REVIEW

The patient with supine hypertension and orthostatic hypotension: a clinical dilemma

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Coexistent supine hypertension and orthostatic hypotension (SH-OH) pose a particular therapeutic dilemma, as treatment of one aspect of the condition may worsen the other. Studies of SH-OH are to be found by and large on patients with autonomic nervous disorders as well as patients with chronic arterial hypertension. In medical practice, however, the aetiologies and clinical presentation of the syndrome seem to be more varied. In the most typical cases the diagnosis is straightforward and the responsible mechanism evident. In those patients with mild or non-specific symptoms, the diagnosis is more demanding and the investigation may benefit from results of the tilt test, bedside autonomic tests as well as haemodynamic assessment. Discrete patterns of SH-OH may be recognisable. This review focuses on the management of the patient with coexistent SH-OH.

literature for guidance to treatment, studies of SH-OH are to be found by and large in patients with autonomic nervous disorders^{2 11 12} or those with chronic arterial hypertension.^{1 5 7} However, the aetiologies and clinical settings of the syndrome of SH-OH would seem to be more varied. The subject has been not fully investigated in the literature and no generally accepted guidelines are available for the management of SH-OH.

In this paper, the dilemma of the practitioner as confronted by the patient with SH-OH will be illustrated with case descriptions of varying aetiologies and prognostic significance. The pathophysiological mechanisms operative in SH-OH will be analysed, methods of its evaluation detailed, and treatment of the condition suggested.

CASE HISTORIES

Primary autonomic failure

A 68 year old white man, was referred to our outpatient clinic in 1990 with the chief complaint of dizziness upon arising from bed. Arterial hypertension had been diagnosed a short time before and was being treated with hydrochlorothiazide 12.5 mg/day and propranolol 80 mg/day. He had a 20 year history of anxiety, chronic constipation, and impotence. On physical examination no relevant abnormalities were noted aside from high BP. The supine BP was 190/108 mm Hg and, after two minutes of standing, it decreased to 110/60 mm Hg with associated dizziness. Results of routine laboratory tests were unremarkable, including blood sugar and HbA1c, vitamin B12 and folate levels. A 10 minute supine 30 minute head up tilt test was performed: the supine BP was 220/108 mm Hg; after one minute of tilt the BP decreased to 90/50 mm Hg; at two minutes of tilt it was 104/80 and remained essentially unchanged until completion of 30 minutes of tilt. The HR remained fixed at 56–58 bpm during the supine and tilt phases. Additional findings included: sinus arrhythmia ratio on controlled breathing of 1.04, Valsalva ratio of 1.1 (age adjusted normal >1.16), Schirmer's test—4 mm of moistening in both eyes (normal >5 mm), abnormal pupillary measurements in response to light and acetylcholine; BP responses to arithmetic mental challenge as well as cold pressor test showed increases of the diastolic BP of 8 mm Hg and 12 mm Hg, respectively. Pure autonomic failure was

Of all the aberrations of blood pressure (BP), the coexistence of supine hypertension (SH) and orthostatic hypotension (OH) in the same patient would seem to pose a particular therapeutic dilemma, as treatment of one aspect of the condition may worsen the other. As the autonomic nervous system plays a critical part in fine tuning the regulation of BP, it may not be surprising that patients with advanced autonomic failure may develop OH to the point where they are unable to stand for more than a few minutes.^{1–4} However, the fact that patients with autonomic failure also have high BP while lying down, is often overlooked.^{1 2 4} Thus, patients with autonomic failure may display both SH and OH. In addition, the population of hypertensives provides a large pool of patients with the background on which SH-OH phenomenon may develop. The patients with essential arterial hypertension may develop OH secondary to desensitisation of arterial baroreceptors by persistent increase of the BP.^{5 6} The frequency of OH in hypertensive patients increases with advancing age and with increasing systolic BP.^{6–9} On the one hand hypertension itself is conducive to the development of SH-OH,^{1 5 6} but on the other hand antihypertensive drugs used to treat the condition may also induce OH or aggravate it when pre-existent.^{8 9}

While OH can be disabling, difficult to treat and predictive of mortality in elderly patients,¹⁰ the subset of patients with SH-OH is even more challenging to deal with. In consulting the

