Renin release during head-up tilt occurs independently of sympathetic nervous activity in tetraplegic man

C. J. MATHIAS*, N. J. CHRISTENSEN†, H. L. FRANKEL‡ AND W. S. PEART*

*Medical Unit, St Mary's Hospital Medical School, London, †National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, U.K., and ‡Department of Internal Medicine and Endocrinology, Herlev Hospital, Herlev, Denmark

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Summary

1. The role of the sympathetic nervous system in the release of renin during head-up tilt has been studied in five normal subjects and in four tetraplegic patients with cervical spinal-cord transection above the sympathetic outflow. Blood pressure, heart rate and concentrations of plasma noradrenaline, plasma adrenaline and plasma renin activity were measured during head-up tilt to $45^\circ$ before and after acute $\beta$-adrenoreceptor blockade with intravenous propranolol.

2. In the normal subjects there were minimal changes in blood pressure during head-up tilt and there was a rise in both plasma noradrenaline concentration and plasma renin activity. After propranolol values of plasma renin activity at rest fell with little change occurring during head-up tilt.

3. In the tetraplegic patients there was a substantial fall in blood pressure during head-up tilt. Concentrations of plasma noradrenaline and adrenaline did not change but there was a marked increase in plasma renin activity. Values of plasma renin activity both at rest and during head-up tilt were unaffected by propranolol.

4. We conclude that in tetraplegic patients renin release during head-up tilt may occur independently of sympathetic nervous activity and is probably largely dependent on activation of renal vascular receptors.

Key words: catecholamines, posture, propranolol, renin, sympathetic nervous system, tetraplegia.

Introduction

In man there is debate over the extent to which the sympathetic nervous system controls renin release. Some workers claim that adrenergic control is dominant and this is thought to be entirely so during orthostasis (Davies & Slater, 1976). However, in subjects with impaired sympathetic nervous function due either to cervical spinal-cord transection (Johnson, Park & Frankel, 1971; Mathias, Christensen, Corbett, Frankel, Goodwin & Peart, 1975) or to widespread autonomic lesions (Bannister, Sever & Gross, 1977), renin release may occur during head-up tilt. Similar changes occur during postural change in bilaterally nephrectomized subjects with denervated transplanted kidneys (Horvath, Baxter, Furby, Hood, Johnson, McGrath & Tiller, 1976). Although these findings suggest that posture-induced renin release may occur independently of the sympathetic nervous system, it may be argued that in these subjects renal $\beta$-adrenoreceptor stimulation, secondary to an elevation in circulating catecholamines, resulted in the rise in renin. To investigate this further we studied tetraplegic patients in whom there was no connection between the brain and the peripheral sympathetic nervous system. In these subjects orthostatic hypotension occurs because of their inability to reflexly increase sympathetic nervous activity. Renin and
catecholamine release during head-up tilt have
been studied before and after acute β-adreno-
receptor blockade with intravenous propranolol.
Similar studies were performed in normal
subjects.

Subjects and methods

Four male tetraplegic patients aged 24–35 years
(mean 28 years) with physiologically complete
cervical spinal-cord transections between C4 and
C8 were studied. All were otherwise in good
health and there was neither biochemical nor
radiological evidence of impaired renal function.

Five healthy normal subjects (three male and two
female) aged between 21 and 35 (mean 25) years
were studied as controls. Neither the tetraplegic
patients nor the control subjects were on drugs.

All subjects were on unrestricted diets and
were studied after resting horizontally for 60 min.

In the tetraplegic patients blood pressure was
measured by an intra-arterial catheter, heart rate
was electronically derived from the arterial
pressure signal (Mathias et al., 1975) and the
electrocardiograph was continuously monitored
on an oscilloscope and intermittently recorded.

From a three-way connector attached to the
arterial catheter blood was withdrawn for
measurement of plasma noradrenaline and
plasma adrenaline. Blood for estimation of
plasma renin activity was simultaneously with-
drawn from a cannula in a forearm vein.

