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CARDIOVASCULAR AND HAEMODYNAMIC RESPONSES TO TILTING AND TO STANDING IN TETRAPLEGIC PATIENTS: A REVIEW

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Summary. This paper has reviewed the acute and long-term responses to changes in vertical posture in normal and tetraplegic subjects. It has discussed physiological mechanisms causing orthostatic hypotension in acute cervical spinal cord injured patients, and subsequent factors contributing to its amelioration over time. The long-term adaptive mechanisms are still controversial, probably involving multiple neurological, endocrine, renal, cardiovascular and haemodynamic factors. These factors include inhibition of vagal tone, plasma catecholamine levels, sensitivity of vascular beds to catecholamines, stretch reflexes in blood vessels, spinal BP reflexes, renin-angiotensin system, aldosterone and plasma volume changes. Individual differences may also interact with these various mechanisms, further complicating the issues. Although the fact that most tetraplegics do improve their orthostatic tolerance over time with repeated tilting is manifest, the precise mechanisms allowing this improvement are not. Research is needed to clarify these adaptive mechanisms, as well as to investigate the physiological effects of long-term therapeutic standing in devices such as standing frames.

Key words: Tetraplegia; Orthostatic hypotension; Tilting.

Introduction

THE purpose of this paper is to review the current research literature concerning the cardiovascular and haemodynamic responses of spinal cord injured tetraplegic individuals to the changes in upright posture inherent in tilting and standing. It deals with acute and chronic responses, and also with several proposed physiological mechanisms by which tetraplegic patients improve their tolerance of tilting and standing over time through orthostatic training.

The significance of this topic should not be underestimated, especially in relation to the acute rehabilitation of tetraplegics. Orthostatic training is an integral part of this process as it allows early wheelchair mobilisation and weightbearing on the lower extremities (Lopes and Figoni, 1981). The literature cites many therapeutic effects of tilting, standing, and weightbearing, including reduced spasticity (Odéen and Knutsson, 1981), improved bladder and bowel function (Gould *et al.*, 1955), prevention of hypercalciuria (Abramson and Delagi, 1961; Hattner and McMillan, 1968; Kaplan *et al.*, 1981), prevention of contractures and reversal of metabolic and physiological deterioration associated with prolonged bedrest (Abramson and Ebel, 1953), reduction of renal calculosis (Comarr, 1955), pathological fractures and heterotopic calcification (Abramson, 1948); relief from sitting

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pressures (Abramson and Ebel, 1953), abolition of orthostatic hypotension (Odéen, 1979), and psychological benefits (Machek and Cohen, 1955).

Normal Responses to Changes in Posture

In normal man several dynamic circulatory changes occur immediately upon assuming the upright posture, with full hydrostatic pressure exerting its influence on arterial and venous columns (Lamb, 1968). The blood pressure (BP) below the heart at foot level increases by 86 mmHg, while the BP above the heart at the base of the skull decreases by 24 mmHg. Right atrial pressure and venous pressure in the superior vena cava above the atrium fall and blood volume redistributes itself towards the lower extremities. Fifteen per cent of the total blood volume may pool in the legs and 10 per cent of the plasma volume is lost to the tissues after 20–30 minutes of passive standing. Central blood volume and available circulating blood volume decline (Thompson, Thompson and Dailey, 1928), stroke volume falls slightly from about 70 to 60 cc; cardiac output decreases up to 25 per cent from about 5 to 4 litres/minute (Bickelmann, Lippschutz and Brunjes, 1961). Heart rate (HR) rises 15 to 25 bpm (Piemme, 1968) to compensate for the reduced venous return and stroke volume. As other vascular reservoirs contract cardiac volume decreases. Cerebral blood flow decreases about 20 per cent, compensated by increased oxygen and glucose extraction by the brain (Scheinberg and Stead, 1949). Coronary blood flow remains constant but renal, splanchnic, and hepatic blood flows fall about 40 per cent (Culbertson *et al.*, 1951). Leg arteries and arterioles contract, preventing excessive venous pooling (Mayerson, Sweeney and Toth, 1939). Leg blood flows may decrease by 50 to 80 per cent (Mayerson, 1942), while blood flow velocities slow in all extremities (Thompson, Alper and Thompson, 1928). The arterio-venous oxygen difference may double to maintain adequate oxygen delivery to the legs (Mayerson, 1942).

