Altered Cardiovascular and Neurohumoral Responses to Head-up Tilt After Heart-Lung Transplantation

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Heart-lung transplantation results in afferent and efferent denervation of the transplanted organs including interruption of the central connections from the low-pressure receptors in the atria and pulmonary veins. We investigated whether the cardiovascular and neurohumoral responses to the postural stimulus of head-up tilt were affected after transplantation. Responses in eight heart-lung transplant recipients were studied and compared with those in eight normal subjects matched for age and sex during passive head-up tilt at 45° for 1 hour. The transplant group had a higher initial heart rate (99±2 versus 68±2 beats/min, p<0.001) and diastolic blood pressure (88±5 versus 76±2 mm Hg, p<0.05) than did the control group. The increases in heart rate and diastolic blood pressure during head-up tilt were similar in the two groups. Systolic blood pressure remained unchanged. The decrease in cardiac output (30% versus 18%, p<0.05) and the increase in systemic vascular resistance (52% versus 28%, p<0.05) were greater in the transplant group. Baseline levels of norepinephrine, epinephrine, vasopressin, and plasma renin activity were similar in the two groups. Atrial natriuretic peptide concentrations were higher in the transplant group (26±3.8 versus 9.7±1.6 pmol/l, p<0.001). During head-up tilt, plasma norepinephrine levels increased to a greater extent in the transplant group than in the control group (83% versus 53%, p<0.01), indicating an increased sympathetic response. In contrast, plasma renin activity increased significantly in the control group but not in the transplant group. Plasma vasopressin concentrations remained unchanged, whereas atrial natriuretic peptide concentrations decreased significantly in both groups. The pattern of cardiovascular and neuroendocrine responses to head-up tilt was altered in heart-lung transplant recipients, who had a greater dependence on sympathetic-mediated vasoconstriction, although their ability to maintain systemic blood pressure during this postural stress was unaffected. (Circulation 1990;82:863–871)

The nervous system plays a central role in the regulation of the cardiovascular system.1 Lung and heart transplantations are now established forms of therapy for a variety of end-stage pulmonary and cardiac diseases. These procedures result in surgical denervation of the transplanted organs. Heart transplantation produces efferent denervation of the heart2 and ventricular deafferentation,3 and it results in altered cardiovascular control and performance.2,4 The most extensive denervation occurs in combined heart-lung transplantation,5 which affects the ventricles, the entire pulmonary circulation, and left atrium. Receptors in these areas play a role in the adaptation to changes in posture6 and circulating volume.7 The potential importance of these receptors in clinical transplantation was recognized in animal studies.8 Passive head-up tilt reduces stroke volume by reducing ventricular preload, and it generates a variety of compensatory responses to maintain systemic blood pressure and cardiac output.6 The afferent pathways of these reflex and neurohumoral responses include the arterial baroreceptors and receptors within the heart and lungs.6 Head-up tilt has been widely used to test the integrity of cardiovascular control mechanisms and to investigate patients with symptoms suggestive of postural hypotension or unexplained syncope.9

The first aim of this study was to determine whether the ability of heart-lung transplant recipi-
ents to maintain systemic blood pressure during a sustained postural stress is impaired. The second aim was to investigate whether the pattern of the cardiovascular and neuroendocrine responses to gravitational stress is altered. We studied the responses of healthy heart-lung transplant recipients to passive 45° head-up tilt and compared them with the responses of normal subjects.

