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 corrections 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%.

In the pre-prazosin era (1961–83) a fatality rate of 25–30% was reported from western India,³ acute pulmonary oedema causing death. We were therefore surprised by the 25% mortality reported by Karnad,⁴ and that two victims died on the third day of hospitalisation; we have similar findings in 1978–82—that is, before prazosin treatment.

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 hyperthermia, tachycardia, pulmonary oedema, and shock (auto- nomic storm).⁵ We believe that the transport of Karnad’s patients to the nearest major hospital contributed to their death; seven of eight had acute pulmonary oedema owing to a delay in reaching a tertiary care hospital.⁶ Scorpion venom inhibits angiotensin converting enzyme (ACE), resulting in accumulation of bradykinin, which is implicated in the development of pulmonary oedema and acute reversible pancreatitis.⁷ Captopril (an ACE inhibitor) has a similar action resulting in hypotension resistant to dopamine agonists.⁸ Bradycardia further enhances nor-adrenaline (norepinephrine) release by a presynaptic mechanism.⁹

Alpha receptor stimulation plays a major role in the pathogenesis of pulmonary oedema.¹⁰ It causes hyperkalaemia and hyper- glycaemia (inhibition of insulin secretions). Angiotensin II stimulates α adrenergic receptors in the myocardium and hypoxia results from coronary spasm as well as accumulation of free radicals and free radicals injurious to myocardium leading to cardiac arrhyth- mias and sudden death.¹¹

At a general hospital at Mahad we successfully treated 658 cases of severe scorpion sting with oral rehydration, oral prazosin, and oxygen and famotidine: 362 (55%) had hypertension, 178 (27%) had pulmonary oedema, 118 (18%) had tachycardia; no patient had lethal arrhythmias. Seventeen patients who died on the way to Mahad had been referred 24 hours after being stung while 13 cases were admitted with multiorgan failure and were moribund and comatose; they died 30–60 minutes after admission despite treatment with dopamine, nitropruss- side, oxygen and Daniel-glucose-drip. The remaining 56 cases with massive pulmonary oedema recovered after treatment with intra- venous sodium nitroprusside.

We travelled throughout western Mahar- adstra where Mesobuthus tamulus scorpion flourishes, 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 mas- sive pulmonary oedema, which was treated with intravenous sodium nitroprusside. Captopril failed to correct haemodynamic abnor- malities in two cases who had cardiac arrhythmias. On post mortem examination we would have been life saving in the two patients treated with captopril who died in Karnad’s report.¹²

As a potent inhibitor of phosphodiesterase, prazosin causes accumulation of cGMP, a second messenger of nitric oxide, in vascular endothelium and myocardium, inhibits the formation of inositol trisphosphate, and activates venom inhibited calcium dependent potassium channel. Therefore, prazosin reverses both inotropic (hypertension), and hypokinetic (pulmonary oedema, hypotension, tachycardia) phases evoked by scorpion envenoming.

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2 Bawaskar HS, Bawaskar PH. Envenoming by scorpion bite: recent advances in their neurotoxins and therapeutics. Trop Med. [In press.]

EDITOR,—The study by Karnad¹ on the haemodynamic patterns encountered in scorpion envenomation raises important con- cerns. 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 sug- gested in animal studies as early as 1980¹ and confirmed by numerous series in human sub- jects. All of these series performed a haemo- dynamic study on PAWP.¹² We 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).

We are particularly concerned by Karnad’s interpretation of the haemodynamic records in the envenomated patients and the treatment strategy he suggests. The haemodynamic, echocardiographic, and angioscintig- raphic studies have shown that severe scorpion envenomation impairs left and right ventricles to the same extent.¹³ Echocardiographic studies showed that LV systolic func- tion might be deeply depressed with a mean LV fractional shortening as low as 12%.¹⁴ Regarding the right ventricle, in eight patients we recorded a mean RV ejection fraction of 24%.¹⁵ In fact, severe scorpion envenomation evokes acute heart failure which tends to recover in a few days. The heart failure might be concealed in some patients by the simulta- neous hypovolaemia that occurs in envenom- ated patients as a consequence of the hypervolaemia and sweating. Hence, the patterns II, III, and IV described by Karnad should not be regarded differently from the multiple facets of the same and only haemodynamic feature that is the profile of acute heart failure (patterns II and IV) that might be mitigated by simultaneous hypovolaemia (pattern III). Moreover, the three reported patients who had simultaneous hypovolaemia exhibited a worsening in their pulmonary oedema with fluid infusion, suggesting an exaggerated increase in PAWP resulting from altered LV function.