These reflex effects are centrally mediated via the carotid sinus and aortic arch baroreceptors, resulting in norepinephrine release at the vascular walls and elevated plasma norepinephrine levels. Vaso constriction and increased arteriolar resistance compensate for the hydrostatic dilation of the lower extremity vessels to maintain cerebral blood flow. The end result is no significant change in central arterial BP upon assuming upright posture.

Additional mechanisms to maintain BP are described by Brown *et al.* (1966). They found a 64 per cent increase in plasma renin concentration after one hour of standing in seven normal men, together with elevated haematocrit and reduced urinary volume and sodium and potassium excretion in the upright position. Gordon *et al.* (1967) suggest that an intact sympathetic nervous system is essential in normal man for this renin release.

They postulate the following sequence for normal males in a state of relative sodium depletion:

upright posture
↓
decreased effective plasma volume
↓
increased sympathetic nervous activity
↓
increased renal afferent arteriolar constriction
↓
increased renin secretion
↓
increased aldosterone secretion

Oparil *et al.* (1970) reinforce the concept that a prompt and potent renin response is necessary for prevention of 'vasovagal syncope'. Twenty-five per cent of their 'normal' subjects fainted after vertical tilting, due, in their view, to inadequate plasma renin activity. The authors conclude that the renin-angiotensin system participates in the acute response to postural change and that it functions abnormally in vasovagal syncope.

Vallbona *et al.* (1966) also found increased secretion of antidiuretic hormone (to conserve body water) and cortisol (in response to the non-specific stress of tilting and rising norepinephrine levels) in normal tilting subjects.

Accessory factors aiding circulation during tilting include:

1. Abdominal and thoracic pump: The alternating increase and decrease in intra-thoracic pressure accompanying breathing aid venous return of blood to the heart.
2. Muscular contractions: Contracting and relaxing of the leg muscles force blood through the capillaries and veins back towards the heart, aided by the venous valves which prevent backflow. Thus, the veins and exercising leg muscles constitute an 'auxiliary heart' (Hellebrandt *et al.*, 1949).
3. Tonus of the resting muscles: The greater tonus of the surrounding muscles, the greater the reduction in the amount of blood pooling in the veins (Kesselman, 1968).

Thus in normally functioning and fully hydrated man, a combination of neurological, endocrine, and mechanical factors contribute to cardiovascular and haemodynamic homeostasis during postural tilting involving increased hydrostatic stress on the circulatory system.

Tetraplegia and Orthostatic Tolerance

In this paper, 'tetraplegia' refers to the functional state of an individual after having sustained a neurologically complete spinal cord injury at or above the first thoracic spinal nerve (T1). The major sequelae of tetraplegia include loss of all centrally mediated voluntary movement, sensation and autonomic function below the level of injury.

Tetraplegia dramatically affects orthostatic tolerance in several ways. This section of the paper deals with acute cardiovascular and haemodynamic

responses of tetraplegics to changes in upright posture, primarily during use of the tilt table.