Noradrenaline and adrenaline were measured by
a double-isotope technique (Christensen, 1973)
and plasma renin activity by radioimmunoassay
(Boyd, Adamson, Fitz & Peart, 1969).

Measurements were made while the patients were
horizontal (−15 and 0 min), after 10, 20 and 30
min of head-up tilt to 45° on an electrical tilting
bed, and 10 and 20 min after return to the
horizontal. The patients then had lunch and
relaxed for 60 min. After they had rested
horizontally for a further 60 min, the study was
repeated while propranolol (0.01 mg min−1 kg−1
body weight) was infused intravenously. Head-up
tilt was performed 30 min after the start of the
infusion which was stopped at the end of the
period of tilt. Blood propranolol concentrations
were measured by gas–liquid chromatography
(McAinsh, Baber, Smith & Young, 1978), 40, 50
and 60 min after the start of the infusion which
coincided with 10, 20 and 30 min of tilt.

In the control subjects, a similar protocol was
used except that blood pressure was measured by
using a sphygmomanometer and heart rate was
calculated from the electrocardiogram. Blood
was collected via a cannula in a forearm vein.

Statistical analysis of the results between
groups was performed using Wilcoxon's rank
sum test for unpaired data. Paired t-tests were
used for data comparisons within groups. Results
are expressed as means ± SEM.

Results

Blood pressure

In the tetraplegic patients, mean resting
systolic and diastolic blood pressure were
107 ± 3.5 and 56 ± 1.9 mmHg respectively and
both were significantly lower than in the controls
(P < 0.05 and P < 0.05 respectively; Fig. 1).
During head-up tilt there was a pronounced fall in
blood pressure (Fig. 2), the maximum change
occurring during the first 5 min of tilt. There was
an initial blood pressure over-shoot after patients
returned to the horizontal.

![Graphs showing blood pressure, plasma renin activity, heart rate, and concentrations of plasma noradrenaline and plasma adrenaline in four tetraplegic patients and five normal subjects. Bars indicate ± SEM.](image-url)
Renin release independent of sympathetic activity

**FIG. 2.** Effect of head-up tilt to 45° on mean values of blood pressure, heart rate and plasma renin activity in four tetraplegic patients before and during an intravenous infusion of propranolol (0.01 mg min⁻¹ kg⁻¹). Systolic and diastolic blood pressure are separately plotted. Bars indicate ±SEM.

**FIG. 3.** Effect of head-up tilt to 45° on mean values of blood pressure, heart rate and plasma renin activity in five normal subjects before and during an intravenous infusion of propranolol (0.01 mg min⁻¹ kg⁻¹). Systolic and diastolic blood pressures are separately plotted. Bars indicate ±SEM.

In the control subjects, head-up tilt resulted in minimal changes in blood pressure and there was no overshoot on return to the horizontal (Fig. 3). In neither group did propranolol affect blood pressure either at rest or during and after head-up tilt.

**Heart rate**

In the tetraplegic patients, mean resting heart rate was 69 ± 1.5 beats/min, similar to the value in the control subjects (67 ± 1.9 beats/min). During head-up tilt, heart rate rose significantly (P < 0.05). Propranolol did not significantly lower resting heart rate and there was no rise in the mean heart rate during head-up tilt because in two tetraplegic patients the heart rate rose whereas in the other two heart rate fell.

In the control subjects, head-up tilt caused a small but significant rise in heart rate (P < 0.05). Within 15 min of infusion of propranolol, resting heart rate had significantly fallen from 68 ± 2.4 to 59 ± 2.3 beats/min (P < 0.01). Head-up tilt during propranolol infusion resulted in an insignificant rise in heart rate.

