Topical Review

Pathophysiological basis of orthostatic hypotension in autonomic failure

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In patients with autonomic failure orthostatic hypotension results from an impaired capacity to increase vascular resistance during standing. This fundamental defect leads to increased downward pooling of venous blood and a consequent reduction in stroke volume and cardiac output that exaggerates the orthostatic fall in blood pressure. The location of excessive venous blood pooling has not been established so far, but present data suggest that the abdominal compartment and perhaps leg skin vasculature are the most likely candidates. To improve the orthostatic tolerance in patients with autonomic failure, protective measures that reduce excessive orthostatic blood pooling have been developed and evaluated. These measures include physical counter-manoeuvres and abdominal compression.

Patients with autonomic failure may be seriously incapacitated in activities of daily living due to orthostatic hypotension. Their low blood pressure is ascribed to a defective increase in arterial resistance and an excessive venous pooling upon standing. Effective pharmacological treatment is now available, but may aggravate supine hypertension and have other undesirable effects. Additionally, pharmacological treatment is less successful for hypotension with physical exercise or in warm surroundings (Bannister & Mathias, 1992). Non-pharmacological measures are regarded as a cornerstone in the treatment of orthostatic hypotension. These measures consist of chronic expansion of the extracellular volume or reducing the vascular volume in which pooling occurs (Bannister & Mathias, 1992). The latter includes protective measures like physical counter-manoeuvres which can be applied by those patients with no major additional neurological and musculo-skeletal disorders, and external support garments which can be recommended to all patients.

We reasoned that selection and use of appropriate protective measures would be facilitated by understanding the fundamental physiological mechanisms that prevent excessive orthostatic pooling in healthy subjects, why these mechanisms fail in patients with autonomic failure, and how these protective measures work. Therefore we reviewed the literature and summarized the available data about the amount and location of venous pooling in patients with autonomic failure and the effectiveness of physical counter-manoeuvres and external support garments.

Regulation of blood pressure and venous capacitance in healthy subjects

In healthy individuals, orthostatic pooling of venous blood in the legs and abdomen begins almost immediately upon the change from supine to the erect posture. It is estimated that depending on the type of orthostatic stress (i.e active standing, lower body-negative pressure or head-up tilt) one half to one litre of thoracic blood is transferred to the regions below the diaphragm (Asmussen, 1943; Sjostrand, 1952; Self *et al.* 1996). The bulk of venous pooling occurs within the first 10 s (Ludbrook, 1966; Kunitsch & de Marees, 1973; Kirsch *et al.* 1980; Ebert *et al.* 1986) and the total transfer is almost complete within 3–5 min of orthostatic stress depending on the region of the body investigated (Asmussen *et al.* 1940; Wolthuis *et al.* 1975; Sejrsen *et al.* 1981). Additional sequestration of venous blood may take place due to a slow continuous relaxation of the dependent capacity vessels (Rothe, 1983; Rowell, 1993). Little is known quantitatively about this process in humans.

Approximately 80 % of the blood pooled in the lower limb is contained in the upper leg (thighs, buttocks) (Ludbrook, 1966; Self *et al.* 1996) with less pooling in the calf and foot (Buckey *et al.* 1988); additionally, there is some modest pooling in the abdominal and pelvic regions (Sjostrand, 1952; Wolthuis *et al.* 1975; Inamura *et al.* 1996; Halliwill *et al.* 1998). The blood pooled in the veins of the feet and calf is arterial in origin, in that it arises as a result of decreased venous drainage of that region. In contrast, the blood pooled in the thighs, buttocks, pelvis and abdomen arises

primarily from venous reflux (Ludbrook, 1966; Wolthuis *et al.* 1975). The pooled blood is not actually stagnant; its mean circulatory transit time through the dependent region is merely increased by changes in the pressure gradient across the vascular bed and by increases in venous volume (Rieckert, 1976).

