 57:784–82.
- 4 Miller GJ, Beckles GL, Maude GH, Carson DC, Alexis SD, Price SG, Byam NT. Ethnicity and other characteristics predictive of coronary heart disease in a developing community: principal results of the St James Survey, Trinidad. *Int J Epidemiol* 1989; 18:808–17.
- 5 Danaraj TJ, Acker MS, Danaraj W, Ong WH, Yam TB. Ethnic group differences in coronary heart disease in Singapore: an analysis of necropsy records. *Am Heart J* 1959; 58:516–26.
- 6 Farooqi IS, Dar S, Farooqi S, Beevers DG, Lip GYH. A comparative study of risk factors for acute myocardial infarction amongst men of Indo-origin in Trinidad and the UK. *Int J Cardiol* 1994;47:44–9.

Quality of life in heart failure treated with enoximone

SIR,—The Enoximone Investigators concluded that in severe heart failure enoximone reduces survival but has a beneficial effect on the quality of life of survivors.¹ As they indicate, if true, this is an important finding with interesting and difficult implications for drug regulatory bodies and for clinical practice. However, a statistical artefact could explain their results without there necessarily being any benefit from enoximone.

At randomisation, the two groups were reasonably well matched for measures of severity and other features. As the trial progressed there was differential mortality between the groups. It is not unreasonable to assume that those who died had more severe disease and a worse quality of life than those who survived. Thus even if there were no change at all in quality of life, the survivors will have a better average quality of life than the study group as a whole. Since more died in the enoximone group, this group will have lost more patients with poor quality of life, and enoximone will appear to have been beneficial.

Other evidence from the paper supports this interpretation of the results, namely, the greater proportion of enoximone treated patients withdrawn from the trial and the greater proportion admitted to hospital. The improvement seen in the disease-specific measure after 2 weeks (when deaths were 8 v 8, from table 3) was probably genuine, but the lack of differences at three months and one year was unlikely to be because of lack of power alone (although 95% confidence intervals for the differences in means were not quoted). Indeed, as one would have expected the group with more

deaths to have a better average quality of life for the reasons given, the possibility arises that quality of life actually diminished on enoximone treatment.

Apart from the baseline comparison, we are not able to interpret the Nottingham Health Profile (NHP) data at all. For example, the median physical mobility score in the enoximone group was 22 at one year, but there is nothing to compare this with. We are not told what the median baseline score was for the enoximone treated survivors: and the placebo treated patients no longer form an adequate control group (as they are no longer matched with the enoximone group). It would have been interesting to see the results on the other NHP dimensions.

There are ways round this problem, but none is fully satisfactory. We can assign all patients who died to the bottom half of the distribution of quality of life scores (for example, by giving them all the worst possible score). The median is then not biased for comparative purposes. However, if more than half the subjects die the median becomes uninterpretable (although the Mann-Whitney U test remains valid). Alternatively, end points can be dichotomised into those alive with improved quality of life on one hand and those who died plus those who are alive with worse quality of life on the other. These can be analysed as proportions, but with consequent loss of statistical power. Finally, changes from baseline can be quoted for survivors only. These can be interpreted as uncontrolled observations (a so-called “before and after” study). So long as the questionnaire has reasonable test-retest reliability, a beneficial treatment effect is the most likely explanation for any improvement seen, although a placebo effect cannot be excluded.

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- 1 Cowley AJ, Skene AM on behalf of the Enoximone Investigators. Treatment of severe heart failure: quantity or quality of life? A trial of enoximone. *Br Heart J* 1994; 72:226–30.

Responses of plasma concentrations of A type natriuretic peptide and B type natriuretic peptide to alacepril, an angiotensin-converting enzyme inhibitor, in patients with congestive heart failure

SIR,—Yoshimura and colleagues showed that the response of plasma brain natriuretic peptide (BNP) after the administration of the angiotensin-converting enzyme inhibitor, alacepril, occurred later and lasted longer than the response of plasma atrial natriuretic peptide (ANP), and that the changes in pulmonary capillary wedge pressure did not correlate with plasma BNP.¹ This lack of correlation may be the result of this difference in responses.