Although attractive from a pathophysio- logical standpoint, Karnad challenges the usefulness of inotropic drugs and claims that they improve only transiently the circulatory failure observed in scorpion envenomation with no effect on mortality. We are unaware of any study specifically analysing the outcome of this issue. Nevertheless, owing to the clearly established haemodynamic pattern of severe scorpion envenomation and on the basis of a pathophysiological approach, we and others have usually treated envenomated patients exhibiting pulmonary oedema and/or peripheral circulatory failure with dobutamine. The physiological effects were as expected, those usually observed in the treatment of heart failure: an increase in cardiac output as a consequence of an increase in stroke volume with enhanced LV performance, a substantial decrease in PAWP, and an increase of arterial pressure.¹⁶

Finally, Karnad suggests that RV failure occurs late in the terminal phase of scorpion envenomation and combines with pre- existing LV failure to produce severe cardio- genic shock. This speculation is not sup- ported by Nouira et al who used a modified Swan–Ganz catheter equipped with a fast response thermistor.¹⁷ This study showed that scorpion envenomation evokes simul- taneous impairment of the LV as well as the RV, the latter being depressed to the same extent as the former. Infusion of dobutamine enhances RV as well as LV performance.¹⁸

In conclusion, scorpion envenomation kills thousands of patients in developing coun-
tries. 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.

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

The efforts of Bavaskar 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 of 658 patients treated with prazosin, of whom only 30 (4.5%) died. They 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. 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. 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 was more severely affected 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 it this right heart dysfunction 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 inotropic catecholamines. The experience of Bavaskar and Bawaskar suggests that inotropic 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 inotropic drugs, have shown that vasodilators are effective in the treatment of cardiovascular manifestations of scorpion envenomation. 12 Vasodilators like prazosin, calcium channel blockers, ACE inhibitors, and nitrates have been used. 13 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 Bavaskar 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 and independent indicator for subsequent development of left ventricular failure and death. 1 In their multivariate analysis the site (anterior v inferio) 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. 2 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 lead to 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. 4 A narrower and standardised time interval 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 that all 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 diagnostic role still needs to be clarified. Measurement of BNP after AMI is unlikely to reduce the need for imaging of ventricular function because of its poor positive predictive value. Its potential use may lie in its ability to identify a high risk population in whom some sort of intervention is feasible before development of "clinical end points". However, at present, there is no evidence to suggest that treating a high plasma BNP in the presence of a normal ejection fraction improves outcome. Clearly this should be an area for further investigation.

BNP and its prohormone derivative (N-terminal proBNP) offer exciting prospects for non-invasive assessment of myocardial function and outcome following infarction. Richards et al have clearly demonstrated the prognostic superiority of BNP over other neurohumoral markers thus supporting their initial hypothesis. Their concluding statement, however, suggests that plasma BNP "could reasonably be included in the routine clinical workup of a patient following myocardial infarction" seems premature.

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 recent 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 injury across the entire group. 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). For these reasons efforts to alter measurement methods 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, and degree of cross reactivity with pro-BNP 1–108 or its N-terminal deleted metabolites. 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% 40 months after MI. Our report also makes it very clear that the persistent high BNP 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 his address the 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. 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 significant 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 a rather ominous outcome or mortality in the presence of neurohormonal activation as indicated by raised plasma BNP. Our findings concur with data from colleagues in Sweden and Norway (T Omland, C Hall, personal 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-immunosuppressed patient resulting from blood transfusion following coronary artery bypass grafting (CABG). 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, sepsis and septicemia. Moreover, histological 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 erthrodermic maculopapular eruption, oral thrush, tachycardia, hypertension, peripheral 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 mononocytic 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 conditions it is more frequent following cardiopulmonary 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. Stress of surgery, use of fresh blood with more frequent following cardiopulmonary 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. Stress of surgery, use of fresh blood with more frequent following cardiopulmonary 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. Stress of surgery, use of fresh blood with more frequent following cardiopulmonary 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. Stress of surgery, use of fresh blood with more frequent following cardiopulmonary 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. Stress of surgery, use of fresh blood with more frequent following cardiopulmonary bypass surgery.
cardiopulmonary bypass may all cause a degree of immune dysfunction.\textsuperscript{1,2} 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 role of this highly dangerous condition with cardiopulmonary bypass surgery. One can only speculate as to the nature of this association.

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

Ghrew et al report a patient with TA-GVHD following elective four-vessel 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 260 cases of TA-GVHD have been reported in immunocompetent individuals.\textsuperscript{3} 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, DRB1*03 with a reported frequency of 6.6%\textsuperscript{1}. Given this haplotype frequency, 0.05% of the transplants 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 for this can be overestimated.

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.\textsuperscript{1} Finally, it is possible, and quite likely, that some cases have remained unrecognised and unreported. We hope that our publication in \textit{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 on the irradiation of cellular blood products for this indication may 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.\textsuperscript{1} We started such a clinic in 1993. Initially this was once a month, becoming semimonthly 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 the development of graft versus host disease after bone marrow transplantation.\textsuperscript{2}

Fifty three per cent of our 260 patients are male, and 25% of the patients have septic defects (both atrial and ventricular). As uncomplicated, 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 Eisenmengers syndrome)
• 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 following comments are derived from this patient group: