Paraplegia **21** (1983) 72–80

ORTHOSTATIC VASOMOTOR RESPONSE IN SPINAL MAN*

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Summary. The cardiovascular adaptation of tetraplegics to the upright position has been previously demonstrated to be deficient. Presumably this is due to the interruption of the spinal pathways linking supraspinal control centres with the peripheral sympathetic motorneurons. Review of previous studies of this phenomenon reveals that vasomotor responses have been determined primarily from blood flow measurements in the extremities. Contradictory conclusions have been drawn. Study of the visceral circulation, in particular renal blood flow, could shed more light on this poorly understood area. Renal clearance tests were carried out on seven healthy controls and eight chronic, clinically complete tetraplegic patients. Renal blood flow, mean arterial pressure, and total renal vascular resistance in both supine and passive head-up tilt positions were calculated from collected data. Renal blood flow and total renal vascular resistance showed significant decrease and increase respectively during tilting in controls and tetraplegic subjects. Although the renal circulation is autoregulated, postural change causes profound alteration of the renal blood flow mediated through the haemodynamic effects of the renal nerves. Sympathetic renal vasoconstriction is mediated by the carotid sinus reflex through the vasomotor centre in the brainstem. In the absence of supraspinal influence the renal vasculature is shown to respond to an orthostatic stimulus with a vigorous vasoconstriction. The adaptation of spinal man to the upright position may involve the recovery of a spinal vasomotor reflex involving the splanchnic circulation.

Key words: Tetraplegia; Head-up tilt; Renal circulation; Vasoconstriction.

Introduction

IN tetraplegic man the cardiovascular response to the upright position is deficient. Presumably this is due to the interruption of the spinal pathways linking supraspinal control centres with the peripheral sympathetic outflow (Fig. 1).

In the acute phase associated with spinal shock there is a marked reduction in blood pressure which results in loss of consciousness shortly after assumption of the upright position. The heart rate increases as the result of decreased vagal tone but this compensatory response is insufficient

*Read at the Annual Meeting of the International Medical Society of Paraplegia, Stoke Mandeville Hospital, Aylesbury, Bucks., England. July 1981.

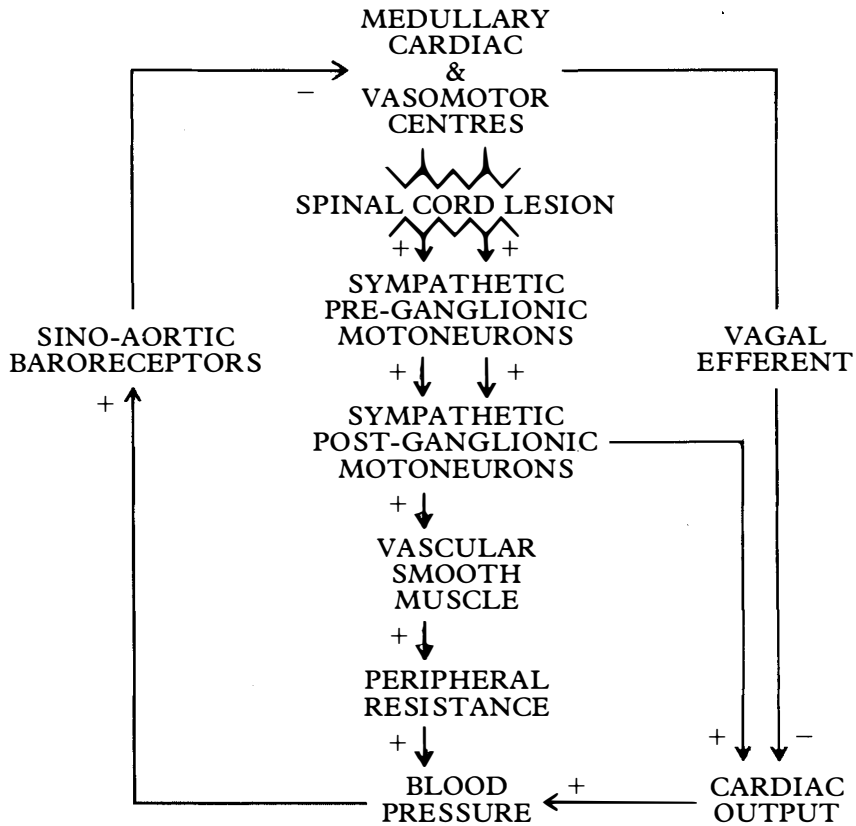

FIG. 1
Disruption of Autonomic Cardiovascular Regulation in Tetraplegia

to maintain an adequate circulating blood volume. There appears to be a lack of sympathetic response to orthostasis in acute cervical spinal cord injury as evidenced by decreased norepinephrine production during tilt (Guttmann *et al.*, 1963).