In addition to this transfer of thoracic blood, central blood volume decreases following transcapillary filtration of fluid into the interstitial spaces in the dependent parts as well. This filtration is the effect of a high intra-capillary pressure with little interstitial counter-pressure on the Starling forces for filtration, and can result in significant haemo-concentration and reduced plasma volume. Earlier studies estimated that plasma volume decreased about 10–15% after 20–30 min in the upright position (Waterfield, 1931; Hagan *et al.* 1978; Hinghofer-Szalkay & Moser, 1986). However, Lundvall *et al.* (Lundvall & Bjerkhoel, 1994; Lundvall *et al.* 1996) recently demonstrated that venous blood sampled from the standing subject underestimated the time course and magnitude of reduction in plasma volume. The underestimation was ascribed to incomplete mixing of venous blood from dependent and non-dependent regions. It was found that in healthy adults plasma volume decreased by about 10% (500 ml) after 5 min and by 15–20% (700 ml) after 10 min during which time the reduction in plasma volume is virtually completed. A profound decrease in plasma volume during orthostatic stress has been observed by others as well (Matzen *et al.* 1991).

As a consequence of gravitationally induced blood pooling and the superimposed decline in plasma volume, the return of venous blood to the heart is reduced and right atrial pressure falls from 5–6 mmHg (supine) to nearly 0 mmHg (upright) (Katkov & Chestukhin, 1980; Matzen *et al.* 1991). This affects the end-diastolic filling of the right ventricle, which in turn leads to a reduction in stroke volume (via the 'Frank–Starling' length–tension relationship; Lewis & Sandler, 1971) and thereby to a fall in cardiac output of ~20% (Stead *et al.* 1945; Wang *et al.* 1960). Despite the fall in cardiac output, a fall in mean arterial pressure is prevented by a compensatory vasoconstriction of the resistance and capacitance vessels in the splanchnic, musculo(cutaneous), and renal vascular beds (Bridgen *et al.* 1950; Rowell *et al.* 1972; Hendriksen & Sjersen, 1977; Ring-Larsen *et al.* 1982; Chaudhuri *et al.* 1992; Vissing *et al.* 1997; Minson *et al.* 1999)

The initial adjustments to orthostatic stress are mediated exclusively by the neural pathways of the autonomic nervous system. During prolonged orthostatic stress, additional adjustments are mediated by the humoral limb of the autonomic nervous system. The main sensory receptors involved in orthostatic neural reflex adjustment are the arterial mechanoreceptors (baroreceptors) located in the aortic arch and carotid sinuses and mechanoreceptors located in the heart and lungs (cardiopulmonary receptors). The cardiopulmonary receptors act in concert with the arterial baroreceptors to effect the necessary adjustment in sympathetic outflow at all levels of orthostatic stress (Rowell, 1993). However, their importance in the initial reflex adjustment to the assumption of the upright posture is suggested to play a minor role (Wieling & Wesseling, 1993). The observation that cardiopulmonary denervation in man does not result in orthostastic hypotension (Banner *et al.* 1990) while orthostatic hypotension is described after arterial baroreceptor denervation, supports this view (Capps & de Takats, 1938; Holton & Wood, 1965; Smiley *et al.* 1967).

The relative influence of the carotid and aortic receptors in orthostatic reflex adjustments are difficult to sort out in humans, but the carotid sinus baroreceptors are likely to be of primary importance during standing. Three points support this notion. First, the observation that carotid sinus receptors respond more vigorously to rapid rather than slow changes in pressure makes it likely that they play the major role in the initial reflex adjustments (Angell-James & Daly 1970). Second, in the upright posture at heart level, mean arterial pressure is increased by 5–10 mmHg and pulse pressure is reduced. The aortic baroreceptors which are located just above heart level sense an increased, instead of decreased mean pressure; only pulse pressure is reduced for these receptors. Due to a 20–25 cm hydrostatic height difference between the carotid baroreceptor area and the heart, the transmural carotid pressure is lowered by about 15 mmHg due to gravity. For these receptors carotid pressure and pulse pressure are reduced and will unload the stretch receptors as long as the upright posture is maintained (Wieling & Wesseling, 1993). Third, surgical denervation of the carotid sinus receptors may result in impaired orthostatic blood pressure control (Capps & de Takats, 1938; Holton & Wood, 1965; Smiley *et al.* 1967; Palatini & Pessina, 1987; Smit *et al.* 1998). However, the outcome of the reverse experiment, i.e the selective denervation of aortic baroreceptors is not available in humans.

