Research Paper

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Vasopressin release during orthostatic hypotension after cardiac transplantation

S.W. Lord BM MRCP[1], **S. Brady**[1], **P.H. Baylis** MD FRCP[2], **J.H. Dark** MB FRCS[1], **R.A. Kenny** MD FRCP FRCPI[3] and **J.M. McComb** MD FRCP[1]

[1]Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne, [2]Department of Medicine, University of Newcastle upon Tyne and [3]Cardiovascular Investigation Unit, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Correspondence and reprint requests: S.W. Lord, Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK.
Tel: (+44) 191 284 3111, Ext. 2444; Fax: (+44) 191 284 1175

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At the time of cardiac transplantation all nerves from the donor ventricles are cut. These nerves may regrow, but there is no method of measuring any regrowth. Arginine vasopressin (AVP) release was studied during hypotension induced by head-up tilt and lower body negative pressure (LBNP) in transplant recipients and in normal controls. Subjects were tilted to 60° for up to 60 min or until symptomatic. Lower body negative pressure (40 mmHg) was applied for 10 min after 30 min rest. Seven of 17 transplant recipients and 11 of 12 controls became symptomatic during tilt testing, and 9 of 12 controls and 9 of 17 transplant recipients became symptomatic after 10 min of LBNP. Symptoms during tilt did not predict symptoms during LBNP. Resting AVP levels were similar but osmolality was greater in transplant recipients. Resting haematocrit was reduced, and atrial natriuretic peptide increased in transplant recipients, suggesting increased plasma volume. In symptomatic subjects, changes in humoral concentrations were similar when compared between transplant recipients and normals, except that the rise in AVP at the time of symptoms was reduced in transplant recipients, with a comparable drop in blood pressure consistent with persistent cardiac afferent denervation in a subset of transplant recipients.

Keywords: syncope; cardiac transplantation; hypervolaemia; reinnervation

Introduction

Head-up tilt testing is a useful method of evaluating otherwise unexplained fainting, and may help to make a diagnosis of vasovagal syncope.[1] The initiation of syncope during tilt testing is not fully understood, and appears to depend upon cardiac nerves, baroreceptor sensitivity and volume homeostasis.[2] These factors are interrelated, and are difficult to measure independently. Further, the act of measurement significantly alters the response to tilt.[3]

The transplanted heart is completely denervated, at least for an initial period after the operation, although a substantial portion of the recipient atria and pulmonary veins remains. The atria have been handled and devascularized, and exhibit electrophysiological changes consistent with partial denervation.[4] Efferent reinnervation takes place to the donor sinus node,[5] and afferent reinnervation may do so, so that the transplanted heart is not necessarily a model of total denervation. There is at present no method of measuring cardiac afferent function.

Arginine vasopressin (AVP) release is greatly increased at the time of tilt-induced syncope.[6] Although this release is known to be stimulated by hypotension and by nausea, it is also possible that cardiac nerves are an important factor, and thus the release of AVP in response to maximal cardiac receptor unloading could be used as a method of detecting afferent reinnervation. In order to stimulate these nerves maximally, we used a high level of lower body negative pressure (LBNP) and an aggressive tilt protocol. We hypothesized that AVP release at the time of hypotension induced by these manoeuvres would be reduced after cardiac transplantation.

Methods

Patient characteristics

Seventeen orthotopic cardiac transplant recipients (16 male) were recruited and compared with 12 normal controls (nine male). The transplant recipients were studied at 23–38 (mean 29.2) months post-transplantation. Haemodynamic changes in seven of these have been described briefly elsewhere.[7] All had undergone transplantation using the standard atrial anastomosis.[8] All controls had no known cardiovascular disease, and were taking no medication. The mean age of transplant recipients was 48.2 (range 20–62) years, and of controls 48.1 (range 37–68) years. Preoperative diagnosis was congenital heart disease in one, idiopathic cardiomyopathy in four and ischaemic cardiomyopathy in the remaining 12. Approval was obtained from the University of Newcastle upon Tyne joint ethical committee, and prior informed consent obtained from all participants.