In the chronic stage the tetraplegic individual still experiences a definite fall in arterial blood pressure when tilted in the head-up position. However, with time and gradual conditioning most tetraplegic individuals are able to tolerate the upright position for prolonged periods without developing signs of cerebral ischaemia. It is not clear by what mechanism this readaptation process occurs.

Previous studies of vasomotor responses of chronic spinal cord injured subjects to tilting have focused on the peripheral circulation. Bidart and Maury (1973) studied venous compliance in the foot during tilting and found venous tone to be unchanged from supine. They concluded that the vasomotor response to tilting is lost below the level of the spinal cord lesion. Corbett *et al.* (1971) reported decreased forearm blood flow and increased peripheral venous pressure during tilting of chronic tetraplegic subjects which they interpreted as evidence of reflex sympathetic vasoconstriction.

The behaviour of the splanchnic circulation is extremely important to the maintenance of cardiovascular homeostasis in the upright position. Knowledge of the splanchnic blood flow in chronic tetraplegia would be helpful in understanding spinal man's readaptation to the erect posture. The kidney presents a splanchnic organ whose haemodynamic responses may be studied accurately and with a minimum of physiological disruption. The object of the present study is to compare the changes in renal blood flow and renal vascular resistance induced by passive head-up tilt (HUT) of chronic tetraplegic subjects with those of able-bodied control subjects.

Methods

Eight tetraplegic subjects were included in this study. All were tetraplegic as the result of traumatic spinal cord injury. The levels of injury were from C4 to C7. The lesions were clinically complete; that is, there was no detectable somatic motor or sensory function below the level of the lesion on physical examination. The duration of tetraplegia ranged from four months to nine years with six of the subjects having been injured eight months or less. All of the subjects had participated or were participating in a rehabilitation programme and could tolerate several hours of wheelchair-sitting each day. They ranged in age from 19 to 30 years with an average of 23 years. Seven were male and one was female. They were free of urinary infection and calculi. All had normal BUN and serum creatinine. The control subjects were seven healthy able-bodied males, aged 25 to 52 years with a mean of 34 years.

All subjects underwent the PAH renal clearance test in the morning after a light breakfast without caffeinated beverages. They were well hydrated having drunk one litre of water an hour before the test. The test was begun with the subject in the supine position on a hand-operated tilt board. A loading dose of PAH was administered intravenously followed by a continuous infusion to maintain an adequate blood level. At this time blood was drawn for control value of PAH. After a thirty-minute equilibration period an indwelling catheter was inserted into the bladder. The bladder was emptied and the urine discarded. Three consecutive 20-minute urine collection periods for PAH assay followed. The bladder was completely emptied at the end of each collection period by multiple irrigations with saline and air. Blood samples for plasma PAH measurements were collected at the midpoint of each urine collection period. Following three collection periods in the supine position the subject was passively tilted to 30°–45° and an equilibration period of 30 minutes was allowed. The bladder was then completely emptied in the manner described above and the urine discarded. Following bladder-emptying three 20-minute collection periods were undertaken for urine and plasma PAH assays as before. The PAH determinations were done by colorimetric analysis (Varley, 1962).

The renal clearance of PAH was calculated from the formula $C = UV/P$: Where C = PAH clearance, U = urine concentration of PAH, P = plasma concentration of PAH and V = urine volume per minute. Since PAH is virtually completely removed from the blood in a single passage through the kidney, its clearance is equivalent to the effective renal plasma flow

(ERPF). The ERPF was standardised to 1·73 square metres body surface area. The renal blood flow (RBF) per 1·73 square metres was then calculated from the formula ERPF/(1-haematocrit).

The blood pressure was taken by auscultation of the brachial artery by the same observer continually during each collection period and from these values mean arterial pressures (MAP) were derived from the formula MAP = DP + [1/3(SP–DP)] (DP = diastolic pressure, SP = systolic pressure). Average mean arterial pressures were calculated for each subject in both the supine and passive head-up tilt (HUT) positions.