Reflex activation of central sympathetic outflow can be reinforced by local 'reflex' mechanisms. When venous filling in the dependent parts raises intravenous pressure to 25 mmHg or more, a local sympathetic 'axon reflex, ' or 'venoarteriolar reflex' is activated. The receptor sites for these reflexes appear to be in small veins in cutaneous, sub-cutaneous adipose, and skeletal muscle tissue and the effector site is the corresponding arterioles (Hendriksen & Sjersen, 1977; Hendriksen & Skagen, 1988; Vissing *et al.* 1997). This venoarteriolar reflex has been reported to be able to reduce the lower limb blood flow up to 30–45% during orthostatic stress (Hendriksen & Sjersen, 1977; Skagen & Bonde-Petersen, 1982; Hendriksen & Skagen, 1988). A myogenic response in the resistance arterioles of the dependent regions (in response to increased transmural

pressure) (Folkow, 1962; Mellander *et al.* 1964; Folkow & Mellander, 1964) may also contribute to the rise in vascular resistance, but this effect is now thought to be less important than the venoarteriolar reflex. In contrast to the veno-arteriolar reflex the myogenic response is not regarded as a sustained response (Johnson, 1980; Rådegran & Saltin, 1998).

The neural pathways of the autonomic nervous system continue to play a pivotal role during prolonged orthostatic stress. Sustained elevation of efferent sympathetic activity is documented by increases in plasma noradrenaline concentration and spillover (Ziegler *et al.* 1977) and by directly recorded sympathetic nerve activity to skeletal muscle (Burke *et al.* 1977; Iwase *et al.* 1987; Joyner *et al.* 1990). During prolonged orthostatic stress additional reflex activation of the neurohumoral system reinforces the action of the cardiovascular reflexes through additional constriction of blood vessels. It also minimizes the loss of body water during prolonged orthostatic stress by activation of the renal blood volume controlling systems. The humoral responses are of importance for cardiovascular adjustment during hypotensive orthostatic stress, but cannot supplant the functions of the neural system (Rowell, 1993).

Under normal circumstances the renin–angiotensin–aldosterone system is activated when the head-up posture is assumed, and even more so in situations of hypotensive orthostatic stress (Hesse *et al.* 1986). The plasma vasopressin increase in response to orthostatic stress is usually small. If salt intake is normal, arterial blood pressure is maintained during passive head-up tilt even when renin release is pharmacologically inhibited by propranolol (Morganti *et al.* 1979) or when angiotensin formation is prevented by an angiotensin-converting enzyme inhibitor (Sancho *et al.* 1976). Under these circumstances, the sympathetic nervous system acts in concert with vasopressin to maintain arterial pressure (Bennet & Gardiner, 1985). Thus, the renin–angiotensin system and the vasopressin system can compensate for each other. Activation of both systems simultaneously appears only of importance in the maintenance of orthostatic blood pressure in salt-depleted states (Sancho *et al.* 1976; Bennet & Gardiner, 1985). The reduction of circulating atrial natriuretic factor leading to fluid conservation during orthostatic stress appears to play a minor role compared with the other neurohumoral factors (Wieling & Wesseling, 1993). A detailed discussion of the humoral responses is beyond the scope of this review.