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diagnosed. Subsequent therapeutic trials with clorazepate 5 mg/day and sulpiride, overnight transdermal nitroglycerin, use of support stockings, and rest in a reclining chair all failed to alleviate symptoms or improve BP. On 24 hour ambulatory BP monitoring, measurements ranged from 84/46 mm Hg to 260/124 mm Hg. Ten years later Parkinson's disease was diagnosed and carbidopa-L-dopa treatment started. During follow up, BP values and oscillations remained as before, with the patient taking two antiparkinsonian drugs and no antihypertensive drugs. Later, cognitive impairment developed. With cognitive impairment, parkinsonism, and autonomic dysfunction present, the diagnosis of Levy body syndrome was made.

Essential HT-OH induced by antihypertensive drugs

A 72 year old man was admitted to the medical ward with pulmonary oedema and uncontrolled hypertension. There was a long history of arterial hypertension and, more recently, a minor stroke, myocardial infarction, and moderate renal failure. His BP was poorly controlled while receiving amlodipine 10 mg/day, doxazosin 4 mg/day, atenolol 100 mg/day and hydrochlorothiazide 12.5 mg/day. After remission of the respiratory distress, supine BP was 220/124 mm Hg and seated BP was 212/125 mm Hg. Treatment with clonidine was started reducing supine BP to 160/90 mm Hg, but resulting in orthostatic dizziness associated with seated BP 100/64 mm Hg. Eventually, the dose of clonidine was tapered to 0.45 mg/day and 10 mg transdermal nitroglycerine was added at night. Orthostatic symptoms disappeared, but BP control was unsatisfactory, with most of the seated BP measurements in the 170–180/90–95 mm Hg range. Examination did not find evidence for secondary hypertension.

PATHOPHYSIOLOGY

Normal BP homeostasis is dependent on the anatomical and functional integrity of the baroreflex arch, including arterial baroreceptors, afferent and efferent autonomic nerves, vasomotor centre as well as effector organs—heart, arterioles, and veins.^{13–15} In addition, numerous factors modulate the response to baroreflex activation and thus influence haemodynamic response to postural challenge: the origin and strength of the activating stimulus; the set point of the reflex; neuronal input from the hypothalamus and cortical and brain stem centres; responsiveness of cardiovascular receptors and organs; modulatory influences of neurohumoral and vasoactive substances; and interactions of the aortocarotid with chemoreflex arcs.^{14 16–20}

For the appropriate management of SH-OH a more detailed understanding of its dual facets would be helpful.

Orthostatic hypotension

When a normal person stands, 10% to 15% of the blood is pooled in the legs thereby secondarily reducing venous return, cardiac output and arterial pressure. This fall in pressure activates baroreceptors with a subsequent reflex increase in sympathetic outflow and parasympathetic inhibition, leading in turn to peripheral vasoconstriction and increased HR and contractility. There may be a slight fall in systolic BP, a slight rise in diastolic BP, and a mild increase in HR (box 1).¹³

OH defines a fall in systolic BP (SBP) of at least 20 mm Hg and/or diastolic BP (DBP) of at least 10 mm Hg within three minutes of standing.²¹ OH is a common condition, its prevalence ranging from 7% in healthy normotensive elderly persons to 30% in patients older than 75 years with systemic disease.^{8 21 22} The major aetiologies of OH may be divided into three categories (box 2): dysautonomia, hypovolaemia, and adverse effects of drugs. Among autonomic neuropathies, primary autonomic failure, multiple system atrophy and

Box 1 Orthostatic BP and HR changes in health and disease

Normal changes

Systolic BP: mean -6.5 mm Hg (-19 to $+11$)
Diastolic BP: mean $+5.6$ mm Hg (-9 to $+22$)
HR: mean $+12.3$ bpm (-6 to $+27$)

Abnormal orthostatic changes

Orthostatic systolic hypotension: decrease of at least 20 mm Hg in systolic BP

Orthostatic diastolic hypotension: decrease of at least 10 mm Hg in diastolic BP

Orthostatic diastolic hypertension: diastolic BP <90 mm Hg in recumbence and >97 mm Hg in standing position