Transplant recipients were recruited at the time of routine surveillance cardiac angiography, which was undertaken within 2 weeks of tilt testing. No control underwent angiography. All cardioactive medication, including calcium channel antagonists and nitrates, was discontinued for at least 36 h before study. Immunosuppression, comprising cyclosporin (trough level on day of study 207 (range 105–284) ng/dl), prednisolone (dose 0.05–0.10 mg/kg) and azathioprine as clinically indicated, was continued throughout.

All subjects underwent 60° head-up tilt for 60 min or until symptomatic, either presyncopal or syncopal. All tests were performed in the morning on a motorized tilt table with footplate support and a shelf at chest height as an arm rest. An intravenous cannula was positioned in the forearm 30 min before the study and a slow-running infusion (20 ml 0.9% saline in 1 h) was used to maintain patency. Subjects were then rested for 30 min before lying supine in a rigid chamber. Lower body negative pressure (40 mmHg) was then applied for 10 min.

Measurements were taken at baseline and at 5, 10, 15, 30 and 60 min during tilt, or at the time of symptoms, and at 0 and 10 min during LBNP. Blood pressure was measured using digital plethysmography (Finapres, Ohmeda). At each sampling time at least 30 ml of blood was removed, up to 180 ml in total. Samples were separated and flash frozen to −70°C, and then stored for subsequent analysis. Although blood was taken, samples from three control subjects did not reach the laboratory.

Plasma AVP was measured by a double-antibody radioimmunoassay after plasma samples had been extracted by the Florisil absorption technique.[9] The limit of detection for plasma AVP was 0.3 pmol/l, the interassay coefficient of variation being 2.7% at 2.0 pmol/l.[9] Plasma atrial natriuretic peptide (ANP) was assayed by a double-antibody radioimmunoassay after extraction of plasma samples.[10] The limit of detection for plasma ANP was 1.2 pmol/l, the interassay coefficient of variation being 5.6% at 10 pmol/l. Plasma osmolality was measured by the depression of freezing point method (Roebling Osmometer, CamLab Mod 2000), reference range 282–295 mosmol/kg. The interassay coefficient of variation was 0.7% at 306 mosmol/kg. Haematocrit was estimated using a Hawkesley microhaematocrit centrifuge. The interassay coefficient of variation was 1.0% at 48%. Plasma renin activity (PRA) was assayed by measuring the rate of production of angiotensin I in the presence of converting enzyme (RIANEN, DuPont). The limit of detection for angiotensin I was 0.4 pmol/l per min. The interassay coefficient of variation was 8.7% at 13.3 pmol/l per min. Aldosterone was measured using competitive binding of [^{125}I]aldosterone to antibody-coated tubes (Coat a Count, Euro DPC). The limit of detection for plasma aldosterone was 44.4 pmol/l. The interassay coefficient of variation was 3.7% at 450 pmol/l.

Statistical methods and data presentation

The proportion of symptomatic subjects was compared between groups using Fisher's exact test. Humoral variables were logarithmically transformed because their distribution was found to be skewed. Changes in haemodynamic and humoral variables were compared using paired t testing. The Mann–Whitney U test was used to compare results in different groups of subjects at comparable times during tilt. Time to syncope was analysed using the log rank test.

Data are presented as absolute resting values, and then as the mean or median of the proportional values at a given time or event for that group. Variation is expressed as standard deviation (SD) for haemodynamic variables, and as range for hormone concentrations. Because of the small numbers involved, symptomatic subjects were compared with asymptomatic subjects among transplant recipients (seven versus ten subjects), and transplant recipients with controls among symptomatic subjects (seven versus 11 subjects). Results are presented as significant at a p value of 0.05 or less.

Results

Symptoms

Eleven of 12 controls, and seven of 17 late transplant recipients became symptomatic during tilt testing (either syncopal or presyncopal, $p < 0.01$ controls versus transplant recipients). The time to tilt-induced symptoms was significantly prolonged in transplant recipients (28.7 (SD 18.8) min versus 12.5 (SD 10.2) min in controls, $p < 0.01$, log rank test). Nine of 12 controls and nine of 17 transplant recipients became symptomatic after 10 min of LBNP (p = NS). Symptoms during tilt did not predict symptoms during LBNP.

Haemodynamic variables

Resting blood pressure and heart rate were higher in transplant recipients than in controls (Table 1). There was no difference between resting haemodynamic variables in symptomatic and asymptomatic transplant recipients.