Patients with autonomic failure

In patients with autonomic failure there is an impaired increase in total peripheral resistance during orthostasis (Hickam & Pryor, 1951; Sieker *et al.* 1956; Bevegård *et al.* 1962; Chaudhuri *et al.* 1992). This is the result of a disturbed neural reflex arteriolar vasoconstriction (Ziegler *et al.* 1977) and is the primary cause of orthostatic hypotension (Hickam & Pryor, 1951; Sieker *et al.* 1956; Bevegård *et al.* 1962). The fall in cardiac output, ∼40 %, is exaggerated in autonomic failure patients (Hickam & Pryor, 1951; Sieker *et al.* 1956; Bevegård *et al.* 1962; Ibrahim *et al.* 1974) compared with normal individuals, and aggravates the fall in orthostatic blood pressure. The excessive fall in cardiac output is ascribed to both increased venous pooling and impaired inotropic and chronotropic cardiac responses (Bevegård *et al.* 1962; Ibrahim *et al.* 1974; Moss *et al.* 1980). However, in normal subjects it has been shown that pharmacological blockade of the cardiac responses does not play an important role in the adaptation to the upright posture (Tyden, 1977). Moreover, patients with cardiac transplants cannot increase heart rate in the upright posture, but do not develop orthostatic hypotension (Mohanty *et al.* 1987; Banner *et al.* 1990). Thus impaired inotropic and chronotropic cardiac responses are questionable as a cause of impaired orthostatic stress adjustments (Wieling & Wesseling, 1993). It is possible that orthostatic hypotension in autonomic failure patients is partially due to decreased blood volume as well; however, results have been contradictory (Stead & Ebert, 1941; Bevegård *et al.* 1962; Bannister *et al.* 1969; Ibrahim *et al.* 1974) and well controlled studies in this area are needed.

The inability to raise vascular resistance allows considerable venous pooling to occur during orthostasis in autonomic failure patients. Excess pooling of blood could occur in any of the dependent vascular regions, including the skeletal muscle, cutaneous, and splanchnic circulations.

Skeletal muscle. Substantial pooling can occur in the legs during quiet standing due to the large hydrostatic pressures that occur (up to ∼70 mmHg). Potentially three counter-regulatory mechanisms could reduce the venous pooling of blood during standing: vasoconstriction of the venous bed, vasoconstriction of the arteriolar bed and activation of the skeletal muscle pump. The veins located within and around limb muscles have scarce sympathetic innervation (Fuxe & Sedvall, 1965) and are largely unresponsive to baroreceptor-mediated increases in sympathetic nerve activity during standing (Samueloff *et al.* 1966). Further, infused vasodilator or vasoconstrictor drugs have little effect on venous tone in the legs (Epstein *et al.* 1968), supporting the fact that autonomic control of the veins does not determine leg volume. In addition, recent work suggests that whole-limb venous compliance is under negligible sympathetic control in humans (Hager *et al.* 1999).

In dogs arteriolar vasoconstriction plays a role in determining venous pooling in skeletal muscle by reducing blood flow and post-capillary pressures (i.e. passive changes in venous volume that depend on changes in flow) (Hainsworth *et al.* 1983). In accordance, in humans it has been shown that increase in vasoconstriction due to increased sympathetic outflow to legs during orthostasis may lead to a reduction in calf volume (Wallin & Sundlof, 1982; Iwase *et al.* 1987; Vissing *et al.* 1989; Hopman *et al.*

1993; Shamsuzzaman *et al.* 1998). However, the magnitude of the effect of changes in blood flow on venous blood volume in human skeletal muscle is not known yet.

In reality, extensive pooling is limited by activation of the skeletal muscle pump (Henderson *et al.* 1936; Franseen & Hellebrandt, 1943; Guyton *et al.* 1962; Ludbrook & Loughlin, 1964; Magder, 1995; Inamura *et al.* 1996). In the upright posture intramuscular pressure in the lower limb increases from 7 to 15 mmHg supine to 12 to 48 mmHg (depending on the muscle investigated) in the quiet-standing position (Ludbrook, 1966). The pressure increase opposes the hydrostatic induced venous pressure, lowering capillary and venous transmural pressure and thereby reducing venous pooling capacity (Buckey *et al.* 1988, 1992). A reduced intramuscular pressure is associated with orthostatic intolerance in otherwise healthy subjects (Mayerson & Burch, 1940; Amberson, 1943).