Orthostatic tachycardia: increase in HR by 30 bpm or more or to 108 bpm

Parkinson's disease, as well as autonomic neuropathy secondary to systemic disorders may cause severe OH.^{1 2 12} With respect to drugs, nitrates, antihypertensives, and tricyclic antidepressant drugs frequently induce OH.^{1 2}

OH-SH

At first glance it may seem paradoxical that many patients with autonomic failure and OH also have supine hypertension.^{6 7} Autonomic failure is a disorder of noradrenergic neurotransmission in which postganglionic sympathetic neurons do not release norepinephrine (noradrenaline)

Box 2 Aetiology of orthostatic hypotension

Neurogenic orthostatic hypotension

- Primary dysautonomia: acute/subacute chronic—pure autonomic failure, multiple system atrophy, Parkinson's disease
- Secondary
 - Congenital—nerve growth factor deficiency
 - Hereditary—familial dysautonomia, dopamine β -hydroxylase deficiency, aromatic
 - L-amino acid decarboxylase deficiency
 - Metabolic: diabetes mellitus, chronic renal failure, chronic liver disease, alcohol induced, vitamin B12 deficiency
 - Inflammatory: Guillain-Barre syndrome, vasculitis
 - Infectious
 - Paraneoplastic
 - Trauma
 - Miscellaneous

Hypovolaemic orthostatic hypotension

- Intravascular hypovolaemia (plasma or erythrocytes)
- Vasodilator excess (mastocytosis, bradykinin excess, carcinoid)
- Excessive pooling in leg veins (varices or impaired constriction in leg veins attributable to segmental autonomic failure)

Drug induced orthostatic hypotension

- Drugs acting on the autonomic nervous system
- Drugs causing autonomic neuropathy
- Vasodilators

appropriately. Subnormal norepinephrine release results in impaired vasoconstriction, absence of appropriate reflex increase in HR, and reduced intravascular volume, which contribute to hypotension.⁴ Any disease that causes peripheral neuropathy can be associated with autonomic neuropathy. In most patients with autonomic failure the aetiology is obvious. Three forms of primary autonomic failure (pure autonomic failure, multiple system atrophy, and autonomic failure in the setting of Parkinson's disease) are diagnosed after exclusion of secondary autonomic failure.

Autonomic failure is characterised by absent baroreflex buffering. This lability of BP control is illustrated in autonomic failure patients by severe decrease in BP on exposure to environmental heat, exercise or food intake, while water drinking may elicit a potent pressor effect.^{23–24} Cardiac function, arteriolar contractility, and venous pooling are important effector mechanisms in BP homeostasis. Malfunctioning of these effector systems is probably involved in the SH-OH syndrome. Few studies have investigated cardiac haemodynamics, total intravascular volume and blood compartments, circulatory mediators, autonomic nervous, and baroreflex functioning in patients with SH-OH.^{12–13–25–26} In many patients, both OH and SH can remain undetected for long periods of time because BP is often measured only in the seated position when it can be normal. In a study of 117 patients with severe autonomic failure, SH was present in 56% of patients, the prevalence of SH being similar in those with primary autonomic failure compared with multiple system atrophy patients.²⁷ Possible explanations of supine HT in this context are impaired baroreflex buffering of the BP, inappropriate natriuresis, higher blood volume, and residual sympathetic tone acting on hypersensitive postsynaptic adrenoreceptors.^{1–6–27–28}

In a subset of patients, SH with mild but progressive decline in BP occurs on postural challenge, often without appropriate reflex increase in HR.²⁹ This is consistent with a milder degree of autonomic neuropathy, compared with the widespread autonomic neuropathy in neurogenic OH.^{6–30} Increased venous pooling of the blood in the lower extremities may be important in this process.¹¹

OH may be present in 5% to 14.6% of patients suffering from chronic hypertension, but only a minority of these have orthostatic symptoms.^{1–6–8} In the cardiovascular health study, the prevalence of OH was 18% in subjects aged 65 years or older, but only 2% of these patients had dizziness when standing.⁸ Desensitisation of the baroreflex by lasting hypertension and residual sympathetic tone acting on hypersensitive postsynaptic adrenoreceptors¹ may play a part in the pathogenesis of SH-OH. This is supported by remission of OH after long term control of the BP.^{31–32} The latter mechanism is not the sole explanation. Diuretics and antihypertensive drugs are often among the aggravating factors of OH and reduction of these drugs usually achieves relief of orthostatic symptoms.^{5–6–33} However, many studies have shown no association between use of antihypertensive drugs and OH.^{6–7–34–36} The tendency to hypertension and age related OH is probably multifactorial in nature. The presence of one factor, such as antihypertensive therapy, may be insufficient to produce OH.^{33–36}