Using the simplified form of Poiseuille's Law of fluid dynamics, Pressure = Flow × Resistance, renal vascular resistance (R) was calculated: R = MAP–RVP/RBF. The renal vein pressure (RVP) was estimated to be

TABLE I

	Controls					
Subjects	RBF (ml/min) Supine-tilt		MAP (mm Hg) Supine-tilt		R (PRU) Supine-tilt	
J.T.	1162	849	108	109	·084	·117
M.K.	1291	1080	102	95	·071	·079
S.B.	1604	987	92	103	·051	·094
I.L.	1318	994	100	108	·068	·099
K.R.	1393	1054	93	93	·060	·079
H.S.	1449	647	94	108	·058	·151
R.G.	1265	929	112	114	·081	·112
Means	1355	934	100	104	·068	·104
Paired-T	$p < ·005$		$p > ·05$		$p < ·05$	

TABLE 2

	Tetraplegics					
Subjects	RBF (ml/min) Supine-tilt		MAP (mm Hg) Supine-tilt		R (PRU) Supine-tilt	
V.D. (C4)	1218	998	88	79	·064	·069
T.S. (C5)	1040	501	116	78	·102	·136
E.H. (C5)	1086	564	95	71	·078	·108
M.D. (C5)	889	567	88	88	·087	·138
R.B. (C5)	1150	828	69	73	·051	·076
G.R. (C6)	861	411	96	88	·100	·190
F.S. (C6)	968	911	78	55	·070	·049
R.P. (C7)	828	525	100	87	·109	·147
Means	1005	663	91	77	·083	·114
Paired-T	$p < ·05$		$p < ·05$		$p < ·05$	

approximately 10 mmHg by Gomez (1951). The renal vascular resistance was expressed in mmHg/ml/min or peripheral resistance units (PRU).

Results

The following results were obtained: (See Tables 1 & 2). In the control group the RBF in the supine position ranged from 1162 to 1604 ml/min per 1·73 sq. metres body surface area. The mean was 1355 ml/min. When tilted the RBF in the controls decreased to a mean of 934 ml/min with a range of 647 to 1080 ml/min. The paired-T test showed the decrease to be significant. The MAP in the supine position ranged from 92–112 mmHg with an average of 100 mmHg. The MAP generally increased during HUT, falling in one subject and remaining the same in another. The average MAP in HUT was 104 mmHg but this did not represent a significant change. In the supine position the renal vascular resistance (R) varied from ·051–·084 peripheral resistance units (PRU) with a mean of ·068 PRU. Renal resistance increased in all controls significantly to a mean of ·104 PRU ranging from ·079 to ·151 PRU.

In the tetraplegic subjects the RBF in the supine state ranged from 828 to 1218 ml/min with a mean of 1005 ml/min. The RBF dropped to 411–998 ml/min during HUT averaging 663 ml/min. This was statistically significant. The MAP of the tetraplegics when supine was 69–116 mmHg and when tilted 55–88 mmHg. The supine and HUT average MAP's were 91 and 77 mmHg respectively. This decrease was significant. In two of the subjects the MAP did not fall. As in the controls the renal vascular resistance rose consistently from supine to HUT. In supine R ranged from ·064–·109 PRU and in HUT it ranged from ·069–·190. Supine mean resistance was ·083 PRU and tilt mean R was ·114 PRU. The P value was less than 0·05. Therefore, the increase was significant.

Discussion

The renal circulation in man is regulated by both intrinsic and extrinsic mechanisms. The isolated, perfused, denervated kidney exhibits the property of autoregulation of its circulation which means that renal blood flow is kept relatively constant as renal artery pressure varies (Pitts, 1974). In the intact human the renal circulation is subject to neurogenic regulation through the sympathetic nervous system.

The renal nerves abundantly supply the kidney's blood vessels with post-ganglionic sympathetic fibres (Pitts, 1974). In dogs the renal sympathetic outlfow outflow is derived from the fourth thoracic to the fourth lumbar spinal segments with the greatest portion coming from the last three thoracic segments (Bradford, 1889). However, studies in man indicate that the sympathetic innervation of the kidney is derived mainly from the twelfth thoracic to the second lumbar spinal segments (Selkurt, 1963; Carstensen *et al.*, 1959). The vasomotor tone in the preganglionic sympathetic neurons is modulated by descending spinal tracts from supraspinal vasomotor centres in the medulla and other centres in the brain such as hypothalamus (Scher, 1974). Normally man in the supine position at rest exhibits a low level of sympathetic activity in the renal nerves and