The unconsious slight body and leg movement during standing (postural sway) is recognised as an important factor in pumping venous blood centrally (Asmussen, 1943; Inamura *et al.* 1996). In body positions where the postural sway is likely to be diminished, as in voluntary relaxed standing or during head-up tilt position, lower intramuscular pressures and higher limb volumes are measured (Asmussen, 1943; Ludbrook, 1966). Voluntary contraction of calf and thigh muscles is very effective at reducing venous pooling. A single maximal contraction can expel about 30% of the blood volume that has been pooled upon standing (Ludbrook, 1966). Repeated contractions such as during walking reduce venous ankle pressure from about 100 to 40 mmHg (Pollack & Wood, 1949). Although firm quantitative data regarding volume displacement evoked by continuous skeletal muscle pumping are needed in man, there seems little question that skeletal-muscle pump is of major importance in counteracting the stress of quiet standing.

Cutaneous. The dermis contains multiple vascular plexuses that are richly innervated. Sympathetically mediated vasoconstriction and venoconstriction are largely under thermoregulatory control. During standing under normothermic conditions, increased central sympathetic outflow to cutaneous arterioles occurs, but has a minimal effect on skin venous capacity due to high resting vasoconstrictor tone and vasoconstriction resulting from local (i.e. hydrostatic- induced veno-arteriolar reflex and myogenic-response) mechanisms (Samueloff *et al.* 1966; Johnson *et al.* 1973; Skagen, 1983; Vissing *et al.* 1997). The cutaneous veins do not appear to react to baroreceptor stimulation (Samueloff *et al.* 1966; Vissing *et al.* 1997).

Factors which augment cutaneous vascular capacity, such as varicose veins, are associated with symptoms of orthostatic intolerance in healthy subjects (Chapman & Asmussen, 1942) and may aggravate orthostatic hypotension in autonomic failure as well. Similarly, local heating of the skin (e.g. exposure to a hot environment) or increased heat production (e.g. fever or exercise) leads to increased skin blood flow and to an additional sequestration of blood in the skin of the lower body. This can cause orthostatic symptoms at standing (Horvath & Botelho, 1949). Due to unrestrained cutaneous vasodilatation (Mosely, 1969; Johnson *et al.* 1973) skin blood flow and venous blood volume are likely to increase even more in patients with peripheral adrenergic failure. Furthermore, autonomic failure patients may be more susceptible to heat stress due to impaired sweating, which results in a diminished ability to dissipate heat (Bannister *et al.* 1967).

Blood volume in the legs represents the venous capacity of both the muscle and cutaneous vasculatures. From the above discussion, one can appreciate that there are redundant mechanisms in place to keep venous pooling from becoming excessive in the legs. Indeed, Ludbrook (Ludbrook & Loughlin, 1964) observed that ganglion blockade (i.e. blocking the sympathetic outflow but not local control mechanisms) produces a negligible extra rise in calf volume (2–5 ml) upon a normal rise of 23–60 ml during orthostasis, an observation supported by others (Brown *et al.* 1949). As such, it is not surprising that in autonomic failure patients profound alterations in lower limb blood pooling have been difficult to observe despite impaired autonomic control (Ellis & Haynes, 1936; Stead & Ebert, 1941; Verel, 1951; Bannister *et al.* 1967).

However, Streeten (Streeten, 1990; Streeten & Scullard, 1996) found an increased blood volume in the calf during standing in a group of patients with mild autonomic insufficiency (characterized by a hyperadrenergic hypotensive response upon standing and findings suggestive of peripheral adrenergic failure of the skin of the lower limbs). Similar findings have been reported by Low (Low *et al.* 1997). In the case of postganglionic adrenergic failure the veno-arteriolar reflex can be expected to be absent (Hendriksen & Sjersen, 1977) resulting in an increased pooling capacity of the skin and possibly muscle beds. Indeed, in patients with peripheral neuropathy associated with diabetes type 1 elevated venous-capillary pressures and a diminished ability to reduce skin blood flow during limb dependency was observed (Rayman *et al.* 1986, 1994). A reduced tone of leg skeletal muscle (Mayerson & Burch, 1940) could be another explanation for the observations of the groups of Streeten and Low, but has not yet been investigated.