**Plasma noradrenaline and adrenaline**

In the tetraplegic patients, mean resting concentrations of noradrenaline, but not adrenaline, were significantly lower than in the control subjects (P < 0.05; Fig. 1). Arterial and venous concentrations of catecholamines in tetraplegic patients are similar (Mathias, Christensen, Corbett, Frankel & Spalding, 1976) and it is therefore acceptable to compare arterial values in the tetraplegic patients with venous values in the control subjects. During head-up tilt, both before and after propranolol, there were minimal changes in catecholamine concentrations (Fig. 2).

In the control subjects, head-up tilt resulted in a significant rise in noradrenaline concentrations (P < 0.05). Propranolol did not significantly change either resting catecholamine values or responses to head-up tilt in either group.

**Plasma renin activity**

In the tetraplegic patients, resting values of plasma renin activity were significantly higher...
than in the control subjects \( (P < 0.05; \text{Fig. 1}) \). Head-up tilt resulted in a marked rise in plasma renin activity \((\text{Fig. 2})\). Propranolol had no effect on plasma renin activity either at rest or during head-up tilt.

In the control subjects, plasma renin activity rose during head-up tilt, although the magnitude of rise was less than in the tetraplegic patients \((\text{Fig. 3})\). Propranolol lowered resting plasma renin activity significantly \( (P < 0.01) \) within 15 min of infusion and effectively suppressed the response to head-up tilt.

**Blood propranolol**

In the tetraplegic patients, mean blood propranolol concentrations 40, 50 and 60 min after the start of the infusion were \( 148 \pm 25, 207 \pm 38 \) and \( 185 \pm 57 \) ng/ml respectively. In the control subjects, concentrations at similar times were \( 141 \pm 23, 157 \pm 8 \) and \( 105 \pm 13 \) ng/ml respectively.

**Discussion**

In the tetraplegic patients there was no connection between the brain and the peripheral sympathetic nerves. The absence of supra spinal impulses resulted in a low resting value of sympathetic activity and this is consistent with the findings of subnormal noradrenaline concentrations and low resting systolic and diastolic blood pressure \((\text{Mathias et al., 1976})\). Resting plasma renin activity in the tetraplegic patients, however, were higher than in the control subjects and were not influenced by propranolol, suggesting that resting values in man need not necessarily be largely dependent on neural mechanisms, as has been previously claimed \((\text{Leonetti, Mayer, Morganti, Tensoli, Zanchetti, Bianchetti, Di Salle, Morselli & Chidsey, 1975})\). The elevated values may be part of a compensatory humoral response to maintain blood pressure, or may reflect intrarenal circulatory events.

Head-up tilt in the tetraplegic patients resulted in a marked fall in blood pressure. There was little change in noradrenaline and adrenaline concentrations, as would be expected if the brain failed to activate sympathetic efferent pathways. Plasma renin activity rose considerably during head-up tilt, suggesting release of renin by mechanisms operating independently of the sympathetic nervous system. It may be argued, however, that sympathetic reflexes operating at a spinal level accounted for the rise in plasma renin activity and that these were not reflected in plasma noradrenaline changes. Propranolol reduced the heart rate response to tilt in two tetraplegic patients, suggesting that neural or humoral stimulation of cardiac \( \beta \)-adrenoceptors may contribute to tachycardia during hypotension, in addition to withdrawal of vagal tone. In tetraplegic patients cutaneous and visceral stimulation can evoke spinal sympathetic discharges associated with hypertension and rise in plasma noradrenaline concentrations \((\text{Guttman & Whitteridge, 1947; Corbett, Frankel & Harris, 1971; Mathias et al., 1976})\). Such stimulation possibly occurred during the period of tilt, but is unlikely to have accounted for the renin responses as there is evidence that such reflex activity does not elevate plasma renin activity \((\text{Nanniga, Rosen & Krumlovsky, 1976})\).