thus minimal adrenergically mediated renal vasoconstriction (Smith *et al.*, 1939). When he assumes the upright position peripheral venous pooling occurs in the dependent vessels of the body and cardiac output falls by about 20% (Tuckman *et al.*, 1966). In response to lower pressure and changed wave forms at the aortic and carotid sinus baroreceptors the rate of afferent action potentials in the ninth and tenth cranial nerves to the medullary vasomotor centre decreases. Reduction in the rate of these inhibitory potentials modifies outflow via the descending spinal tracts to the intermediolateral cell column so that the activity to the pre- and post-ganglionic sympathetic neurons is increased (Fig. 1). The resultant augmented vasomotor tone increases total systemic arteriolar resistance by approximately one-third. Consequently, mean arterial pressure at the level of the heart increases slightly.

There is abundant evidence showing that the centrally-mediated autonomic response to orthostasis also increases the resistance of the renal vascular bed. It has been shown repeatedly that stimulation of the renal nerves in animals produces a rise in renal vascular resistance (Bradford, 1889; Kottke *et al.*, 1945; Celander, 1954; Takeuchi *et al.*, 1965). Stimulation of both the spinal cord and medullary vasomotor centres has resulted in similar changes in renal resistance (Wise *et al.*, 1960; Takeuchi *et al.*, 1962; Takeuchi *et al.*, 1964; Folkow *et al.*, 1966). In addition, changes in perfusion pressure of the carotid sinus have produced reciprocal changes in action potentials recorded from the sympathetic nerve fibres entering the kidney (Kezdi *et al.*, 1968; Coote *et al.*, 1969). Finally, clearance studies in humans have shown that orthostasis induces renal vasoconstriction (Smith, 1940; Brun *et al.*, 1945; King *et al.*, 1954; Robinson *et al.*, 1963; Werko *et al.*, 1949).

The results in the able-bodied controls of this study confirm what earlier investigators have found concerning the response of the renal circulation to orthostasis and passive HUT in particular. There is a vigorous vasoconstriction resulting in a marked rise in renal resistance which in the face of constant or slightly increased MAP lowers the RBF significantly. It is important to note that this sino-aortic baroreceptor-mediated, sympathetic vasoconstriction involves not only the renal arterioles but the veins as well, thereby decreasing the renal circulation's capacity making more blood available to other critical organs (Heyman, 1950).

In the tetraplegic subjects the rise in renal vascular resistance during HUT demands a different explanation. The cervical spinal cord disruption prevents the sympathetic pre-ganglionic neurons from receiving excitation from the medullary vasomotor centre. How then does orthostasis in spinal man result in renal vasoconstriction which is equally as effective in reducing RBF as in normal man?

One explanation might be the production of a circulating pressor substance which causes renal vasoconstriction. Increased plasma renin levels have been demonstrated during HUT in tetraplegics which reflects activation of the pressor octapeptide angiotension (Mathias *et al.*, 1975; Kamelhar *et al.*, 1978). Also studies have shown increases in blood levels of norepinephrine directly and indirectly in both tetraplegics and able-bodied during HUT (Kamelhar *et al.*, 1978). This is evidence for increased sympathetic activity from the isolated spinal cord which would support the postulation of a spinal sympathetic vasomotor reflex pathway responsive

to postural changes. Corbett *et al.*, (1971) argued for the existence of such a spinal reflex involving the peripheral circulation to explain the decrease in forearm blood flow during HUT in tetraplegics. They observed a venoconstriction which could not have been caused by a humoral agent.

Gammon and Bronk in 1935 discovered the presence of vascular receptor activity in the Pacinian corpuscles adjacent to the mesenteric arteries of the cat. These organs are stimulated by distention of the mesenteric vessels and have been demonstrated to have an effect on the haemodynamics of the splanchnic circulation. Heyman *et al.*, (1936) showed that an increase in arterial pressure in the isolated, perfused spleen of the dog resulted in splanchnic vasodilation which persisted following cervical cord transection and was abolished only after spinal cord ablation or total sympathectomy (Heyman *et al.*, 1936). They concluded that the splanchnic vasomotor response to changes in systemic blood pressure in spinal dogs is mediated by spinal vasomotor reflexes activated by changes in splanchnic blood flow.