Both groups of patients showed similar haemodynamic changes during each phase of tilt and during LBNP (Table 2). The changes during tilt are illustrated in Figure 1. Heart rate was greater than resting at the time of maximum systolic blood pressure. At the time of symptoms the proportional fall in systolic blood pressure was comparable in all symptomatic subjects. Heart rate

Table 1. Resting haemodynamic and humoral variables in all subjects

	Transplant recipients (17)	Controls (12)
HR (beats/min)	85 (±13.6)*	62 (± 8.6)
SBP (mmHg)	141 (± 13.5)*	117 (± 15.4)
DBP (mmHg)	82 (± 12)*	67 (± 11)
PRA (pmol/l per min)	34.6 (13–73)*	15 (12–53)
Aldo (pmol/l)	302 (72–1380)	216 (146–763)
AVP (pmol/l)	0.5 (< 0.3–2.5)	0.4(< 0.3–5.6)
ANP (pmol/l)	13 (1.7–39)*	2.4 (0.6–4.9)
Osmolality (mosm/kg)	297 (± 5.21)*	289 (± 1.81)
Haematocrit (%)	37 (± 4.7)*	43 (± 3.6)

Values are mean (± SD) or median (minimum–maximum). Transplant values marked * are significant compared to controls ($p < 0.05$). HR, Heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; Aldo, aldosterone; AVP, arginine vasopressin; ANP, atrial natriuretic peptide; PRA, plasma renin activity.

Table 2. Changes in haemodynamic variables during tilt testing compared between late transplant recipients (TS, symptomatic and TNS, asymptomatic, at 30 min) and symptomatic controls (CS), expressed as proportion of resting value (mean (± SD))

		At SBP max.	At symptoms	At end of tilt
SBP/SBP_{rest}	CS	1.05 (± 0.06)*	0.45 (± 0.14)*	0.98 (± 0.14)
	TS	1.06 (± 0.15)	0.36 (± 0.17)*	0.97 (± 0.13)
	TNS	1.08 (± 0.08)	0.94 (± 0.15)	0.98 (± 0.09)
DBP/DBP_{rest}	CS	1.09 (± 0.09)	0.52 (± 0.17)*	1.02 (± 0.11)
	TS	1.04 (± 0.06)	0.36 (± 0.25)*	1.02 (± 0.05)
	TNS	1.13 (± 0.13)	1.04 (± 0.15)	1.06 (± 0.17)
HR/HR_{rest}	CS	1.07 (± 0.13)	0.82 (± 0.2)*#	0.95 (± 0.09)
	TS	1.03 (± 0.09)	1.05 (± 0.15)	1.0 (± 0.07)
	TNS	1.11 (± 0.08)*	1.17 (± 0.08)*	1.02 (± 0.05)

Significant ($p < 0.05$) differences from resting are marked *, and differences between symptomatic controls and symptomatic transplant recipients, or between symptomatic and asymptomatic transplant recipients are marked #. For the reasons outlined in the text, controls were not compared statistically to asymptomatic transplant recipients. Abbreviations as in Table 1.

fall from maximum to time of tilt-induced symptoms was 52.8% (SD 18.7%) in 11 controls and 19.1% (SD 15.0%) in seven late transplant recipients ($p < 0.01$). The only difference between symptomatic transplant recipients at time of tilt-induced symptoms (average 28.7 min) and asymptomatic transplant recipients at a similar time (30 min) was the fall in blood pressure. By 30 min after tilt, all haemodynamic variables had returned to values similar to resting in all subjects.

Humoral variables

Resting AVP was similar in both groups (Table 1). Plasma renin activity was higher in transplant recipients than in controls, although aldosterone levels were not. Resting osmolality was greater in both early and late transplant recipients, and haematocrit was lower. Resting ANP concentration was greater in transplant recipients. There was no difference between resting humoral variables in symptomatic and asymptomatic transplant recipients.