It may be relevant to recall that BNP has a longer half life than ANP, and that the fall in BNP is bi-exponential, with a slow phase of about 20.7 minutes, as estimated by Nakao's group.² My own estimate of the slow half life was 37 minutes.³ In addition, there may also be a qualitative difference in the synthesis and release of BNP. In

Risk factor profile of men admitted to hospital with acute myocardial infarction in Trinidad and Birmingham

	UK (%)	Trinidad (%)	P value
Prevalence of:			
Diabetes	32	36	NS
Hypertension	32	35	NS
Smokers	63	71	0.03
Regular alcohol use	42	91	<0.05
Regular exercise	21	11	<0.05
Mean waist to hip ratio (mean (SD))	0.95 (1.01)	1.01 (0.05)	<0.001

rats, atrial stretch induces a rapid increase in BNP mRNA but not in ANP mRNA, although both peptides are released.⁴ The secretion of BNP seems to result from increased gene expression. This might explain the clinical observation that intravenous saline loading raises plasma ANP but not plasma BNP within 60 minutes, but ingestion of salt tablets raises the plasma concentration of both peptides after 5 days.⁵ Indeed, the response of plasma BNP to saline loading is slower than the ANP response in patients with right ventricular failure (Morice AH, personal communication). Further studies of the relation between BNP and volume status may shed light on this important subject.

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- 1 Yoshimura M, Yasue H, Tanaka H, Kikuta K, Sumida H, Kato H, *et al*. Responses of plasma concentrations of A type natriuretic peptide and B type natriuretic peptide to alacepril, an angiotensin-converting enzyme inhibitor, in patients with congestive heart failure. *Br Heart J* 1994;72:528-33.
- 2 Mukoyama M, Nakao K, Saito Y, Ogawa Y, Hosoda K, Suga S, *et al*. Brain natriuretic peptide (BNP) as a novel cardiac hormone in humans—Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J Clin Invest* 1991;87:1402-12.
- 3 Cheung BM, Dickerson JE, Ashby MJ, Brown MJ, Brown J. Effects of physiological increment in human alpha-atrial natriuretic and human brain natriuretic peptide in normal male subjects. *Clin Sci* 1994;86:723-30.
- 4 Mantymaa P, Vuolteenaho O, Marttila M, Ruskoaho H. Atrial stretch induces rapid increase in brain natriuretic peptide but not in atrial natriuretic peptide gene expression *in vitro*. *Endocrinology* 1993;133:1470-73.
- 5 Lang CC, Choy AM, Turner K, Tobin R, Coutie W, Struthers AD. The effect of intravenous saline loading on plasma levels of brain natriuretic peptide in man. *J Hypertens* 1993;11:737-41.

This letter was shown to the author, who replies as follows:

SIR,—Plasma concentrations of ANP and BNP increase in patients with heart failure and correlate well with the degree of left ventricular function in patients with chronic heart failure.¹ Plasma concentrations of ANP and BNP both increase as the heart becomes overloaded. However, ANP concentrations increase before BNP concentrations.^{2,3} Plasma ANP increases mainly through secretion from vesicles that store ANP in the atria (regulated pathway). None the less, BNP mRNA is expressed earlier than ANP mRNA.³ This is probably because BNP mRNA has the characteristics of an acute phase reactant whereas ANP mRNA does not.^{4,5} Clinical studies showed that BNP is secreted mainly from the ventricles in normal subjects and patients with heart failure.¹ Though we can not disregard the amount of BNP secreted by the atria, nearly all the circulating BNP originates from the ventricles.

I and my colleagues showed that the time courses of changes in plasma ANP and plasma BNP were different when cardiac overload was reduced by administration of an angiotensin-converting enzyme inhibitor.⁶ The mechanism is probably related to the different secretion sites and pathways of ANP and BNP: ANP is mainly secreted by a regulated pathway in the atria and BNP

by a constitutive pathway in the ventricles. Other factors may also be involved in the mechanisms—for example, the direct action of angiotensin-converting enzyme inhibitor on the degradation of ANP and BNP. Thus the mechanisms of the changes in plasma ANP and BNP may vary when the cardiac load is increasing and decreasing. As Dr Cheung indicates, regulation of the natriuretic peptide system is important and complex. The mechanisms responsible for the changes in plasma ANP and BNP involve different patterns of synthesis, storage, secretion, and degradation.