Cerebrovascular autoregulation acts as a safeguard to protect the brain against excessive oscillations of BP. Cerebral blood flow and vascular physiology has been reviewed recently.³⁷ Under normal physiological conditions, changes in mean arterial BP (MAP) between 60 and 160 mm Hg in the average person produce little or no change in cerebral blood flow.³⁸ Cerebral autoregulation ensures that as MAP increases there is increased resistance with a reduction in the calibre of the small cerebral arteries and arterioles. This protects the cerebral arterioles and the brain from increase in

MAP. This adaptive mechanism also maintains adequate cerebral blood flow when MAP or cerebral perfusion pressure decreases. Thus, cerebral arterioles dilate as MAP decreases and constrict as MAP increases. Beyond these limits of autoregulation, cerebral blood flow is directly proportional to MAP and is "pressure passive". Thus, when MAP exceeds 150–160 mm Hg cerebral blood flow begins to increase and vessels may begin to leak with extravasation of blood into the extravascular space. On the other hand, a sudden decrease in cerebral blood flow occurs at the lower limit of autoregulation. The precise physiological process accounting for cerebral autoregulation is unknown, and may represent a combination of metabolic, myogenic, and neurogenic mechanisms. The metabolic mechanism may be mediated by the release of vasodilator substances that regulate the cerebrovascular resistance to maintain constant cerebral blood flow. Although no specific mediator fits all experimental findings, adenosine, a potent cerebral vasodilator, is a prime candidate.³⁹ Other transmitters/substances that have been proposed as mediators of autoregulation are NO, protein kinase C, melatonin, prostacyclin, activated potassium channels, and intracellular second messengers.^{37–40} The myogenic theory states that the basal tone of the vascular smooth muscle is affected by change in perfusion or transmural pressure with the muscle contracting with increased MAP and relaxing with decreased MAP. However, constant pressure increase is probably not a sufficient stimulus to maintain sustained vascular contraction. Some investigators believe the myogenic mechanism sets the limits of autoregulation, whereas the metabolic mediators are responsible for cerebral autoregulation itself. Perivascular nerve fibres may also modulate vascular response to changes in BP. However, the specific mechanisms by which the central nervous system exerts control on the cerebral vasculature are poorly understood.⁴¹

Although the limits of cerebral autoregulation are often considered to be 60 to 160 mm Hg, there is considerable variation in the limits among normal persons. Pathologically, these limits can be affected by a number of conditions. Classic examples are chronic hypertension and traumatic brain injury. In chronically hypertensive adults, the autoregulatory curve is shifted to the right and a MAP >160 mm Hg may not cause any increase in CBF. In patients with traumatic brain injury, cerebral autoregulation may be impaired, abolished, or similarly shifted to the right.^{42–43} Neurological disorders where autoregulatory impairment may contribute to the pathophysiology include ischaemic cerebrovascular disease, subarachnoid haemorrhage, and traumatic brain injury. Hypercapnia ($P_{aCO_2} > 60$ mm Hg) will consistently impair cerebral autoregulation. Abnormal autoregulation can range from minimal impairment to complete loss. In patients with absent autoregulation, systemic hypertension may lead to cerebral haemorrhage and oedema formation, whereas a decrease in BP may further areas with ischaemia into becoming areas of infarction.³⁷

CLINICAL EVALUATION

It may be speculated that clinically silent isolated supine hypertension (SH) may be more prevalent than appreciated, because the standard measurement of BP is taken in the sitting position. Apart from those undergoing evaluation for orthostatic symptoms, this entity then may come to attention only in those who are bedridden, including hospital inpatients. Clinicians should be aware of possible SH-OH in the settings of dysautonomia or arterial hypertension as well as in patients presenting symptoms of orthostatic intolerance. However, atypical or non-specific symptoms such as visual disturbances, impaired cognition, suboccipital pain, fatigue, nonspecific dizziness or increased nicturia, may also be because of OH. In the initial evaluation of such patients a