The reduction in haematocrit and in osmolality was the same in all three groups. ANP at time of tilt-induced symptoms was lower in transplant recipients when compared to controls, although each difference was not significant when compared to baseline. Figure 2 shows changes in AVP during tilt expressed as the ratio of resting values. At the time of tilt-induced symptoms, AVP rose dramatically in symptomatic subjects compared to asymptomatic subjects and when compared to baseline, and the rise was significantly greater in controls than transplant recipients (log ratio 2.54 range (1.43–2.63) versus 1.52 (0.79–2.31) $p = 0.04$; Table 3). Similarly, although LBNP induced symptoms in a different subset of the transplant recipients, in whom the fall in systolic blood pressure was similar to controls (48 (23–66) versus 53 (26–83) mmHg), AVP rise was significantly greater at the time of LBNP-induced symptoms in the control subjects (log ratio 2.00 (1.63–2.34) versus 0.99 (–0.37–2.06) $p = 0.02$). Further, there was a wider distribution of AVP release in response to hypotension in the transplant recipients than in the controls (Figure 3).

Plasma renin activity and aldosterone rose and fell in parallel until the last sample, when PRA was falling

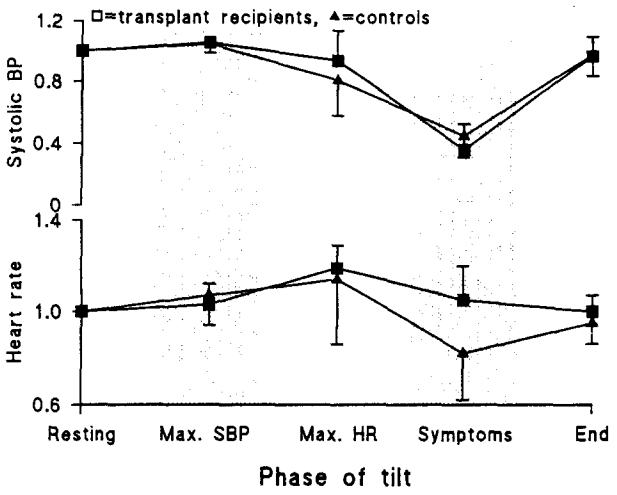

Figure 1. Haemodynamic changes during tilt in symptomatic subjects expressed as ratio of resting values, plotted at rest, at maximum systolic pressure (Max. SBP), at maximum heart rate (Max. HR), at time of symptoms, and at the end of tilt

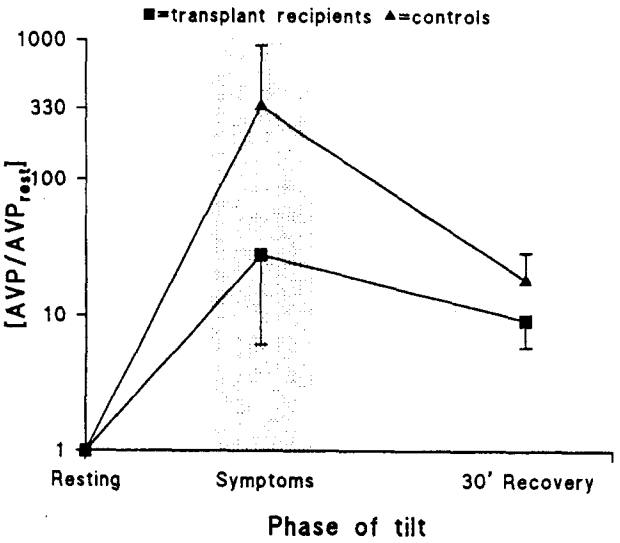

Figure 2. Arginine vasopressin (AVP) during tilt in symptomatic subjects, plotted at rest, at time of symptoms and at the end of tilt, expressed as ratio of resting values (logarithmic scale)

Table 3. Changes in humoral variables at the time of symptoms compared between late transplant recipients (TS, symptomatic and TNS, asymptomatic, at 30 min) and symptomatic controls (CS), expressed as the change in logarithm of resting value (median (range))

	CS	TS	TNS
PRA/PRA_{rest}	0.19 (0.04–0.26)#	0.29 (0.10–0.45)*	0.18 (–0.21–0.36)
$Aldo/Aldo_{rest}$	0.29 (0–0.43)	0.31 (0.07–0.45)*	0.24 (0.18–0.35)
AVP/AVP_{rest}	2.54 (1.43–2.63)*#	1.52 (0.79–2.31)*	0.43 (0.00–1.00)#
ANP/ANP_{rest}	–0.15 (–0.26–0.25)#	–0.06 (–0.30–0.21)	–0.11 (–0.39–0.10)