Splanchnic. The splanchnic vascular bed is richly innervated and is a major site of autonomic regulation during orthostatic stress. It contains a large, highly compliant, venous circulation which can contain ~25% of the blood volume at rest (Gaehtgens & Uekermann, 1971; Hainsworth, 1990). During orthostasis its capacity is restricted by baroreflex-mediated arteriolar vasoconstriction (Rowell *et al.* 1972; Johnson *et al.* 1974; Burke *et al.* 1977; Abboud *et al.* 1979; Chaudhuri *et al.* 1992; Minson *et al.* 1999). The increase in

splanchnic vascular resistance causes a passive expulsion of blood out of the large venous reservoir of the splanchnic bed by elastic recoil of venous vessels (Hainsworth, 1990; Rowell, 1993).

Active constriction of the splanchnic capacitance vessels is potentially of great importance in mobilizing additional venous blood to maintain the cardiac filling pressures and, hence, stroke volume during orthostatic stress. In dogs, baroreflex-mediated active venoconstriction occurs in the venous beds of the liver and spleen in particular (Karim & Hainsworth, 1976; Noble *et al.* 1997, 1998). The rich innervation and the great sensitivity and rapidity of the reflex responses of the splanchnic capacitance vessels to very low frequencies of sympathetic discharge are supportive of their importance in responding to postural changes (Shepherd, 1986; Hainsworth, 1990). However in humans, due to technical and ethical constraints, it is not possible to differentiate between the effects of active venoconstriction and the passive effects caused by arteriolar vasoconstriction and the resulting reduction in blood flow through the region (Karim & Hainsworth, 1976).

Impairment of splanchnic innervation leads to a reduced orthostatic tolerance and orthostatic hypotension in humans (Gambill *et al.* 1944; Wilkins *et al.* 1951; van Lieshout *et al.* 1990) by the following steps. Impaired vasoconstriction allows splanchnic blood flow (Chaudhuri *et al.* 1992), and thus splanchnic blood volume (Rowell *et al.* 1972; Johnson *et al.* 1974; Abboud *et al.* 1979), to remain high during standing. A high standing splanchnic blood volume leads to a marked fall in right atrial pressure (Bevegård *et al.* 1962) and results in a reduced cardiac output.

In splanchnic denervated animals (e.g. dogs), the rigid abdominal wall reduces the magnitude of orthostatic hypotension when this animal is held upright (Hill, 1895). Likewise, poor abdominal muscular tone has been associated with impaired orthostatic tolerance in humans (Sewall, 1916; Schirger *et al.* 1961), suggesting that the muscle tone of the human abdominal wall plays a role in maintaining orthostatic blood pressure as well (Rushmer, 1946). However, no prospective studies have evaluated the possible role of abdominal muscle tone in orthostatic blood pressure regulation.

Physical counter-manoeuvres and pressure garments

Most patients with orthostatic hypotension will recognise that immobility will worsen their orthostatic symptoms, whereas bending forward, sitting, or moving around will improve their symptoms (Sewall, 1916; Bickelman *et al.* 1961; Wieling *et al.* 1993). During ambulation, contraction of lower extremity muscles squeezes venous blood from the leg upward (Guyton *et al.* 1962; Ludbrook & Loughlin, 1964; Rådegran & Saltin, 1998). The same effect can be achieved by deliberate isometric or dynamic muscle contractions (Mayerson & Burch, 1940; Newburry *et al.* 1970; Smith *et al.* 1987), and is the basis for physical counter-manoeuvres like leg-crossing and skeletal muscle pumping, which are used to reduce venous pooling in the legs.