1. Heart Rate and Blood Pressure

Many investigators have documented the decrease in BP and increase in HR of acute tetraplegics before initiation of orthostatic training (Cole *et al.*, 1967; Corbett *et al.*, 1971c; Downey *et al.*, 1966; Engel and Hildebrandt, 1976; Freyschuss and Knutsson, 1969; Hamilton and Lindan, 1967; Johnson and Park, 1973; Kamelhar *et al.*, 1978; Lopes, Figoni and Perkash, 1984; Mertens *et al.*, 1960; Vallbona *et al.*, 1963; Wolf and Majora, 1976). 'Orthostatic hypotension', excessive decrease in BP upon assuming upright posture, is the rule for this population during the early phases of their rehabilitation. Easily assessed BP and HR responses of tilting tetraplegics abound in the literature. In the extreme case (Guttmann *et al.*, 1963), all tetraplegic and high paraplegic subjects fainted upon rapid tilting from supine to vertical. All studies agree that BPs decrease initially but with some subjects BPs gradually recover or oscillate during tilting. Reflex sympathetic cardiac acceleration occurs in some patients with incomplete cervical injuries but not those whose pathways that transmit efferent cardioaccelerator impulses to the pacemaker have been disrupted (Vallbona *et al.*, 1965). Cardiac acceleration may be affected in complete tetraplegics by inhibition of vagal tone (Freyschuss and Knutsson, 1969). Central venous pressure falls from about 3·5 to 0·8 mmHg, and systemic vascular resistance rises from about 1710 to 1930 dynes (Vallbona *et al.*, 1965).

2. Stroke Volume and Cardiac Output

Corbett *et al.* (1975) found a decrease in stroke volume from 58 to 27 ml and a drop in cardiac output from 3·9 to 2·3 l/min in 23 chronic tetraplegics. No other investigators have reported stroke volume or cardiac output data on tetraplegics during tilting or standing.

3. Peripheral Blood Flows

Corbett *et al.* (1971c) found a 22 per cent decrease in forearm blood flow with forearm vasoconstriction in seven tetraplegics during 60° tilts. No researchers have reported lower extremity blood flows during tilting or standing. Nanda *et al.* (1974) studied cerebral blood flow in five tetraplegics during changes of position from supine to sitting. Even though systolic BPs fell as low as 70 mmHg, cerebral blood flow remained constant during hypotension, indicating that the mechanisms controlling cerebral blood flow are less dependent on BP above a certain level.

4. Fluid Balance and Haematocrit

Acute tetraplegic patients are usually restricted to bedrest for several weeks, leading to general deconditioning and loss of blood volume. During the first month after injury tetraplegics are in negative fluid balance with a relatively high extracellular fluid compartment (Claus-Walker and Halstead, 1981). Haematocrit rises slightly (about 2 per cent) after 2 hours of tilting

to 85°, probably resulting from further reduction in plasma volume occurring with prolonged upright posture (Brown *et al.*, 1966).

5. Endocrine Changes

(a) *Catecholamines:* Complete cervical spinal cord injuries interrupt all spinal sympathetic efferent pathways, including reflex baroreceptor control of blood vessels in the legs and viscera. When tilted, plasma catecholamine levels rise with epinephrine, often exceeding norepinephrine levels (Guttmann *et al.*, 1963). This catecholamine response is, however, inadequate for prevention of venous pooling in the legs and abdomen during sudden positional changes. The hydrostatic circulatory load passively dilates the blood vessels of the lower extremities and viscera. Without normal peripheral resistance venous pooling in these denervated areas results. Additionally, the myocardium does not contract forcefully enough to compensate for the decreased venous return. Venous return is hindered further by lack of the leg muscle pump, causing more pooling and extravasation of plasma in the dependent extremities. Consequently, cardiac output and circulating blood volume decline, causing orthostatic hypotension. Reflex sympathetic cardiac acceleration will not occur and remedy this situation if efferent cardio-accelerator pathways are interrupted (Vallbona *et al.*, 1965).

(b) *Antidiuretic Hormone, Cortisol, and Aldosterone:* The aforementioned, irreversible, hypotensive situation may stimulate further emergency endocrine reactions. Vallbona *et al.* (1966) noted increased levels of antidiuretic hormone, cortisol, and aldosterone with decreased urinary output and sodium/potassium ratio, prompted by lack of cardiac acceleration or secondary hypotension. Brown *et al.* (1966) found high plasma levels of aldosterone and a lower aldosterone liver clearance rate during and after tilting of tetraplegics. They suggest that this reflects the body's attempt to retain sodium and water to maintain plasma volume and BP. Claus-Walker *et al.* (1969) also observed high aldosterone excretion in tetraplegics within 8 months of injury attributing this finding to daily tilting treatments. Vallbona *et al.* (1966) question the value of a slow release of fluid-retaining hormones during an acute orthostatic hypotensive crisis. They suggest that repeated tilting episodes may cause sustained production of these hormones with subsequent increased circulating blood volume.