Box 3 SH-OH: scheme of investigation

- **Clinical suspicion:**
 - Setting: dysautonomia, arterial hypertension, bed-ridden
 - Symptoms of orthostatic intolerance
 - Atypical or non-specific symptoms: visual disturbances, impaired cognition, suboccipital pain, fatigue, non-specific dizziness, increased nocturia
- **Screening test—bedside postural test**
- **Autonomic function testing according to clinical context**

scheme of investigation may be useful (box 3). More extensive investigations may be performed in patients with suspected autonomic neuropathies.⁴⁴

The bedside postural test

The diagnosis of SH-OH may be established at the bedside. The patient's BP is measured after 5 to 10 minutes in the supine position and is repeated after the patient stands motionless for three to five minutes, with the patient's arm supported at heart level. The mercury column sphygmomanometer is preferred by us because of its reliability. Automatic arm cuff devices, as they are programmed to repeat and confirm measurements when discrepant values are recorded, may be therefore at disadvantage after the rapidly dropping BP during OH. Patients with severe autonomic failure have an immediate fall in BP on standing and are easily diagnosed with this simple method.¹⁶ However, there are situations associated with delayed appearance of OH, requiring up to 30 minute of standing for the diagnosis to be established and may, therefore, be missed by the bedside postural test.^{1 26} A more comprehensive evaluation may be obtained with the head up tilt test.

The head up tilt test (HUTT)

This method uses a controlled passive postural stress to challenge the cardiovascular response as measured in BP and HR changes. Various protocols are used in performing this test. According to recommendations of the European Society of Cardiology, the supine pre-tilt phase should last at least five minutes, when no venous cannulation is performed, and at least 20 minutes when venous blood sampling is part of the study; the tilt angle recommended is 60 to 70 degrees; and the duration of passive tilt should be a minimum of 20 minutes and maximum of 45 minutes.^{1 45} Repeated measurements are taken at 30 second intervals when dizziness or faintness occur and the test is stopped in the event of loss of consciousness. The BP can be measured conveniently with a mercury column sphygmomanometer at pre-established intervals and the HR recorded on an electrocardiographic monitor. With this method it is preferable to use continuous BP and HR monitoring with finger plethysmography.¹⁶ There is uncertainty as to the minimum duration of head up tilt needed to detect OH. In a recent study,⁴⁶ 88% of patients developed OH by one minute of tilt, with an additional 11% developing OH by two minutes and the remaining 1% developing OH by three minutes. Two broad patterns of SBP response to head up tilt were seen: an initial drop in SBP ≥ 20 mm Hg, which remained stable until tilt back or an initial drop ≥ 20 mm Hg followed by a progressive decline in SBP until tilt back. Recognition of the group with progressive fall in BP is important as this group may be at greater risk of orthostatic syncope.⁴⁶

In addition to showing OH, the concurrent finding of HR response with this method may permit the separation out of the different types of hypotensive reactions. Neurogenic OH for one is typically associated with a blunted HR response on standing or passive tilt, while hypovolaemic OH on the other hand is characterised by postural tachycardia. You need to be alert to exceptions such as when HR is slowed by drug treatment or when there is a paradoxical increase in HR in patients with autonomic failure, presumably attributable to parasympathetic withdrawal.¹¹

The reproducibility of both the bedside postural test and the HUTT in assessing OH is imperfect. In one study of symptomatic elderly patients, with measurements on consecutive visits, a consistent drop in systolic BP of >20 mm Hg on postural challenge occurred in only 67.5% of patients. OH was reproduced in 79% of those in whom autonomic function tests were abnormal, while it was reproducible in only 57% of those with normal autonomic functioning.⁴⁷ Similar lack of reproducibility of results has been reported by others.^{48 49} Indeed, the phenomenon of OH is highly variable over time: it is most prevalent in the morning when patients first arise and when supine BP is highest⁵⁰; the time it takes to reach the lowest systolic BP is variable, ranging from 1–12 minutes in one study; and the systolic BP nadir in the morning is lower than in the afternoon. Thus, the magnitude of OH may be underestimated if BP is measured immediately after arising or if it is measured in the afternoon.⁵¹ It has been suggested that the orthostatic fall in systolic BP may be greater with passive tilt than on standing,⁵¹ but data on this are scarce.