Significant ($p < 0.05$) differences from resting are marked *, and differences between symptomatic controls and symptomatic transplant recipients, or between symptomatic and asymptomatic subjects are marked #. Controls were not compared statistically to asymptomatic transplant recipients. Abbreviations as in Table 1.

while aldosterone continued to rise. Both rose during tilt in symptomatic and asymptomatic subjects, and rises were no different at the time of symptoms in transplant recipients and in controls. Renin and aldosterone levels at the time of symptoms (28.7 min) in symptomatic subjects were not different from renin and aldosterone levels taken at a similar time (30 min) in asymptomatic subjects. Similarly, changes in renin and aldosterone during LBNP were not related to symptoms, and were not different between transplant recipients and controls.

Discussion

This study extends our previous observations that cardiac transplant recipients can faint in response to orthostatic stress.[7] However, fewer transplant recipients than controls became symptomatic, and those who did, did so later during tilt. Thus cardiac transplantation protects against (pre)syncope during tilt testing, and this protection not only reduces the number of subjects with symptoms, but also delays the time of onset of symptoms. When the cardiac transplant recipients became syncopal, AVP release was reduced when compared to controls with similar symptoms and fall in blood pressure. Reduced AVP release was also observed in a different group of subjects during LBNP. These observations suggest a contribution of cardiac afferent nerves to AVP release at the time of syncope, and that afferent reinnervation may have taken place in some subjects.

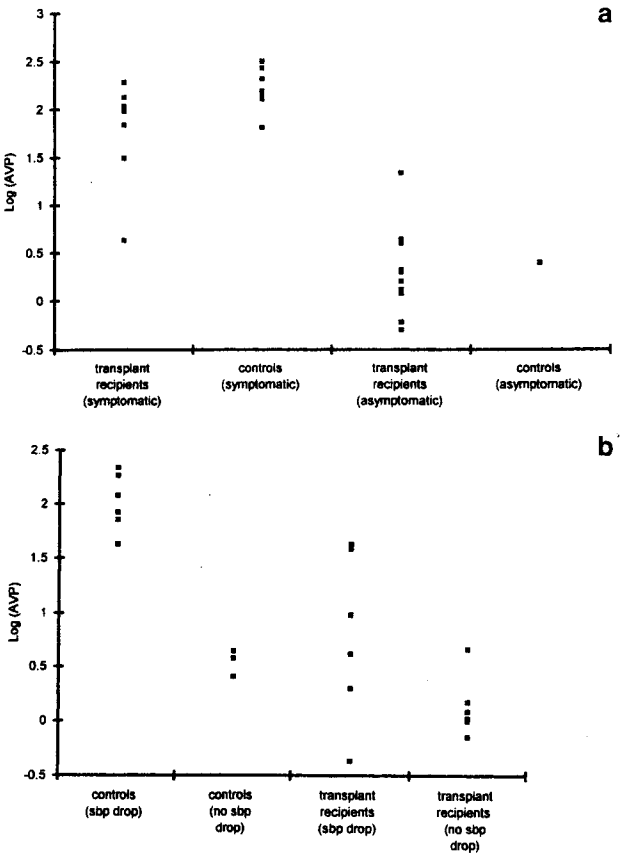

Figure 3. Comparison between rise in AVP during symptoms and at rest; (a) during tilt testing and (b) during lower body negative pressure. sbp, Systolic blood pressure

It has previously been noted that cardiac transplant recipients faint during head-up tilt,[11,12] suggesting that either the classical Bezold Jarisch reflex is not responsible for syncope, or that sufficient cardiac afferent innervation remains intact or has grown back. The low reproducibility of the tilt test and uncertain nature of the stimulus make tilt-induced syncope a poor test of afferent reinnervation. Other methods of detecting such reinnervation including the response to intracoronary contrast,[13] and the presence of chest pain[14] have not proven useful. It is important to detect any reinnervation because of its potential contribution to increased plasma volume and hypertension, and we suggest that the release of AVP after a given hypotensive stimulus would be a method of measuring it.