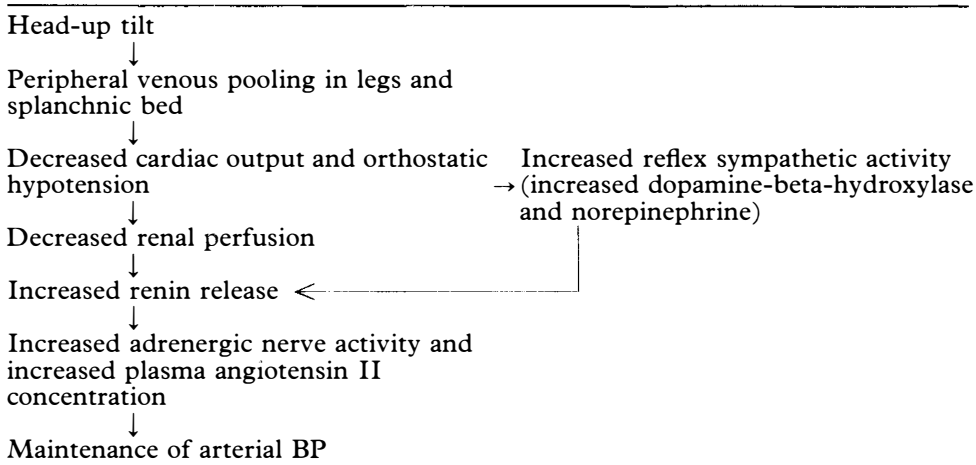
6. Renin-Angiotensin System

Another consistent finding in tilting tetraplegics is elevated plasma renin concentration. Johnson *et al.* (1971) and Love *et al.* (1971) observed that the renin-angiotensin system can be activated in tetraplegics without intact sympathetic nervous systems. Their subjects had high resting plasma renin concentrations, suggesting a compensatory (though not fully sufficient), role in combatting orthostatic hypotension. Kamelhar *et al.* (1978) suggest that increased plasma renin concentration may be caused by decreased renal perfusion pressure and increased sympathetic stimulation during tilt hypotension.

Decreased renal blood flow in normal subjects causes the kidney to release renin which catalyzes the formation of angiotensin. This leads to

(a) aldosterone secretion by the adrenal cortex, and sodium and water retension, and (b) vasoconstriction, both increasing arterial BP and renal blood flow (Langley *et al.*, 1969). Tetraplegics fail to make full and adequate use of this mechanism over the short-term to maintain BP and renal integrity.

Several physiological mechanics contribute to orthostatic hypotension in tetraplegics during tilting, including peripheral venous pooling and failure of the renin-angiotensin or adrenergic/sympathetic nervous systems. Kamelhar *et al.* (1978) provide a summary outlined as follows:



Other Factors Influencing Orthostatic Hypotension in Tetraplegics

Several internal and external stimuli have been used experimentally or clinically to help reduce orthostatic hypotension in tetraplegics during tilting or standing. Muscle spasms, bladder percussion, or spontaneous micturition reportedly raise BP and HR during tilting (Corbett *et al.*, 1971a, 1971b). The occurrence of a spasm at the beginning of a tilt session delayed the fall in BP and a spasm at the end of a tilt caused an overshoot in BP beyond pre-tilt levels. Bladder percussion and/or spontaneous urination during tilt also tended to oppose the fall in BP. Spontaneously induced skeletal muscle spasm also caused vasoconstriction in the hand and foot, and lowered blood flow through the hands.

In addition to daily tilting sessions techniques for preventing excessive orthostatic hypotension during tilting include the following.