Methods

Subjects

Eight recipients of combined heart-lung transplantations were studied and compared with eight control subjects matched for age and sex. The transplant group had a mean (±SD) age of 28.3±9 years compared with 29.9±7 years in the control group. There were six men and two women in each group. The indications for transplantation were primary pulmonary hypertension (two patients), emphysema (three), cystic fibrosis (two), and Eisenmenger’s syndrome (one). The transplant recipients were clinically well at the time of study, with no cardiovascular or respiratory symptoms, no evidence of cardiac failure or fluid retention, and stable lung function tests. None of the patients had experienced episodes of dizziness or syncope, and none developed hypotension when standing. Left ventricular ejection fraction was assessed by gated radionuclide angiography.10 Their ejection fraction was 64±7% at rest and 73±7% during supine exercise at a work load of 45 W. The low yield of cardiac biopsies in heart-lung transplant recipients has led us to abandon biopsy as a method of monitoring heart-lung transplant patients,11 and, therefore, cardiac biopsy data are not available for these subjects. The studies were conducted a mean of 20 months (range, 4 to 30 months) after transplantation. All recipients were receiving cyclosporin, and five were receiving azathioprine. The mean trough plasma cyclosporin level, measured with a polyclonal radioimmunoassay (Instar Corp., Stillwater, Minn.) was 246±139 ng/ml. Other treatments were low-dose aspirin (five patients), dipyridamole (five), nifedipine (three), ranitidine (two), allopurinol (one), and pancreatic enzyme supplements (two). None of the patients were receiving α- or β-blockers, angiotensin converting enzyme inhibitors, diuretics, or steroid therapy. All medication, apart from cyclosporin, was omitted on the day of the study.

The normal subjects were well, had no history of cardiopulmonary disease, and were not receiving any medication. The transplant and the control groups were similar in height (172±10 and 169±7 cm, respectively) and weight (63±9 and 62±9 kg, respectively). The transplant recipients had a significantly higher serum creatinine level (151±32 versus 93±16 μmol/l, p<0.001).

Surgical Techniques and Consequent Denervation

The transplant operations were performed with techniques previously described.11 The heart and lungs were transplanted en bloc to replace the recipient’s diseased organs. Anastomoses were made between donor and recipient tracheas just above the carina and between donor and recipient ascending aortas. In five patients, the donor’s right atrium was anastomosed to a remnant of the recipient’s right atrium. In the other three patients, the operation was modified by performing separate anastomoses of the superior vena cava and inferior vena cava rather than the conventional anastomosis of donor to recipient right atrium; this modification allowed the heart-lung transplant recipient’s heart to be used for a subsequent “domino” heart transplant.12 In these three patients, no recipient atrial tissue was left in situ. The transplanted heart with the parenchyma and blood vessels of the transplanted lungs are completely denervated after transplantation. The arterial baroreceptors in the carotid sinus remain intact, although the extensive dissection required to remove the recipient’s diseased organs may affect the baroreceptors within the aortic arch. Persistent cardiac denervation was confirmed by the absence of a heart rate response to slow, deep respiration, to carotid sinus massage, or within 30 seconds of moving from a lying to a standing position.13 These are primarily tests of vagal innervation. A previous immunocytochemical study of hearts removed from heart-lung transplant recipients, at the time of retransplantation, showed them to contain nerves and ganglia that were positive for general neural markers and acetylcholinesterase. There was a marked reduction in neuropeptide tyrosine and tyrosine hydroxylase immunoreactive nerves, which is consistent with a loss of postganglionic sympathetic neurons after extrinsic cardiac denervation.14

Study Protocol

The subjects were studied in the late morning or the early afternoon, after a light breakfast and having fasted completely for 4–6 hours. The protocol was approved by the District Ethical Committee, and informed consent was obtained from all subjects. An intravenous cannula was inserted into a forearm vein near the antecubital fossa of the opposite arm to that used for blood pressure measurements. This was kept patent by intermittent flushing with heparinized saline for subsequent blood sampling.

The subjects lay supine on an electrically driven tilt table (Philips MT2, Philips Medical Systems, London) for 30 minutes. The table was then elevated to produce a head-up tilt of 45° with the subject supported by a foot board. The subjects were instructed not to contract their leg muscles during the procedure. The head-up posture was maintained for a period of 1 hour. Heart rate was measured at 5-minute intervals with a conventional electrocardiographic recorder at a paper speed of 50 mm/sec. Blood pressure was determined at 5-minute intervals with an automatic oscillometric blood pressure unit (Omega 1400, In Vivo Research Labs Inc., Broken Arrow, Okla.) with an appropriately sized cuff
applied to the upper arm. Cardiac output was measured at 15-minute intervals with Doppler aortic velocimetry.