Our tilt protocol led to symptoms in about half of the late transplant recipients, and almost all normal controls. This is likely to be due to the cannulation and regular blood sampling required to estimate hormonal changes. The difference in response to tilt and LBNP may be due to the physical characteristics of the test but is more likely to be related to the poor reproducibility of these manoeuvres.

The previous studies of orthostatic stress in cardiac transplant recipients are summarized in Table 4. Changes in both haemodynamic and humoral variables in transplant recipients who become symptomatic have not been described before. Our results differ from those of Fitzpatrick *et al.*,[12] who found that a similar proportion of subjects and controls were symptomatic. They used a tilt protocol similar to ours, but involving saddle support. The difference could be

Table 4. Previous studies of orthostatic stress in transplant recipients

	Subjects	Time post-transplantation (months)	Provocation	Proportion of subjects (controls) symptomatic	Time or degree of LBNP
Fitzpatrick *et al.*[12]	10 H	22 (6–38)	60° HUT 60 min	7/10 (7/12)	41 (37) min
Lightfoot *et al.*[15]	6 H	40 (18–72)	Graded LBNP	6/6 (6/6)	83 (75) mmHg
Banner *et al.*[16]	8 HL	20 (4–30)	45° HUT 60 min	0/8 (0/8)	60 (60) min
Mohanty *et al.*[17]	23 H	(2–12)	Graded LBNP	0/23 (0/13)	40 (40) mmHg

H, Heart transplant recipients; HL, heart-lung transplant recipients; HUT, head-up tilt; LBNP, lower body negative pressure. Controls are in parentheses.

explained by a different effect of cannulation on the central component of baroreflex sensitivity in transplant recipients and controls. It should also be noted that Fitzpatrick's controls were younger than his subjects, whereas ours were age matched.

Resting blood pressure and heart rate are known to be raised in cardiac transplant recipients. In our study there was no significant difference in resting haemodynamics between transplant recipients who subsequently became symptomatic and those who did not. Similarly, resting haemodynamics are comparable in those who faint and those who do not among subjects with a history of syncope,[18] and so cannot be used to predict susceptibility to tilt-induced syncope.

We have demonstrated similar changes to those found by other investigators[19] in normal controls during tilting in our subjects, both controls and transplant recipients. Thus the haemodynamic responses of transplant recipients at the time of syncope or presyncope do not suggest an explanation for the protective effect of transplantation. Other investigators have related propensity to faint to reduced intravascular volume,[2,20] to increased cardiovascular reflex sensitivity,[2,20] and to the effects of cardiovascular drugs.[21] Abnormalities in all of these factors are likely in transplant recipients, and require further investigation.

ANP is abnormal immediately after cardiac transplantation, but rises to normal or supranormal levels within the first week after the operation.[22,23] In transplant recipients, ANP rises appropriately in response to rises in right atrial pressure, in contrast to the situation in patients with cardiac failure in whom the response is blunted.[24] ANP has been shown to fall in normal subjects during tilt testing, and it has been assumed that this fall is due to decreasing right atrial pressure.[25] In our study, ANP change from baseline during tilt testing was not significant in either transplant recipients or controls at the time of symptoms, although ANP did fall in transplant recipients when compared to controls, suggesting a greater fall in thoracic blood volume before symptoms in transplant recipients. These observations differ from those of Banner *et al.*[16] who noted comparable falls in ANP during tilt in heart-lung transplant recipients and in controls. It is possible that the different atrial geometry in heart and heart-lung transplant recipients explains this difference.