1. Compression of the abdomen with an elastic binder or pneumatic corset (McCluer, 1967, 1968).
2. Compression of the lower extremities with long support stockings.
3. Compression of the lower body with an inflatable pressure suit (Vallbona *et al.*, 1963).
4. Neurotransmitter drugs, such as epinephrine and ephedrine.
5. Voluntary upper extremity muscular contraction (Freyschuss and Knutsson, 1969).
6. Elicitation of skeletal muscle spasms (Corbett *et al.*, 1971a).
7. Bladder percussion (Corbett *et al.*, 1975).
8. Inhalation of 5 per cent carbon dioxide air mixture (Downey *et al.*, 1966).

9. Adequate hydration and carbohydrate ingestion (Claus-Walker and Halstead, 1982).
10. Sodium chloride supplementation to sensitise alpha adrenergic receptors to endogenous catecholamines (Claus-Walker and Halstead, 1982).

Long-Term Responses to Tilting and Standing

Weeks or months of progressive tilt table treatment of tetraplegics usually results in minimisation of orthostatic hypotension during tilting and standing, despite Engel and Hildebrandt's (1976) warning that it is not possible to achieve decisive circulatory stabilisation in high paraplegics. Frequently, orthostatic hypotension is abolished, and the patient is assumed to have finally adapted physiologically to changes in vertical posture. Several mechanisms have been postulated to explain this adaptation in the absence of normal baroreceptor reflex control of BP.

Freyschuss and Knutsson (1969) suggest that tetraplegics accelerate their HRs by learning to inhibit vagal tone. The vagus nerve, part of the parasympathetic nervous system, slows down HR. Inhibition of vagal tone would allow some cardiac acceleration in the absence of sympathetic stimulation.

As mentioned previously, Guttmann *et al.* (1963) noted elevated catecholamine levels in the peripheral plasma when tetraplegics were tilted to vertical. Johnson *et al.* (1971) suggest that the sensitivity of subjects' blood vessels to catecholamines increases. Mathias *et al.* (1976) found that tetraplegics have an enhanced pressor response to noradrenalin infusions, not necessarily indicating post-ganglionic denervation. They state that it may be partly due to exaggerated adrenergic receptor responses but is probably caused by loss of those baroreceptor reflexes with sympathetic efferent pathways. These apparently facilitate return of vascular tone even though reflex venous activity is absent (Sharpey-Schafer, 1961).

Several investigators postulate that chronically denervated blood vessels may develop increased activity in responses to stretch (Bayliss, 1902; Folkow, 1962). Similarly, Sommers (1979) detected no changes in the HR or pre-ejection period/left ventricular ejection time ratio in tetraplegics passively tilting to 30° after administration of the sympatholytic drug, propranalol. He speculates that the gradual improvements of the cardiovascular response to tilting in tetraplegics are due to the increases in inherent smooth muscle myogenic activity which elevates the level of basal vascular tone of pre-capillary vessels (Folkow, 1962).

Many investigators attribute improvement of tilt tolerance to cardiovascular reflexes in the isolated spinal cord which elevate BP. Several animal models demonstrating this concept have stimulated this line of thought, although such pathways have not been discovered in man. Beachem and Kunze (1969) found that increasing renal BP in cats caused a sympathetic reflex to the kidneys, subsequently lowering BP. Niijima (1971) demonstrated this same reflex in the renal blood vessels of rabbits, and Andrews *et al.* (1971) described this phenomenon in mesenteric blood vessels of rabbits. Brown and Malliani (1971) also present evidence for reflex homeostatic regulation of BP at the spinal level in vagotomised spinal cats, where an increase in left coronary blood flow caused an increase in BP in

this vessel stimulating increased reflex sympathetic discharge through the white ramus of the third thoracic spinal nerve and inferior cardiac nerve.

Johnson *et al.* (1969) suggest that baroreceptors may exist elsewhere in the venous and arterial circulation besides the carotid sinus and aortic arch. They also speculate about different reflex pathways through the cord but not the brain. Other established autonomic reflexes passing through the isolated cord include finger vasoconstriction, hypertension, bradycardia, and facial and nasomucosal vasodilation in tetraplegics (Guttmann and Whitteridge, 1947) and inspiratory vasoconstriction in normal (Gilliatt, 1948) and tetraplegic subjects (Gilliatt *et al.*, 1948). The same authors propose the upper thoracic region as the probable location of such a purely spinal BP reflex.