Other non-invasive tests of autonomic functioning^{1 16}

An evaluation of autonomic function should be part of the treatment of SH-OH. A number of tests are in common use. Respiratory sinus arrhythmia is assessed during controlled breathing at a rate of six deep breaths per minute, the sinus arrhythmia ratio calculated by dividing the longest by the shortest RR interval. Patients with autonomic failure usually have sinus arrhythmia ratio <1.2 . Another simple test is measurement of the HR change in response to Valsalva manoeuvre. This test is performed by having the patient blow against a 40 mm Hg pressure for 10 seconds with HR monitoring on the electrocardiogram. Typically, the HR increases during the hypotensive phase of the Valsalva manoeuvre and decreases during release of the intrathoracic pressure. The Valsalva ratio is calculated by dividing the fastest HR by the slowest HR during the Valsalva manoeuvre. Patients with autonomic failure usually have a Valsalva ratio <1.4 . More demanding but more accurate in assessment of autonomic failure is the simultaneous monitoring of beat to beat BP and HR by finger plethysmography. The increase in intrathoracic pressure during Valsalva strain produces a transient fall in BP early on and partial recovery of BP later during the strain phase. The BP consistently overshoots above the baseline values immediately after release of increased intrathoracic pressure. Patients with autonomic failure exhibit a different BP response to the manoeuvre, with continued BP decline during the late strain phase and blunted overshoot upon release. Another useful test is measurement of the BP 30 minutes after meal ingestion. Postprandial hypotension is probably caused by pooling of blood in the splanchnic circulation, analogous to that which occurs in the lower limbs when standing.

The above described tests of autonomic function have not been well validated.⁵² In one study rating the utility of these tests in patients with autonomic failure, the sensitivity of the sinus arrhythmia ratio was rated 4 on a scale of 1 to 5, while the reproducibility and the sensitivity of the Valsalva ratio

Figure 1 Supine hypertension and early onset severe OH. The moderate increase in HR may be caused by parasympathetic withdrawal.¹¹

were rated as 3. The reproducibility of postprandial hypotension test was rated as good in one study.⁴⁹

PROPOSED CLASSIFICATION OF SH-OH

There is no accepted taxonomy of the SH-OH syndrome but such classification may be useful for purposes of study and evaluation of treatment options. Classification of SH-OH may be attempted according to symptomatology, chronicity of course, pathophysiology, patterns on tilt test, or results of autonomic and haemodynamic tests (box 4). The following are our proposed classifications:

By symptoms

(1) Typical presentation with characteristic orthostatic symptoms and large supine standing BP differences. (2) Atypical presentation such as patients with symptoms of non-specific dizziness or unexplained fatigue. (3) Clinically silent SH-OH, which may be diagnosed incidentally.

By clinical course

(1) Acute SH-OH in hypertensive patients may occur when intercurrent infection or dehydration interferes with BP homeostasis such as in the second patient in the above case histories. (2) The chronic syndrome is exemplified in this review by autonomic failure in a patient with the Levy body syndrome such as the one described above. The list of aetiologies of primary and secondary autonomic failure has been reviewed elsewhere.⁵³ Chronic SH-OH also seems to be frequent among patients with essential hypertension.^{7 54 55} Some authors prefer to avoid this term, because frequently

despite an observed decrease BP remains high, and propose using the term "exaggerated orthostatic fall in BP".⁵⁶ Its prevalence was 14.6% in one study of primary care patients.⁵⁷

Box 4 Classification of the SH-OH syndrome

By clinical picture:

- Typical, atypical, occult
- Acute, chronic

By pathophysiology:

- Autonomic failure
- Partial autonomic failure
- Impaired baroreflex in essential hypertension
- Baroreflex failure
- Effector organ failure: heart failure, venous insufficiency, capillary leak
- Hypovolaemia
- Drug induced

By haemodynamic patterns on head up tilt:

- Supine hypertension with typical neurogenic OH
- Supine hypertension with sustained hypotensive reaction on tilt
- Supine hypertension with late onset vasovagal reaction
- Supine hypertension, early onset transient orthostatic hypotension and late cardioinhibitory reaction

Figure 2 Severe supine hypertension with progressive, substantial but asymptomatic decrease in BP. The HR remained unchanged.