Blood samples were obtained twice, at 5-minute intervals, before the commencement of the head-up tilt and then 30 and 60 minutes later. A total volume of 40 ml was removed on each occasion. The samples to be assayed for catecholamines, vasopressin, and renin levels were taken into chilled tubes containing lithium heparin. The atrial natriuretic peptide (ANP) sample was collected in a tube containing EDTA and aprotinin. The samples were immediately separated by centrifugation at 1,500 rpm for 10 minutes at 4°C. The plasma was stored in liquid nitrogen for subsequent analysis.

**Doppler Measurement of Cardiac Output**

Cardiac output measurements were obtained non-invasively with Doppler aortic velocimetry. The method and its validation have been described previously. Briefly, flow velocity was measured in the ascending aorta with the suprasternal approach with a 2-MHz pulsed Doppler instrument (Vingmed Pedof, Doptek, Chichester, U.K.). This was interfaced with a dedicated Fourier transform spectrum analyzer and display unit (Cardiology Doppler analyzer 9011, Doptek, Chichester). The position, angulation, and sampling depth of the probe were adjusted to maximize the peak velocity recorded while minimizing the spectral broadening of the signal. The audio frequency Doppler signals and electrocardiogram were recorded on magnetic tape for subsequent analysis. The recordings were replayed through the spectrum analyzer, and the signal amplitude of the 80 frequency bands were logged to a laboratory microcomputer (Research Machines 380Z, Research Machines, Oxford, UK) every 5 msec. The signals of at least 20 beats were ensemble averaged for each measurement by gating to the QRS complex of the electrocardiogram. The intensity-weighted mean frequency was calculated for each 5-msec period and converted to velocity with the Doppler equation. This velocity was integrated over the cardiac cycle to derive the ‘stroke distance.’ The aortic root diameter was measured by two-dimensional directed M-mode echocardiography ( Biosound ND256-8, Biosound Inc., Indianapolis, Ind.) and used to calculate aortic area. Stroke volume was calculated as the product of stroke distance and cross-sectional area.

An index of systemic vascular resistance, in arbitrary units, was calculated from the ratio of mean arterial pressure in millimeters of mercury (calculated as two thirds diastolic pressure plus one third systolic pressure) to cardiac output in liters per minute, assuming that the central venous pressure was negligible.

**Hormone Assays**

Norepinephrine and epinephrine concentrations were measured with high-performance liquid chromatography as described previously. Briefly, plasma samples were extracted by adsorption onto alumina, and catecholamines were back extracted with acetic acid. As an internal standard, 3,4-dihydroxybenzylamine was used. Chromatography was performed with a 25-cm, 5-μm Ultrasphere ODS analytical column (Beckmann-RIIC Ltd., High Wycombe, U.K.) with a reverse-phase ion pair system and an electrochemical detector (Coulochem model 5100A, ESA Inc., Bedford, Mass.). The detection limit for both catecholamines in plasma was 0.02 nmol/l.

ANP was measured by radioimmunoassay as previously described. Plasma was extracted with Sep-Pak columns (Waters Associates, Boston, Mass.), was reconstituted in phosphate buffer, and was assayed with rabbit antiserum to α-human ANP (Peninsula Laboratories, Merseyside, U.K.), 125I-labeled ANP (Amersham International, Amersham, U.K.), and synthetic atriopeptin III standard (Peninsula Laboratories). The detection limit for ANP in plasma was 2.0 pmol/l.

Plasma renin activity was measured by radioimmunoassay of angiotensin I generated by incubation of 1-ml plasma samples for 2 hours at 37°C at pH 6 in the presence of angiotensin converting enzyme inhibitors. The assay used angiotensin I standard (Peninsula Laboratories), 125I-labeled angiotensin I (Amersham International), and specific antiserum (gift from Professor W.S. Peart, Department of Medicine, St.Mary’s Hospital School, London, UK).