The basic haemodynamic disadvantage of orthostasis appears to be venous pooling which results in a decreased cardiac output. Together the renal and splanchnic circulations receive as much as 50% of the cardiac output. Therefore effective renal and splanchnic vasoconstriction particularly venoconstriction, since two-thirds of the circulating blood volume is in the venous side, would be very important in the maintenance of arterial blood pressure during orthostasis. In tetraplegic individuals whose sino-aortic baroreceptor-vasomotor mechanism is deficient there may exist a splanchnic baroreceptor-vasomotor mechanism which functions at the spinal level. The eventual recovery of this spinal vasomotor reflex following spinal shock phase may explain why spinal man can at least partially adapt to the erect posture and lead an active life from a wheelchair.

Résumé

Il a été démontré que les tétraplegiques ont une insufisante adaptation cardiovasculaire à la verticalisation. Il est probable que cette insufisance est due à l'interuption des tracrs de le moelle epinière, qui relient les centres supra-spinaux de contrôle avec les neurons moteurs du système sympatique periphérique. Les articles publiés sur ce sujet montrent que l'évaluation des réponses vasomotrices fut déterminés par la mesure du débit sanguin dans les membres. Des conclusions contradictoires furent obtenues. Uen étude sur la circulation viscerale, en particulier sur le débit sanquin rénal, pourrais aider à elucider le problème. Des mesures de clearance rénale (coefficient d'épuration) furent effectuées chez sept sujets normaux et huit sujets cliniquement complèment tetraplégiques et dans le stage chronique. Nous avons évalué le débit sanguin rénal, la pression moyenne arterielle, et la résistance vasculaire totale du rein, dans la position supine et pendant la verticalisation passive. Chez tous les sujets le débit sanguin diminue et la résistance vasculaire totale augmente durant la verticalisation. Malgré l'auto régulation de la circulation rénale, le changement de position produit une altération profonde du débit sanguin rénal en réponse à l'action hemodynamique des nerfs rénaux. La vaso constriction d'origine sympatique est produite par le réflexe du sinus carotidien via le centre vasomoteur du bulbe rachidien. Lorsque les influences supraspinales sont absentes, les vaisseaux rénaux répondent à la stimulation de la verticalisation par une vasoconstriction vigoureuse. L'adaptation de l'homme spinal a lá position debout est probablement reliée au retour des réflexes vasomoteur de la moelle, et comprend la circulation splanchnique.

Zusammenfassung

Die kardiovaskulaere Adaptation der Tetraplegiker zu der aufrechten. Lage wurde schon

frueher als ungenuegend festgeftellt. Es wird vermutet, dass die Ursache die Unterbrechung der Verbingung zwischen Spinalnerven und supraspinalen Centern ist. Fruehere Untersuchungen dieses Phenomens haben sich auf Circulationsmessungen der Extremitaeten beschraenkt. Die Ergebnisse haben nicht uebereingestimmt. Untersuchung der inneren Organe, besonders der Nieren sollte mehr Licht in dieses ungeklaerte Gebiet bringen. Nierenfunktionsuntersuchungen wurden deshalb an sieben normalen Kontrollen und acht chronischen Tetraplegikern vorgenommen. Nierenblutfluss, mittlerer Arterienblutdruck und totaler Circulationsonswiderstand in horizontaler und aufrechter Lage, wurden kalkuliert. Blutcirculation und Nierengefaesswiderstand waren erheblich veraendert nach passiven Aufrichten von der horzontalen Lage. Obwohl die Nierencirculation sich selbst reguliert verursachte ein Lagewechsel eine erhebliche Hinderung des Nierenblutflusses vermittelt durch den hemodynamischen Einfluss des autonomischen Nervensystem. Sympathische Kontraction der Nierenblutgefaesse wird von dem Carotid Sinus Reflex reguliert. In der Abwensenheit von supraspinaler regulierung verursachte ein orthostatischer Reiz eine erhebliche Nierengefaesskontraktion. Die Adaptation eines Spinalmenschen zu der aufrechten Lage erfordert wahrscheinlich Widerherhellung eines Rueckenmarkreflexes der die splanchnische Circulation einschliesst.

Acknowledgement: This study was supported in part by grants from the Edmund Guggenheim Research Fund, the Murry and Leone Guggenheim Fund, and the Office of Human Development, Rehabilitation Services Administration, Department of Health, Education and Welfare, U.S.A.

The authors wish to express their gratitude to N. Eric Naftchi, PhD., and Margaret Demeny, PhD. for their assistance in collection of the data; and to G. Heiner Sell, M.D., and Edward W. Lowman, M.D. for their encouragement and support of this investigation.

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