AVP and osmolality have not been previously studied in fainting transplant recipients. The reason for the higher resting osmolalities in transplant recipients is probably related to the mild renal impairment seen in our subjects. Higher serum osmolalities in the presence of normal AVP suggest that extracellular volume regulation is abnormal. This is consistent with the reduced haematocrit observed in the transplant recipients and with the observations of others, notably Braith and colleagues, who have shown qualitatively different behaviour of AVP release during volume loading in cardiac transplant recipients and controls taking cyclosporin.[26] AVP rose dramatically at the time of symptoms in both transplant recipients and controls, consistent with previous observations in normal subjects.[6] The fact that the proportional rise in AVP was less in transplant recipients in the presence of similar changes in blood pressure suggests that volume sensing is inappropriate in this group, perhaps related to persistent cardiac afferent denervation. This effect is thus a potential measure of cardiac afferent reinnervation, although its reproducibility is not known, and it is unpleasant to induce. There are many alternative explanations which remain to be excluded. AVP release may be inhibited by glucocorticoids in the transplant recipients, as it is in rats.[27] Cyclosporin affects hypothalamic function, although it did not affect the AVP response to volume loading in Braith's cohort of liver transplant recipients[26] and potential effects of azathioprine have not been controlled for. The very different resting values of PRA and ANP could potentially interact with AVP release, as could different levels of catecholamines. An independent effect of hypertension is also possible, likely related to the prevalence of left ventricular hypertrophy in this population. Finally, cardiac transplant recipients are survivors of cardiac failure, and it is possible that abnormalities of central haemodynamic control persist, or only partially resolve.

Raised resting PRA in the presence of normal or raised intravascular volume suggests that volume sens-

ing is inappropriate. This is consistent with data from animal models of cardiac afferent denervation, which produces the same effects on renal blood flow, renal renin secretion and sodium excretion as renal efferent denervation.[28] The similarity of the response of these hormones between symptomatic and asymptomatic subjects suggests that they make no direct contribution to syncope, at least among transplant recipients.

We also need to comment on the limitations of the study. Sampling was irregular, and less frequent later during tilt, when more transplant recipients fainted. Subjects were cannulated and depleted of up to 180 ml of blood, so that this protocol is not directly comparable to others. The presence or absence of a positive response to tilt is known not to be reproducible, although the time to occurrence of symptoms has been found to be more reproducible using a similarly aggressive protocol.[2]

Conclusions

We have observed that cardiac transplantation protects against tilt-induced syncope but does not prevent its occurrence.

Resting heart rate, blood pressure, PRA, haematocrit, and osmolality were different in transplant recipients, when compared to normal controls, and were consistent with relative hypervolaemia. These values could not be used to predict the occurrence of syncope in this group of subjects.

The pattern of haemodynamic changes during symptoms in late transplant recipients is similar to that observed in controls, except that donor heart rate does not fall at the time of syncope, presumably a consequence of continuing sinus node denervation in most subjects. Hormonal changes were also little different except that the rise in AVP at the time of fainting was lower in transplant recipients, consistent with partial cardiac afferent denervation. It may be possible to use this phenomenon as a measure of afferent reinnervation.

The fact that changes in other haemodynamic and humoral variables are similar suggests that the underlying mechanism of syncope is the same in both groups of subjects, and that the reduced prevalence of tilt-induced syncope in transplant recipients may be explained by abnormal volume homeostasis.

