LETTERS TO THE EDITOR

Scope

Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation

Letters should be:
- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors

They may contain short tables or a small figure. Please send a copy of your letter on disk. Full instructions to authors appear in the July 1999 issue of Heart (page 116).

Management of scorpion sting

EDITOR,—We read with great interest the haemodynamic pattern in patients with scorpion envenomation.1 We have studied this acute time sensitive medical emergency since 1976 and have tried various regimens including antiscorpion venom.2 Since the advent of prazosin (1983–84)—an α adrenergic blocker which acts as an antidote to venom—the mortality of scorpion sting victims is less than 1%.3

In the pre-prazosin era (1961–83) a fatality rate of 25–30% was reported from western India,4 acute pulmonary oedema causing death. We were therefore surprised by the low mortality of scorpion sting victims reported by Karnad,1 and that two victims died on the third day of hospitalisation; we have similar findings in 1978–82—that is, before prazosin treatment.5

We have reported that the severity of scorpion sting depends on the victim's age, the season, and the time between sting and administration of prazosin. The symptoms following the sting are hypotension, tachycardia, pulmonary oedema, and shock (autoimmune storm).6 We believe that the transport of Karnad's patients to the nearest major city appeared to be a consequence of vomiting and diarrhoea. Karnad claims that the mechanism of acute pulmonary oedema recovered after treatment with intravenous sodium nitroprusside.7

We travelled throughout western Mahar-ashtra where Mesobuthus tamulus scorpions flourish, and taught all peripheral doctors how to treat scorpion sting victims. There has not been any deaths over the past two years due to scorpion sting reported from this region. Moreover, only two patients had massive pulmonary oedema, which was treated with intravenous sodium nitroprusside. Capto- pril failed to correct haemodynamic abnormalities in two cases who had cardiac arrhythmias. We believe that had we been alive saving the two patients treated with captopril who died in Karnad's report.8 As a potent inhibitor of phosphodiesterase, prazosin causes accumulation of gMP, a second messenger of nitric oxide, in vascular endothelium and myocardium, inhibits the formation of inositol triphosphate, and activates venom inhibited calcium dependent potassium channels.9

Thus prazosin reverses both inotropic (hypertension), and hypokinetic (pulmonary oedema, hypotension, tachycardia) phases evoked by scorpion envenoming.10

H S BAWASKAR
P H BAWASKAR
Banawaskar Hospital & Research Centre Mahad, Raigad, Maharashtra India 402301

2 Bawaskar HS, Bawaskar PH. Envenoming by scorpion and snake (elapidae), their neurotoxins and therapeutics. Trop Doct. [In press.]
7 Ismail M, Farani AJY, Dabees TT. Experimental treatment protocols for scorpion envenomation: Results common therapies and an effect on kaliuretic-kinin inhibitors. Toxicol 1992;30:1257–70.

Edward—The study by Karnad on the haemodynamic patterns encountered in scorpion envenomation raises important concerns. Karnad claims that the mechanism of pulmonary oedema observed in scorpion envenomation had not previously been established as pulmonary artery wedge pressure (PAWP) had not been measured. However, the haemodynamic mechanism of pulmonary oedema in scorpion envenomation was suggested in animal studies as early as 1980 and confirmed by numerous series in human subjects.1 All of these series performed a haemodynamic study and confirm that this speculation is not surprising with Karnad's findings and observe that they are consistent with our previous reports suggesting similar effects of the Indian red scorpion Mesobuthus tamulus and the yellow scorpion of North Africa (Androctonus australis).

We are particularly concerned by Karnad's interpretation of the haemodynamic records in the envenomed patients and the treatment strategy he suggests. These are therefore not surprised with Karnad's findings and observe that they are consistent with our previous reports suggesting similar effects of the Indian red scorpion Mesobuthus tamulus and the yellow scorpion of North Africa (Androctonus australis).

tried. First line clinicians need comprehensive and meaningful insights regarding the pathophysiology and valuable treatments of this dreaded accident. The clearer and simpler the message on this issue the better the effect in daily clinical practice.

F ABRoug, S NOUIRA, S ELATROUS
ICU CHU F Bourgiba,
5000 Monastir, Tunisia

6 El Atrous S, Nouira S, Besbres-Ouames L, et al. These letters were shown to the author, who replies [in press].

These letters were shown to the author, who replies as follows:

The efforts of Bawaskar and Bawaskar in popularising prazosin treatment in western India are truly commendable, and the effect on mortality following scorpion envenomation is impressive. They cite their personal experience with 38 patients treated with prazosin, of whom only 30 (4.5%) died. They had previously reported 526 patients treated with prazosin, of whom only 30 (4.5%) died. They on mortality following scorpion envenomation.

Abroug et al. have, in a previous study, shown that left ventricular ejection fraction measured by echocardiography was severely depressed (26%) following scorpion envenomation. They showed a threefold improvement to 75% during recovery.1 In another study, they assessed right ventricular function using a pulmonary artery catheter; right ventricular ejection fraction was 24% following envenomation and improved to 39% during recovery.2 Unfortunately simultaneous right and left ventricular functions have not been studied.

Our patients with pattern II showed severely raised PAWP and subnormal left ventricular stroke work index, while right ventricular stroke work index and right atrial pressures were normal, suggesting that the left ventricle has been affected more than the right. In pattern IV, however, as well as right ventricular stroke work indices were severely depressed and both PAWP and right atrial pressures were grossly raised suggesting that at this stage right ventricular function was also severely deranged.

Abroug et al mention that they have been using dobutamine in scorpion envenomation with good results. Their patients also received antivenom, which is not available in India. It may be possible that antivenom favourably alters the response to isotropic catecholamines. The experience of Bawaskar and Bawaskar suggests that isotropic treatment given to patients who have not received antivenom does not decrease mortality. Although no controlled studies exist, studies using historical controls treated conventionally, including isotropic drugs, have shown that vasodilators like prazosin, calcium channel blockers, ACE inhibitors, and sodium nitroprusside have been used.3,4 However, whether any one of them is superior has not been studied. Currently available evidence indicates that these are equally effective and the suggestion that prazosin may have been effective in patients who did not improve with captopril as suggested by Bawaskar can only be considered speculative.


Is BNP ready for use in clinical practice?

EDITOR,—Richards et al suggest that brain natriuretic peptide (BNP) measured 24–96 hours after acute myocardial infarction (AMI) is a powerful independent predictor of mortality.5 They also indicate that BNP is a useful indicator for subsequent development of left ventricular failure and death.1

In their multivariate analysis the site (anterior v inferior) and type (Q wave v non-Q wave) of infarction do not appear to have been included. The important prognostic value of these indicators has been established.1,7 One might expect the anterior infarcts (39% of their study population) to demonstrate greater left ventricular dysfunction, higher BNP concentrations, and a poorer prognosis than the inferior infarcts (31%). A similar relation may exist between type of infarct and outcome, although figures for each type are not given. It would be interesting to see whether BNP is still a powerful prognostic variable if site and type of AMI were included in their analysis.

Two further confounding variables that may have weakened the association between BNP and outcome are the timings of the radionuclide ventriculography and blood sampling (1–4 days after AMI). Assessment of ventricular function in the first 24–48 hours after AMI can have an overestimation of damage due to the phenomenon of myocardial stunning.3 The time course of BNP shows a peak at 16 hours followed by a significant decline in the next 48–72 hours.2 A narrower and standardised time window for ventriculography and venesection may have improved the correlations.

It would have been useful to know the area under their receiver operating characteristic (ROC) curve for BNP, which is highly relevant in assessing the true value of a test.5 They demonstrated a negative predictive value of 100% for BNP at a threshold of 20 pmol/l, but they used different thresholds for looking at the sensitivity and specificity and predictive power for left ventricular ejection fraction and left ventricular failure (25 and 33 pmol/l, respectively). Although these values were derived from their ROC analyses, it is difficult to envisage what BNP results should then be interpreted in clinical practice.

If the additional prognostic value of BNP is confirmed once site and type of infarct are incorporated into the analysis the role of BNP as a routine clinical marker of AMI seems premature.6

Letters

K KHAN
Clinical Research Fellow, Department of Medicine & Therapeutics, Clinical Sciences Building, Leicester Royal Infirmary, Leicester LE2 7LR, UK
khkm2@le.ac.uk

6 Hanley JA, McNeill BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29–36.

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

Dr Khan’s letter raises a number of interesting points. First, when the site of myocardial infarction (anterior or inferior) is included in multivariate analysis of data reported in our recently published paper, plasma BNP remains an independent prognostic indicator for both death and development of heart failure. This is not surprising as division of patients according to inferior or anterior site of infarction creates crude categories, which both include a broad spectrum of injury from mild to very severe. In contrast, plasma BNP is a continuous variable and is related to the severity of myocardial injury across the entire range. This finding is also predictable in view of the fact that already published reports have indicated BNP has prognostic power independent of left ventricular ejection fraction (LVEF).1,2 LVEF acts as a common indicator of degree of severity of injury regardless of site of infarction.