Leg-crossing, which involves contraction of agonist and antagonist muscles, has been shown to be a simple and effective counter-manoeuvre to increase cardiac output and thereby blood pressure (van Lieshout *et al.* 1992; Wieling *et al.* 1993; ten Harkel *et al.* 1994; Bouvette *et al.* 1996; Smit *et al.* 1997). When leg-crossing is practised routinely in patients with autonomic failure, standing systolic and diastolic blood pressures can be increased by ~20/10 mmHg (van Lieshout *et al.* 1992; ten Harkel *et al.* 1994; Bouvette *et al.* 1996; Smit *et al.* 1997). Larger increases ~30/15 mmHg (Smit *et al.* 1997) can be seen with the additional voluntary contraction of the leg musculature, thighs, and buttocks. Leg-crossing can increase seated blood pressure as well (Takeshita *et al.* 1991; Smit *et al.* 1997). In healthy subjects an increase in cardiac output is also observed during leg-crossing but not in blood pressure since a baroreflex-mediated reduction in vascular resistance occurs (ten Harkel *et al.* 1994).

Manoeuvres that use skeletal muscle pumping are 'toe raising' and repeated knee flexion (marching on the spot) (Mayerson & Burch, 1940; ten Harkel *et al.* 1994; Bouvette *et al.* 1996). However, their effects on standing blood pressure in patients with autonomic failure vary. Ten Harkel found that toe raising did not consistently increase standing blood pressure in patients with orthostatic hypotension, but responses varied greatly (ten Harkel *et al.* 1994). In contrast, Bouvette found that toe raising and marching on the spot could increase systolic blood pressure 20–23 mmHg (Bouvette *et al.* 1996). We investigated the effect of both manoeuvres and found they increased standing blood pressure to a similar degree (~13/5 mmHg) in patients with orthostatic hypotension, as presented in Fig. 1. The variable responses may stem from differences in the degree of sympathetic vasomotor failure in the patients. The absence of sympathetic vasoconstrictor activity in non-active and active muscles may lead to an excessive peripheral vasodilatation during muscular work that cannot be compensated for by the increase in cardiac output that occurs during dynamic exercise (Puvi-Rajasingham *et al.* 1997). As a consequence blood pressure falls, and as the patient develops muscle fatigue and stops exercising, a further drop in blood pressure occurs (Marshall *et al.* 1961; Puvi-Rajasingham *et al.* 1997). Therefore, physical counter-manoeuvres using dynamic muscle contraction to combat orthostatic dizziness should be taught to the patients with caution.

Air-pressurized (or anti-gravity) suits were first developed for use in military aviation, in order to protect pilots from high acceleration forces generated during aerial combat in high-performance aircraft. These suits were adapted for use in the treatment of patients with orthostatic hypotension in

the mid fifties (Sieker *et al.* 1956). By applying pressure (20–50 mmHg) equally to the calf, thighs and abdomen, orthostatic blood pressure is increased (Sieker *et al.* 1956; Bannister *et al.* 1969; Fox, 1971). This effect results from shifting blood volume from the dependent regions centrally, resulting in augmented end-diastolic right ventricular pressure and volume and increased cardiac output (Sieker *et al.* 1956; Bevegård *et al.* 1962; Rosenhamer & Thorstrand, 1973; Gaffney *et al.* 1981) without a notable change in total peripheral resistance (Bevegård *et al.* 1962; Gaffney *et al.* 1981). Despite their effectiveness in restoring the ability of a patient to participate in the activities of daily life (Fox, 1971; Rosenhamer & Thorstrand, 1973), their use is cumbersome. The use of air-pressurized suits has ended with the development of elastic body garments. Elastic body garments for the prevention of orthostatic hypotension have the advantage of being more comfortable and aesthetically more acceptable than pressurized suits (Bannister *et al.* 1969; Sheps, 1976).

Recent work has shown that when using compression in patients with orthostatic hypotension, the abdomen is the most important single site for compression (Denq *et al.* 1997). In children with hyperadrenergic orthostatic hypotension and syncope, abdominal compression with a binder and inflatable bladder reduces the fall in thoracic blood volume, arterial blood pressure, and symptoms during standing (Tanaka *et al.* 1997). Since the aim of using counter-pressure garments is not to obtain a maximal blood pressure increase, but to increase blood pressure sufficiently so as to reduce symptoms without being too cumbersome; abdominal binders may be the most suitable device currently available.