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References

1. Kenny RA, Ingram A, Bayliss J, Sutton R. Head up tilt: a useful test for investigating unexplained syncope. *Lancet* 1986; **i**: 1352–1355.
2. El-Sayed H, Hainsworth R. Salt supplementation increases plasma volume and orthostatic tolerance in patients with unexplained syncope. *Heart* 1996; **75**: 134–140.
3. McIntosh SJ, Lawson J, Kenny RA. Intravenous cannulation alters the specificity of head up tilt testing for vasovagal syncope in elderly patients. *Age and Ageing* 1994; **23**: 317–319.
4. Holt ND, Brady S, Dark JH, McComb JM. Does the recipient atrial remnant exhibit normal physiology? *PACE* 1996; **4**(II): 711.
5. Lord SW, Brady S, Holt ND, Mitchell L, Dark JH, McComb JM. Exercise response after cardiac transplantation: correlation with sympathetic reinnervation. *Heart* 1996; **75**: 40–43.
6. Riegger GA, Wagner A. Excessive secretion of vasopressin during vasovagal reaction. *Am Heart J* 1991; **121**: 602–603.
7. Morgan-Hughes NJ, Dark JH, Kenny RA, McComb JM. Vasovagal reactions after cardiac transplantation: relationship to reinnervation status. *Clin Aut Res* 1994; **4**: 125–129.
8. Stinson EB, Dong E, Iben AR, Shumway NE. Cardiac transplantation in man III: surgical aspects. *Am J Surg* 1969; **118**: 182.
9. Rooke P, Baylis PH. A new sensitive radioimmunoassay for plasma arginine vasopressin. *Journal of Immunoassay* 1982; **3**: 115–131.
10. Burrell LM, Palmer J, Charlton JA, Thomas T, Baylis PH. A new radioimmunoassay for human alpha atrial natriuretic peptide and its physiological validation. *Journal of Immunoassay* 1990; **11**: 159–175.
11. Giannattasio C, Grassi G, Mancia G. Vasovagal syncope with bradycardia during lower body negative pressure in a heart transplant recipient. *Blood Pressure* 1993; **2**(4): 309–311.
12. Fitzpatrick AP, Banner N, Cheng A, Yacoub M, Sutton R. Vasovagal reactions may occur after orthotopic heart transplantation. *J Am Coll Cardiol* 1993; **21**: 1132–1137.
13. Arrowood JA, Goudreau E, Minisi AJ, Davis AB, Mohanty PK. Evidence against reinnervation of cardiac vagal afferents after human orthotopic cardiac transplantation. *Circulation* 1995; **92**: 402–408.
14. Connolly DL, Chauhan A, Roberts M *et al.* Intracoronary adenosine causes chest pain in patients after cardiac transplantation. *Br Heart J* 1994; **71**(suppl): P39.
15. Lightfoot JT, Rowe SA, Fortney SM. Occurrence of presyncope in subjects without ventricular innervation. *Clin Sci* 1993; **85**: 695–700.
16. Banner NR, Williams TDM, Patel N, Chalmers J, Lightman SL, Yacoub MH. Altered cardiovascular and neurohumoral responses to head up tilt after heart-lung transplantation. *Circulation* 1990; **82**: 863–871.
17. Mohanty PK, Thames MD, Arrowood JA, Sowers MD, McNamara C, Szentpetery S. Impairment of cardiopulmonary baroreflex after cardiac transplantation in humans. *Circulation* 1987; **75**: 914–921.
18. Sneddon JF, Counihan PJ, Bashir Y, Haywood GA, Ward DE, Camm AJ. Assessment of autonomic function in patients with neurally mediated syncope: augmented cardiopulmonary baroreceptor responses to graded orthostatic stress. *J Am Coll Cardiol* 1993; **21**: 1193–1198.
19. Hainsworth R, Al-Shamma YMH. Cardiovascular responses to upright tilting in healthy subjects. *Clin Sci* 1988; **74**: 17–22.
20. Ludwig DA, Convertino VA. Predicting orthostatic intolerance: physics or physiology? *Aviation, Space and Environmental Medicine* 1994; **65**: 404–411.
21. Raviele A, Gasparini G, Di Pede F *et al.* Nitroglycerin infusion during upright tilt: a new test for the diagnosis of vasovagal syncope. *Am Ht J* 1994; **127**: 103–111.
22 Weston MW, Cintron GB, Giordano AT, Vesely DL. Normalization of circulating atrial natriuretic peptides in cardiac transplant recipients. *Am Ht J* 1994; **127**: 129–142.
23. Starling RC, O'Doriso TM, Malarkey WB, Murray KD, Myerowitz PD, Cody RJ. Preserved atrial natriuretic peptide secretory function after cardiac transplantation. *Am J Cardiol* 1991; **68**: 237–241.
24. Volpe M, Tritto C, De Luca N *et al.* Failure of atrial natriuretic factor to increase with saline load in patients with dilated cardiomyopathy and mild heart failure. *J Clin Invest* 1991; **88**: 1481–1489.
25. Perko G, Payne G, Linkis P *et al.* Thoracic impedance and pulmonary

atrial natriuretic peptide during head up tilt induced hypovolaemic shock in humans. *Acta Physiol Scand* 1994; **150**: 449–554.
26. Braith RW, Mills RM, Convertino VA. Breakdown of blood pressure and body fluid homeostasis in heart transplant recipients. *JACC* 1996; **27**: 375–383.
27. Raff H. Glucocorticoid inhibition of neurohypophysial vasopressin secretion. *Am J Physiol* 1987; **252**: R635–R644.
28. Miki K, Hayasi Y, Tajima F, Iwamoto J, Shiraki K. Renal sympathetic nerve activity and renal responses during head up tilt in conscious dogs. *Am J Physiol* 1989; **257**: R337–R343.