In a previous study \((\text{Mathias et al., 1975})\) we observed, in addition to the rise in renin activity, a slow but progressive rise in noradrenaline concentration during head-up tilt. The maximum rise, however, was still far less than that achieved by normal subjects. Angiotensin II interacts with the sympathetic nervous system and may have raised noradrenaline concentrations either by increasing its biosynthesis, facilitating its release or inhibiting its uptake \((\text{Khairallah, Davila, Papanicolau, Glende & Meyer, 1971; Roth, 1972; Zimmerman, Gomer & Liao, 1972})\). Alternatively, the rise in noradrenaline may have stimulated the release of renin. Experimental studies indicate that catecholamines release renin by stimulation of \( \beta \)-adrenoreceptors \((\text{Vandongen, Peart & Boyd, 1973})\) and not \( \alpha \)-adrenoreceptors \((\text{Vandongen & Peart, 1974})\); there is, in fact, evidence that stimulation of the latter inhibits release of renin \((\text{Vandongen & Peart, 1974; Pettinger, Keaton, Campbell & Harper, 1976})\). In the tetraplegics it was unlikely that stimulation of intrarenal \( \beta \)-adrenoreceptors accounted for the rise in renin activity during tilt as propranolol had no effect on the renin response. Substantial \( \beta \)-adrenoreceptor blockade was probably achieved as blood propranolol concentrations were similar to those known to cause almost 100% cardiac \( \beta \)-adrenoreceptor blockade to endogenous sympathetic stimuli in normal man \((\text{Coltart & Shand, 1970})\). Furthermore, after an identical dose-infusion of propranolol, tetraplegic patients need over 30 times the pre-propranolol isoprenaline dose before cardiac and vascular receptors are similarly stimulated \((\text{Mathias, 1976})\).

In the control subjects, the cardiovascular and hormonal responses to head-up tilt both before and after propranolol were consistent with previous observations \((\text{Tuckman & Shillingford, 1976})\).
propranolol, both at rest and during head-up tilt, indicates a role for the sympathetic nervous system and in particular for β-adrenoreceptors in the release of renin. In the tetraplegic patients, however, the inability of propranolol to affect plasma renin activity, either at rest or during head-up tilt, suggests that in them renin release occurred independently of the sympathetic nervous system and may have been largely dependent on activation of renal vascular receptors (Blaine, Davis & Prewitt, 1971). A major stimulus to release renin is probably autoregulatory vasodilatation and this may be modulated and potentiated by sympathetic impulses (Eide, Løyning & Kiil, 1973, 1974). This is in agreement with studies in normal subjects made hypertensive by infusion of sodium nitroprusside in whom the marked elevation in plasma renin activity was the major factor in the release of renin.

In man, propranolol raises systemic vascular resistance and reduces peripheral blood flow and this is thought to be the sum of blockade of vasodilator β₂-adrenoreceptors and unopposed α-adrenoreceptor-mediated vasoconstriction, often in the face of raised circulating catecholamines (Christensen, Trapp-Jensen, Clausen, Noer, Krosgaard & Andree-Larsen, 1975; Hanson, Hesse & Christensen, 1978; McSorley & Warren, 1978). Propranolol reduces renal blood and plasma flow by a combination of reduced cardiac output and the mechanisms described above (Carriere, 1969; Abdel-Razzak, 1977; Falchi, Odengård & Norman, 1979). The case for renin release being more dependent on vasodilatation in the afferent arteriole than on any other factor is compelling; this allows for opposing effects of vasoconstriction and vasodilatation, produced by sympathetic nerve stimulation, by drugs or by autoregulation, to be interpreted in relation to stretch of the afferent arteriole (Pearl, 1979). It is possible that in normal man propranolol affects renin release by its renal vascular effects of β-adrenoreceptor blockade, with concomitant lack of vasodilatation, and increased α-adrenergic activity, with vasoconstriction. In the tetraplegic patients, it is tempting to speculate further and attribute the inefficacy of propranolol in suppressing plasma renin activity to its inability to significantly alter afferent arteriolar dilatation in kidneys with impaired neural and humoral vasoconstrictor activity.

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