Dr Khan also comments on a potential weakening of the association between BNP and outcome (although the context of his comment is unclear) he means LVEF rather than morbidity or mortal outcomes) due to the timing of radionuclide ventriculography and blood sampling. We find a fall in BNP following early postinfarction BNP (1–4 days) and both early (1–4 days) and late (3–5 months) radionuclide ventriculography.3,4 In addition, repeated BNP measurements at four months (unpublished data) continued to show a similarly strong correlation, albeit with an offset regression because of mean BNP falling somewhat from early postinfarction concentrations. In other words, a similar correlation is observed between BNP and ejection fraction regardless of early or late measurements of either variable. This suggests that the time window involved is not overly important provided reference data are established to allow for the systematic fall in plasma BNP over months after infarction. However, multivariate analyses show that BNP and left ventricular ejection fraction are independent predictors of death or later heart failure following myocardial infarction, and their independent nature implies their correlation will not be overly strong. The association of BNP with prognosis may well reflect the influence on plasma BNP concentrations of diastolic dysfunction and left ventricular mass as well as systolic function.1,5,6 For these reasons efforts to alter measurement method or timing simply to improve the correlation of BNP with LVEF are likely to be unproductive.

The statement by Dr Khan “The time course of BNP shows a peak at 16 hours followed by a significant decline in the next 48–72 hours” does not take into account the conflicting nature of the literature. The pattern of BNP change is dependent on the severity of infarction, the exact nature of the BNP assay employed, the degree of cross-reactivity with pro-BNP 1–108 or its N-terminal deleted metabolites.1,6 In our hands the time profile shows a plateau between 24 and 72 hours and hence our election of a 1–4 day sampling window.

Dr Khan’s comment that it is “difficult to envisage how a BNP result should then be interpreted in clinical practice” is disingenuous. Our published paper clearly points out that plasma BNP of less than twofold the upper limit normal within 1–4 days postinfarction has 100% negative predictive value for an ejection fraction of <40% four months after MI. Our report also makes it very clear that the positive predictive value for BNP above this level is very weak (that is, BNP above the normal range within the early postinfarct period is a weak predictor of reduced LVEF), and we do not recommend the routine use of plasma BNP as a substitute for measurement of left ventricular ejection fraction. However, the prognostic value of BNP is strong and, at the very least, early postinfarct BNP measurements will allow better risk stratification and therefore better targeting of surveillance in the follow up period.

The most important and insightful part of Dr Khan’s letter is the addressee’s possible potential for BNP together with ejection fraction to identify high risk populations in whom some sort of intervention is feasible before development of “clinical endpoints”. He states correctly that at present there is no evidence to suggest that treating a high plasma BNP in the presence of a normal ejection fraction improves outcome.5 In a manuscript now in preparation, the Christchurch Group is able to report follow up data on over 500 MI patients with a mean follow up period of approximately two years. This group has been divided according to both plasma BNP and radionuclide LVEF. Notably, over 20% of the group have an early postinfarct LVEF in excess of 40% but a concomitant BNP of over 25 pmol/l (2.5 times the upper limit of normal). This subgroup has a significantly greater risk of mortality and of developing heart failure than the group with LVEF above 40% and plasma BNP < 25 pmol/l. Furthermore, in patients who have ejection fractions below the 40% threshold but BNP < 25 pmol/l, there is a higher increase in risk of either death or heart failure over two years compared with that group with low BNP concentrations and high ejection fraction. In other words, reduction in ejection fraction only predicts mortality but not morbidity or mortality in the presence of neurohormonal activation as indicated by raised plasma BNP. Our findings concur with data from colleagues in Sweden and Northern England (oral communication), and it is becoming clear that a randomised controlled trial of treatment in asymptomatic patients with LVEF > 40% but clear neurohumoral activation should be done.

Transfusion associated graft versus host disease

Editor,—Ahya et al reported a case of transfusion associated graft versus host disease (TA-GVHD) in a non-immunocompromised patient resulting from blood transfusion during coronary artery bypass grafting (CABG).1 They concluded that this devastating complication of transfusion is probably underreported. There is no doubt that diagnosing this condition needs a high index of suspicion because its manifestations can be seen in other more common conditions such as sepsis or acute respiratory distress syndrome. Moreover, historical diagnosis needs specialist expertise in tissue typing.