Arginine vasopressin was measured by radioimmunoassay as previously described after extraction from plasma with Sep-Pak columns. The First International Standard for arginine vasopressin (National Institute for Biological Standards, Hampstead, U.K.), 125I-labeled arginine vasopressin (Amersham International), and specific arginine vasopressin antiserum (gift from Dr. P.H. Bayliss, Department of Medicine, Royal Victoria Infirmary, Newcastle-Upon-Tyne, UK) were used in the assay. The detection limit in plasma was 0.2 pmol/l.

**Statistical Analysis**

Results are expressed as mean±SEM. The baseline characteristics of the two groups were compared by use of Student’s t test for independent samples. A p value less than 0.05 in a two-tailed test was considered significant. The changes that occurred during the tilt procedure were evaluated with analysis of variance for repeated measures. The patterns of response were compared by examining the interaction of group and time effects within the analysis of variance.

**Results**

All the subjects tolerated the procedure well, and none developed symptoms suggestive of a vasovagal reaction.

**Cardiovascular Response**

All subjects were in sinus rhythm. The transplant recipients had a higher initial heart rate than did the
control subjects (99±2 versus 68±2 beats/min, p<0.001) (Figure 1). Baseline systolic blood pressure tended to be higher in the transplant group (140±5 versus 127±6 mm Hg, p=NS). Initial diastolic pressure was significantly higher in the transplant group (88±5 versus 76±2, p<0.05).

The heart rate of both groups rose significantly (p<0.001) within 5 minutes of head-up tilt. No significant change occurred in systolic blood pressure in either group. Diastolic blood pressure increased after head-up tilt in both groups, although the increase was significant only in the control group (p<0.05).

Baseline stroke volumes of the transplant group tended to be lower than those of the control group (63±7 versus 81±11 ml, p=NS) (Figure 2). Cardiac output tended to be slightly higher in the transplant group (5.9±0.6 versus 5.3±0.5 l/min, p=NS) because of their higher resting heart rates. The index of systemic vascular resistance was similar in the two groups. After head-up tilt, stroke volume decreased in both groups (p<0.001) and so did cardiac output (p<0.001). The decrease was proportionately greater in the transplant group (30% versus 18%, p<0.05). The index of systemic vascular resistance increased significantly in both groups (p<0.001), and the increase was significantly greater in the transplant group (52% versus 28%, p<0.05).

**Neuroendocrine Response**

The initial norepinephrine concentration was similar in the transplant recipients and the control subjects (2.8±0.5 versus 2.2±0.4 nmol/l, p=NS) (Figure 3). After head-up tilt, norepinephrine concentrations increased significantly in both groups (p<0.001), and the increase was significantly greater in the transplant group (83% versus 56%, p<0.01). Epinephrine concentrations were an order of magnitude lower than those of norepinephrine. The initial concentrations tended to be higher in the control group (0.17±0.07 versus 0.28±0.06 nmol/l, p=NS). During head-up tilt, the levels increased significantly...
FIGURE 3. Plots of norepinephrine and epinephrine levels before and during head-up tilt. ●, Heart-lung transplant recipients; ○, control subjects. See text for statistical analysis.

FIGURE 4. Plots of plasma renin activity (PRA), vasopressin, and atrial natriuretic peptide (ANP) before and during head-up tilt. AI, angiotensin I. ●, Heart-lung transplant recipients; ○, control subjects. See text for statistical analysis.

(p<0.001), and the pattern of response was similar in the two groups.

Baseline plasma renin activity was similar in the transplant recipients and the normal subjects (2.38±0.75 versus 2.93±0.42 ng Ang I/ml/hr, respectively) (Figure 4). After head-up tilt, there was a significant increase in plasma renin activity in the control group (p<0.001) but not in the transplant group. The pattern of response was significantly different in the two groups (p<0.05).

Initial ANP concentrations were considerably higher in the transplant recipients (26±3.8 versus 9.7±1.6 pmol/l, p<0.001). The mean ANP concentration in the three patients in whom no recipient atrial tissue was present was 30.9±9.6 compared with 23±2.4 pmol/l in the patients with a conventional atrial anastomosis (p=NS). After head-up tilt, ANP concentrations decreased in both groups (p<0.05). The patterns of response were similar.