Kamelhar *et al.* (1978) cite the high levels of dopamine-beta-hydroxylase during tilt hypotension in tetraplegics as evidence that reflex sympathetic nerve stimulation persists despite spinal transection. Corbett *et al.* (1971c) attribute their observations of forearm vasoconstriction and reduced forearm blood flow in tilting tetraplegics to possible spinal cardiovascular reflexes in peripheral blood vessels. Mertens *et al.* (1960) noticed in five new cervical spinal cord injured patients that within 2 months after injury (after spinal shock has passed), vasomotor tone returned with the development of spinal 'automatism'. During this stage, marked or extensive stimulation of pressure and stretch receptors below the level of injury caused general vasoconstriction with occasional hypertension and bradycardia of central origin. This autonomic hyperreflexia and resulting peripheral vasoconstriction helps compensate for low cardiac output and BP characteristic of orthostatic hypotension.

Sommers (1979) represents the only dissenting voice on this issue. He insists that his results of no changes in HR or pre-ejection period/left ventricular ejection period ratio in tetraplegics tilting to 30° after being administered propranalol fail to support existence of postural cardiovascular reflexes operating via the isolated spinal cord.

Muscular paralysis and deconditioning due to bedrest both contribute to dehydration and hypotension during acute tetraplegia. As mobilisation and rehabilitation ensue, a training effect may be increasing circulating blood volume (Johnson *et al.*, 1969). The acute endocrine responses described earlier in tilting tetraplegics persist and aid chronic tilt adaptation (Johnson *et al.*, 1971).

Résumé

Cet article résume les recherches concernant les réponses cardiovasculaires/hemodynamiques des tetraplégique aux changements de position verticale associés au clinostatisme er à l'orthostatisme. Il discute des mechanismes physiologiques aigus que provoquent l'hypotension orthostatique chez les malades atteints à la moelle épinière cervicale et, par ailleurs, des variables qui contribuent à son amélioration dans le temps. Des réponses à court terme entrainent un déficit veineuse périphérique, une augmentation de la pression artérielle, une diminution de rhythme cardiaque, et l'hypotension. La plupart des tetraplegiques ameliore leur tolérance orthostatique dans le temps un clinostatisme répété, mais les mechanismes adaptifs, précis et à long terme qui permettent cette amélioration sont peu connus. Des variables proposés comprennent l'inhibition des tonus vague, des taux élevés des plasma catécholamine, une sensibilité accrue des vaisseaux déclives aux catecholamines, des réflexes d'allongement dans les vaisseaux sanguins, le système rénin-angiotension, l'aldostérone, et des changements dans le volume de plasma.

ZUSAMMENFASSUNG

Dieser Artikel gibt einen Überblick der Forschungsberichte im Bereich der kardiovasculären/hämodynamischen Reaktionen von komplett Querschnittsgelähmten auf Veränderungen der vertikalen Stellung verbunden mit Kippen und Stehen. Die akuten physiologischen Mechanismen, welche bei Patienten mit Halswirbelsäulenverletzungen orthostatische Hypotonie verursachen, und nachfolgende Faktoren, die zu ihrer Verbesserung über die Zeit beitragen, werden diskutiert. Kurzfristige Reaktionen schliessen in sich ein: periphäre venöse Blutansammlung, erhöhte Pulsfrequenz, verminderte Herzschlagvolumen und Hypotonie. Die meisten komplett Querschnittsgelähmten verbessern ihre orthostatische Toleranz über die Zeit bei wiederholtem Kippen, aber die genauen Langzeit-Anpassungsmechanismen, die diese Verbesserung erlauben, sind unklar. Vorgeschlagene Faktoren sind: Hemmung des Vagotonus, erhöhte Katecholamingehalte im Plasma, gesteigerte Empfindlichkeit des Gefässbettes fur Katecholamine, Dehnungsflexe in den Blutgefässen, Aldosteron, und Volumenänderungen des Plasmas.

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