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- 2 Lang CC, Choy AMJ, Turner K, Tobin R, Coutie W, Struthers AD. The effect of intravenous saline loading on plasma levels of brain natriuretic peptide in man. *J Hypertens* 1993;11:737-41.
- 3 Mantymaa P, Vuolteenaho O, Marttila M, Ruskoaho H. Atrial stretch induces rapid increase in brain natriuretic peptide but not in atrial natriuretic peptide gene expression *in vitro*. *Endocrinology* 1993;133:1470-3.
- 4 Kojima M, Minamino N, Kangawa K, Matsuo H. Cloning and sequence analysis of cDNA encoding a precursor for rat brain natriuretic peptide. *Biochem Biophys Res Commun* 1989;159:1420-6.
- 5 Morita E, Yasue H, Yoshimura M, Ogawa H, Jougasaki M, Matsuyama T, Mukoyama M, Nakao K. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. *Circulation* 1993;88:82-91.
- 6 Yoshimura M, Yasue H, Tanaka H, Kikuta K, Sumida H, Kato H, Jougasaki M, Nakao K. Responses of plasma concentrations of A type natriuretic peptide and B type natriuretic peptide to alacepril, an angiotensin-converting enzyme inhibitor, in patients with congestive heart failure. *Br Heart J* 1994;72:528-33.

Transcatheter occlusion of cardiac defects

SIR,—Gatzoulis, Redington, and Rigby *et al* reported their experience with transcatheter occlusion of the ductus arteriosus¹ and of atrial² and ventricular³ septal defects with the Rashkind ductal umbrella device. We are somewhat surprised that they made no mention of the buttoned device that we and others used in transcatheter occlusion of the ductus arteriosus⁴ and atrial septal defect.⁵⁻⁷ We now have considerable experience with this device in nearly 400 patients with atrial septal defects, 120 patients with a patent ductus arteriosus (PDA), and eight patients with ventricular septal defects (unpublished observations).

Patent ductus arteriosus—Our experience with the buttoned device^{4,8} indicates that it has several advantages over the Rashkind device. Gatzoulis *et al* had to exclude large tubular ducts with no obvious stenosis at the pulmonary end.¹ All sizes and types of ductus^{4,8} can be successfully closed with the buttoned device because it is adjustable. In all infants and children we were able to implant the device through a 7F delivery sheath rather than 8F and 11F sheaths,

which had to be used in most of Gatzoulis's patients. The success rate for device implantation was 86% for the Rashkind device and 97.5% for the buttoned device. Problems such as embolisation into the left pulmonary artery, inability to occlude the duct satisfactorily, and severe haemolytic anaemia reported by Gatzoulis were not seen in our 120 patients. Residual shunts on colour flow mapping, particularly in infants who had 17 mm Rashkind umbrella devices implanted were higher than those that we saw with the buttoned device. Finally, there has been increasing concern about the development of stenosis of the left pulmonary artery after implantation of the Rashkind device, especially in young children. Thus the buttoned device seems to have several advantages over the Rashkind device and it is hoped that, with further clinical trials, the buttoned device will prove to be useful in transcatheter occlusion of arterial ducts of all types and sizes.

Atrial septal defect—Redington and Rigby² modified the Rashkind PDA occluder and used it to close interatrial communications of various types. Of the 11 patients with fenestrated Fontan, there were two (18%) procedural failures. They were successful in closing the defect in two of the four patients with left-to-right shunts; the two remaining patients required surgical removal of the device and closure of the defect. In our more recently reported experience, which analysed the data of the first 180 patients,⁹ 14 devices (7.7%) were dislodged. The dislodgement rate has improved with experience and with successive generations of the device. First and second generation devices became dislodged in about 10% of patients. However, in the third generation device the device dislodgement rate was 3.1% (2 of 65)⁹; this has further decreased to less than 1% in the fourth generation buttoned device (unpublished observations). Redington and Rigby placed a bend in the arm of the device. Such a bend is thought to be the reason why the arms of the clamshell device broke and why the device was withdrawn from clinical trials.

Ventricular septal defect—Rigby and Redington concluded that their data do not support the routine use of a Rashkind PDA occluder to close perimembranous ventricular septal defects. We agree. Our own experience in occluding ventricular septal defect with buttoned device, though successful, is limited. Therefore, we cannot draw definitive conclusions on the superiority of the buttoned device.

In conclusion, the reports of Gatzoulis, Redington and Rigby¹⁻³ showed the usefulness of the Rashkind PDA occluder in highly selected patient subgroups. We submit that the buttoned device has a greater utility in a wider range of patient subsets, although definite conclusions can only be drawn after longer clinical trials.

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- 1 Gatzoulis MA, Rigby ML, Redington AN. Umbrella occlusion of persistent arterial duct in children under two years. *Br Heart J* 1994;72:364-7.