Baseline vasopressin concentrations were similar in the transplant and control groups (2.6±0.5 pmol/l versus 2.5±0.5 pmol/l, respectively, p=NS). Neither group showed a significant increase in vasopressin concentration after head-up tilt.

Discussion

Head-up tilt produces a decrease in stroke volume by reducing venous return and ventricular preload. This activates cardiopulmonary and arterial baroreceptor reflexes, resulting in increased heart rate and contractility with vasoconstriction and associated neuroendocrine changes. The stimulus used in the present study was sufficient to activate the arterial baroreceptors in normal subjects. In the absence of input from cardiopulmonary receptors, in the heart-lung transplant group, the response to gravitational stress was largely dependent on the arterial baroreceptors. Arterial baroreceptor function has not been previously studied in heart-lung transplant recipients, but it has been shown to return to normal soon after heart transplantation. None of the heart-lung transplant recipients experienced postural hypotension on standing. Passive head-up tilt provides a greater orthostatic stress than standing, which increases skeletal muscle activity and can augment venous return to the heart. The heart-lung transplant recipients were able to maintain their systemic blood pressure under the conditions of the study and tolerated the procedure well without developing any symptoms. A more severe orthostatic stress might have produced symptoms in the transplant group, but
such stimuli can also provoke vasovagal reactions in normal subjects.23

**Potential Limitations of Doppler Measurement of Cardiac Output**

Noninvasive measurement techniques have the advantages that they can be readily applied to normal subjects and they reduce the chance of altering the system being studied. This is particularly important in head-up tilt studies because of the high incidence of vasovagal reactions that occur with invasive monitoring.24

Doppler measurement of cardiac output is subject to errors due to a possible angulation of the Doppler beam to the true direction of flow and to uncertainty in the cross-sectional area at the point where flow is measured.25 Although these factors could affect the absolute values of cardiac output, they would be constant in any subject throughout the study, and the relative changes in stroke volume and cardiac output would not be affected. The change in stroke volume in the control group in this study was 32%. This is similar to a previous study that found a 41% reduction in stroke volume with 45° head-up tilt26 and another that found a 37% reduction in stroke volume with 60° head-up tilt27 in normal subjects.

**Cardiovascular Response**

The higher initial heart rates of the transplant group were due to the absence of vagal tone.2 Despite efferent cardiac denervation, the increase in heart rate was similar to that in the control group, although it was proportionately less in the transplant recipients. Because stroke volumes tended to be lower in the transplant group, there was no significant difference in initial cardiac output.

The greater decrease in cardiac output in the transplant recipients after tilting was unlikely to be due to impaired left ventricular function. All the subjects were in a stable clinical condition with no signs of cardiac failure, and their left ventricular ejection fractions were normal. Left ventricular contractile function and reserve have been shown to be normal after heart transplantation.28 A previous study found that left ventricular ejection fraction and volumes were similar in healthy heart and heart-lung transplant recipients.29 Left ventricular diastolic function appears to be normal after heart-lung transplantation.29 The altered cardiac response can, however, be related to the effect of denervation on cardiac performance because of elimination of direct sympathetic augmentation of heart rate and contractility.30 The sympathetic nervous system may play an indirect role in the cardiac response through the effects of circulating catecholamines (see below).

The higher initial blood pressure in the transplant group was probably due to cyclosporin therapy, which is known to be associated with hypertension in heart31,32 and kidney33 transplant recipients. Blood pressure was maintained during head-up tilt by a greater degree of systemic vasoconstriction in the transplant group.

Our aim was to determine the response to a sustained postural stress. Rapid beat-by-beat responses of heart rate are dependent on cardiac innervation and are abolished after transplantation, but the transient response at the onset of tilting was not assessed in this study.