In summary, in patients with autonomic failure, orthostatic hypotension results from an impaired capacity to increase vascular resistance during standing. This fundamental defect leads to increased downward pooling of venous blood and a consequent reduction in stroke volume and cardiac output that exaggerates the orthostatic fall in blood pressure. The location of excessive venous blood pooling has not been established so far, but present data suggest that the abdominal compartment (i.e. splanchnic circulation) and perhaps skin vasculature are the most likely sites. Measures like leg-crossing that reduce 'normal and excessive' orthostatic pooling of venous blood result in an augmented venous return to the heart and thereby increase cardiac output and blood pressure in patients with autonomic failure. Abdominal belts are thought to counteract the excessive venous pooling in the splanchnic region.

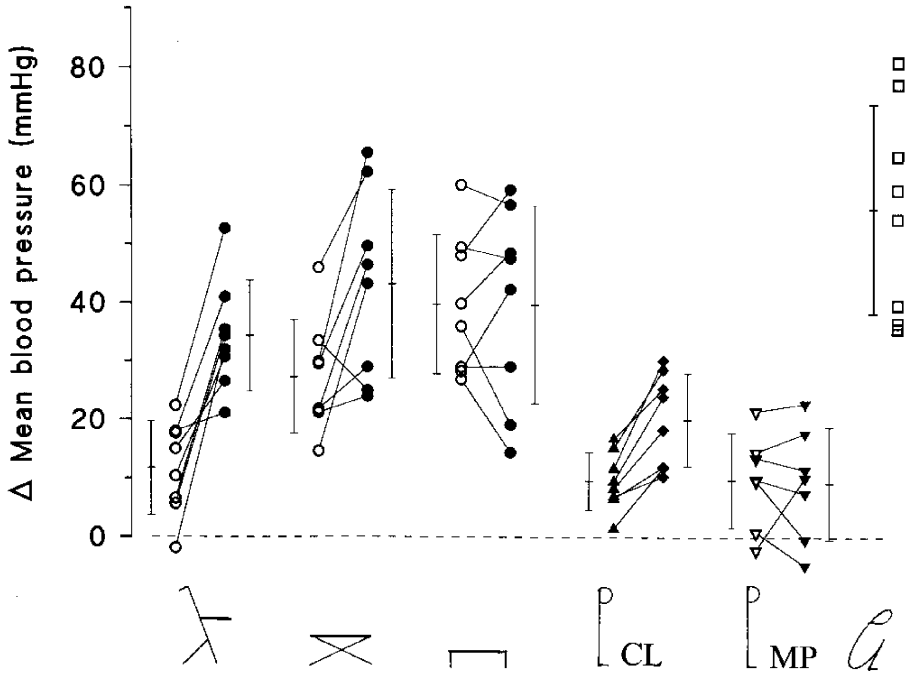

Figure 1. The efficacy of sitting, crossing legs, muscle pumping and squatting to improve orthostatic hypotension in patients with autonomic failure

Mean finger arterial blood pressures (Finapres) are expressed as the blood pressure change in the second 30 s of response from the pre-manoeuvre standing blood pressure. For muscle pumping the second 15 s of response from the pre-manoeuvre standing blood pressure. From left to right: sitting on a Derby chair (height 48 cm), a fishing stool (height 38 cm), and a foot stool (height 20 cm), without (○) and with (●) crossed legs; standing in crossed-legs position (CL) without (▲) and with (◆) contraction of lower extremity musculature; standing while muscle pumping (MP), marching on the spot (▽) and toe raising (▼); and squatting (□). The vertical lines represent means and S.D. (Adapted from Smit *et al.* 1997 with unpublished observations (A. A. J. Smit & W. Wieling) on muscle pumping.)

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