We report another patient with TA-GVHD acquired following elective four-vessel CABG and perioperative transfusion of a total of six units of blood. A 68 year old man was admitted three weeks after surgery with a seven day history of skin rash, breathlessness, cough, and expectoration of brown sputum. He had an extensive erythrodermic maculopapular eruption, oral thrush, tachycardia, hypotension, and general chest crepitations, and mild hepatomegaly. His condition worsened progressively with development of profound pancytopenia, disseminated intravascular coagulation, metabolic acidosis, hepatitis, and acute renal failure. His bone marrow was aplastic and skin biopsy showed mononuclear infiltration with cellular apoptosis supporting the clinical diagnosis of TA-GVHD. Treatment with high dose steroids, ciclosporin, and OKT3 was initiated but despite maximum support he died within seven days of readmission. Although TA-GVHD does occur in immunocompetent individuals who had blood transfusion for other medical conditions, it is much more frequent following cardiac pulmonary bypass surgery. This type of major surgery appears to induce a transient immunodeficiency state, the mechanism of which is poorly understood and likely to be multifactorial. The use of fresh blood with multiple phlebotomies, immunosuppressive effect of multiple transfusions, and transient reduction of T-cell interfilker 2 but not 4, genetic lymphocyte transformation following

cardiopulmonary bypass may all cause a degree of immune dysfunction. If the donor’s blood happens to be homozygous for one of the recipient’s major HLA types, this transient immune dysfunction may facilitate donor’s lymphocyte engraftment and development of TA-GVHD.

We emphasise the relation of this highly dangerous condition with cardiopulmonary bypass surgery. One can only speculate as to the nature of this association.

M H GHREW
T RINGROSE
D YOUNG
T PETO
Norfield Department of Medicine,
John Radcliffe Hospital,
Oxford OX3 9DQ, UK


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

Ghrew et al report a patient with TA-GVHD following elective four-vees CABG and perioperative transfusion of six units of blood. It would be interesting to know in this case about the freshness of the transfused blood and whether shared haplotypes between the donor(s) and recipient was a feature in addition to the transient immunomodulatory effect of cardiopulmonary bypass.

The Oxford report re-emphasises that TA-GVHD as a complication of cardiopulmonary bypass surgery is seen in Europe. The association was first made in Japan, where the reported frequency of one way matching or sharing HLA haplotype in a non-first degree relative ranges from 1:312 to 1:874 and, probably, as a result, more than 25% of cases of TA-GVHD have been reported in immunocompetent individuals. Greater HLA diversity probably accounts for the reduced incidence in immunocompetent white patients, but it is clear that shared haplotype is not the sole requirement for the development of TA-GVHD after cardiopulmonary bypass. This is supported by data from the USA where in the Caucasian population the most common haplotype is HLA A1, B8, DRBI*03 with a reported frequency of 6.6%. Given this haplotype frequency, 0.05% of the transfusions in this population would be expected to result in a one way match. If shared haplotype was the sole requirement for the development of TA-GVHD then around 1500 cases might be expected each year. The reported frequency is well below this (less than 10 reports in total of which we are aware). Several explanations for this can be offered.

First the transfused units may contain an insufficient number of immunocompetent lymphocytes; second, some recipients may be able to destroy the donor lymphocytes on the basis of subtype differences in the class I or other minor histocompatibility antigens between the donor and recipient. Finally, it is possible, and quite likely, that some cases have remained unrecognised and unreported.

We hope that our publication in Heart of two cases of TA-GVHD after cardiac surgery will heighten awareness of this complication of transfusion, and result in full investigation and reporting of all suspected cases to SHOT (serious hazards of transfusion). It is necessary to establish the true incidence of TA-GVHD in cardiac surgery so that cost–benefit analysis and informed review of guidelines for the irradiation of cellular blood products for this indication can be completed.


Outpatient clinics for adults with congenital heart disease

EDITOR,—We agree with the views expressed by Gatzoulis et al concerning the need for dedicated clinics for adults with congenital heart disease. We started such a clinic in 1993. Initially this was once a month, becoming semi-monthly in 1995 and weekly in 1999. The clinic is in a district general hospital serving a population of 650 000, and the initial numbers may have been present because of the early work of Bill Oliver in establishing catheter facilities on this site and the link with Great Ormond Street visiting cardiologist. One of us also runs a paediatric clinic and the other has experience in adult congenital heart disease.

Forty three per cent of our 260 patients are male, and 25% of the patients have septal defects (both atrial and ventricular). As lesions complicated, closed defects are not followed up all these patients have additional lesions or residual sequelae of the original repair.

- 12% have had a tetralogy of Fallot repaired. 11.5% have bicuspid aortic valves.
- 8.7% have had a coarctation repaired.
- 11% have cyanotic heart disease (5% with the Eisenmenger complex).
- 5% have left ventricular outflow tract abnormalities.
- 5% have transposition of the great arteries—all of whom have had the Mustard repair.
- 12.1% of patients have Marfan’s syndrome (although patients with Marfan’s are also seen in general clinics).

The remaining 9.9% have varied condition from complex congenital heart disease including tricuspid atresia with Fontan opera-

L J FREEMAN
A J PAGE
Department of Cardiology,
Norfolk and Norwich Health Care Trust,
Brunswick Road, Norwich, Norfolk NR1 3SR, UK