**Sympathetic Response**

Circulating norepinephrine levels are frequently used as an index of sympathetic nervous system activity.34 The main source is spillover of norepinephrine released from the axon terminals of sympathetic neurons. About half of the norepinephrine in the venous blood from the forearm originates from local tissues and the remainder from arterial blood.35 The concentrations measured in this study, thus, were biased toward measuring sympathetic activity in the forearm. Sympathetic responses often vary between regions; for example, one study found that postural changes affected vascular resistance in the forearm but not that in the leg.36 The increase in norepinephrine concentration in normal subjects during head-up tilt reflects increased sympathetic activity produced by the activation of baroreceptor reflexes to maintain blood pressure.37 A number of factors might have contributed to the increased sympathetic response in the transplant group. It might have been due to an increased activation of the arterial baroreceptor reflexes related to the greater decrease in cardiac output. Another possible mechanism for the increased response is the loss of tonic inhibition of the sympathetic nervous system from cardiac and pulmonary afferents after denervation.38 In addition, the lack of plasma renin response in the transplant recipients would result in a loss of angiotensin II-mediated vasoconstriction,39 requiring a greater degree of sympathetic activity to produce vasoconstriction. Furthermore, the response of the peripheral vasculature to sympathetic stimulation might have been altered in the transplant recipients. Evidence for this possibility comes from a study that found that heart transplant recipients required an increased dose of the α1-agonist methoxamine to produce an equivalent rise in blood pressure compared with normal subjects.40

The concentration of norepinephrine during head-up tilt for the transplant and control groups remained below the threshold that produces hemodynamic effects in normal subjects.41 Norepinephrine, however, might have contributed to the heart rate response in the transplant group because the transplanted, denervated heart has been found to be supersensitive to endogenous catecholamines in animals42 and humans.43 Epinephrine levels were an order of magnitude lower than norepinephrine in both groups. Epinephrine is, however, 10 times more potent than norepinephrine, and the threshold for producing hemodynamic effects lies within the physiological range.44 Thus, the small increase in epi-
Atrial Natriuretic Peptide during nephrine infusion in heart transplant recipients.46 The renin response to isoprenaline infusions in heart transplant recipients receiving cyclosporin is blunted.47 Cyclosporin could also have indirectly affected plasma renin activity by altering renal function and circulating volume. Volume expansion can result in suppression of plasma renin activity and elevated ANP levels. None of the transplant recipients had clinical evidence of fluid retention or volume overload. Because circulating volume was not measured in the present study, we cannot exclude the possibility that a mild degree of volume expansion contributed to the absence of a renin response. An expansion of plasma volume has been described in hypertensive heart transplant recipients treated with cyclosporin.48 The subjects in that study were also receiving prednisolone, whereas none of the patients in the present study were treated with steroids.

The high concentration of ANP in the transplant group might have suppressed the renin response because infusion of ANP can inhibit the renin response to head-up tilt in normal subjects.49 The role of atrial and pulmonary innervation in renin release is discussed below.

Atrial Natriuretic Peptide and Vasopressin Responses

The high levels of ANP in the transplant group were similar to those that have been observed in heart transplant recipients.50 The mechanism underlying this increase in ANP has not been established. It is not due to cyclosporin therapy because it is seen in heart transplant recipients treated with steroids and azathioprine.51 In heart transplant recipients, it may be due to the excess atrial tissue that is present after the transplant procedure. This is unlikely to be the case in heart-lung transplant recipients because of the minimal excess of atrial tissue present. Although the number of subjects was small, ANP levels actually tended to be higher in the patients in whom no recipient atrial tissue remained. The ANP response in the transplant group indicates that ANP secretion is modulated by physiological factors acting directly on the heart rather than by the central nervous system.

Vasopressin levels did not increase significantly during head-up tilt in either group. This is consistent with the results of a study that used a similar protocol in normal subjects.21 Other investigators have shown an increase in vasopressin concentration during head-up tilt,23 but the subjects were dehydrated before the procedure and were tilted at a greater angle (85°). Thus, the difference probably relates to the strength of the stimulus used. Theoretically, the reflex release of vasopressin could be impaired in heart-lung transplant recipients after denervation of cardiopulmonary receptors, but this could not be demonstrated under the conditions of the present study. There was, in fact, a suggestion of a vasopressin response in the transplant recipients that might have been due to increased arterial baroreceptor activation in this group.

Comparison With Heart Transplant Recipients

The objective of the present study was to examine blood pressure control during sustained postural stress in human subjects after complete cardiopulmonary denervation. It is of interest to consider the results in the light of information available on heart transplant recipients. Both types of transplantation result in efferent and afferent denervation of the heart. In heart transplantation, portions of the recipient's atria and the pulmonary circulation remain innervated, whereas these structures are denervated after heart-lung transplantation.

The altered control of heart rate and cardiac output seen after denervation are common to both groups. Heart transplant recipients have increased resting heart rates due to an absence of vagal tone, and the heart rate response is heavily dependent on circulating catecholamines.4 Consequently, they have a sluggish heart rate and cardiac output response to dynamic exercise52 and no cardiac response during transient isometric exercise.53 An increased sympathetic response has been observed during dynamic exercise that may be due to altered cardiac performance.17

The enhanced sympathetic response in the heart-lung transplant group in the present study contrasts with the findings of a previous study in heart-transplant recipients in whom the response to lower-body negative pressure was impaired.5 In that study, lower-body negative pressure did not activate the arterial baroreceptors, and the lack of response was attributed to ventricular deafferentation. The results are consistent with those of another study conducted in heart transplant patients in whom lower-body negative pressure sufficient to reduce arterial pressure and stimulate arterial baroreceptors resulted in an exaggerated sympathetic response.54

The lack of a renin response in the heart-lung patients in the present study could be related to the effects of cyclosporin on the kidney and high levels of ANP. The observation that hypovolemia increases...
renin levels in heart transplant recipients receiving cyclosporin\textsuperscript{55} suggests, however, that this is not the mechanism. An alternative explanation relates to the denervation of the atria and pulmonary veins. In subprimate mammals, there is a specific relation between the activity of atrial stretch receptors and sympathetic nerve traffic to the kidney.\textsuperscript{7} Interruption of vagal afferent input from cardiopulmonary receptors inhibits the renin response to hypovolemia in anesthetized dogs.\textsuperscript{56} Thus, the failure of renin levels to increase in the heart-lung transplant group could have been a consequence of the complete loss of afferent input from cardiopulmonary receptors.

Heart-lung transplant recipients were selected for the present study because, if clinically important problems with blood pressure control did not occur, they would be unlikely to occur in either lung or heart transplantations where denervation is less extensive. It was recently observed, however, that although diastolic left ventricular function is impaired in human cardiac allografts it is normal in heart-lung allografts.\textsuperscript{29} The reason for this difference is unknown. It could be due to the different organ preservation techniques used in heart and heart-lung transplantation, or it could be due to immunologic protection of the transplanted heart by the transplanted lungs.\textsuperscript{11} This raises the possibility that cardiopulmonary receptors are more sensitive to orthostatic stress because of a greater dependence on ventricular preload. One study found that heart transplant recipients could maintain blood pressure during hypovolemia induced by diuretics and upright posture; there was an associated increase in heart rate, but cardiac output was not measured.\textsuperscript{55}

Further studies involving the direct comparison of heart and heart-lung transplant patients are required to clarify these issues.

Conclusions

Afferent information from cardiopulmonary receptors and efferent cardiac innervation were not essential to maintain systemic blood pressure under the conditions of this study. The type of gravitational stress used was sufficient to activate arterial baroreceptors and was selected to look for abnormalities with important clinical implications. The transplant group tolerated the procedure without developing symptoms, but the pattern of the cardiovascular and neuroendocrine responses was altered. The decrease in cardiac output was greater, indicating that the compensatory mechanisms available may be less effective. Systemic blood pressure was maintained by a greater degree of vasoconstriction that appeared to be due to an increased sympathetic response. The increase in circulating catecholamine levels probably accounted for the heart rate response of the transplant group. The impaired renin response might have been due to the effects of cyclosporin on the kidney or on circulating volume, cardiopulmonary deaferentation, or the high level of ANP in the transplant group.

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