By pathophysiology

Autonomic failure, impaired baroreflex, and effector organ failure are the main impairments responsible for SH-OH.

By reaction patterns on HUTT

SH may be associated by four patterns of hypotensive reactions on HUTT: (1) typical neurogenic OH,¹⁶ characterised by the sudden and severe drop in BP within three minutes of head up tilt, associated with dizziness and light headedness or loss of consciousness (fig 1); (2) typical vasovagal reaction with late onset on tilt,⁴⁵ characterised by hypertensive values when supine as well as during tilt, until a sudden cardioinhibitory reaction, vasodepressor reaction or mixed bradycardia-hypotension takes place; (3) sustained hypotensive reaction on tilt also called "delayed orthostatic intolerance",²⁶ characterised by graduated, progressive but ultimately substantial decrease of BP after tilting the patient (fig 2); (4) early onset transient orthostatic hypotension and late cardioinhibitory reaction—a mixture of the other three cardiovascular reaction patterns (fig 3). This pattern has also been called "atypical vasovagal reaction".¹¹

While the HUTT provides a window into changes in the cardiovascular reactivity, attempts to determine the pathophysiology of SH and associated postural hypotensive reactions by outcomes on HUTT should be undertaken with caution. Studies in this field are insufficient, reproducibility of discrete hypotensive patterns and their pathophysiological correlates have not been adequately investigated. We could not find, in searching the literature, population based studies on the frequency of different SH-OH patterns. Longitudinal studies on the quality of life, outcome, and specific treatment in patients presenting different patterns of SH and associated postural hypotensive reactions remain to be performed.

TREATMENT

Of all patients with SH-OH, those who have significant orthostatic symptoms require the most clinical attention. Certainly, those with syncope or presyncope should be treated as stated in the recent Guidelines on Management of Syncope⁵⁷ under class 1 recommendations. All patients should be educated to factors that influence systemic BP, such as avoiding sudden head up postural change, standing still for a prolonged period of time, prolonged recumbence during daytime, straining during micturition and defecation, hyperventilation, high environmental temperatures, severe

physical exertion, large meals especially with refined carbohydrates, and alcohol and drugs with vasodepressor properties. Even simple water intake increases have been shown to be beneficial. In addition, exercise of leg and abdominal muscles, especially swimming, may be useful.^{1 4 57}

In the management of patients with primary and secondary autonomic failure, the following measures may be helpful during daytime: avoiding the supine position and preferring rest in a chair, making use of portable chairs during ambulation, use of abdominal binders and/or waist high support stockings or garments, dividing the meals as to avoid profound postprandial hypotension with preference for small frequent meals with reduced carbohydrate content. During night time: sleeping in the head up position so as to diminish nocturnal sodium loss and improve orthostatic hypotension in the morning. In addition, application of transdermal nitroglycerin during night time to diminish SH.^{1 57}

In many instances the management entails only modification of drug treatment for concomitant conditions including reduction of antihypertensive or diuretic drugs, modification of antiparkinsonian regimen, and use of alternative antipsychotics. In selected cases, cautious administration of short acting pressor agents during the day may be tried.^{1 29 57} Their use is best restricted to a dose in the early morning and early afternoon when orthostatic symptoms are at their worst. This schedule permits two to three hours of upright activity after each dose. Patients must be instructed to avoid lying down after drug treatment and to rest in a seated rather than supine position if they grow tired during the day. Symptoms of orthostatic hypotension tend to lessen during the evening, and it is recommended to avoid pressor agents at that time of day. Midodrine^{58–60} seems to be of particular interest given the rapidly expanding and generally positive experience with this agent as per class 2 recommendations in the Guidelines on Management of Syncope. Rarely, however, midodrine induced supine hypertension has been suggested to cause severe cerebrovascular complications.^{61 62} If the combination of fludrocortisone and sympathetic vasoconstrictor drugs does not produce the desired effect, then referral to medical centres specialising in the evaluation and treatment of autonomic failure should be considered. These centres may have access to investigational agents and/or may be more experienced in the use of drug combinations.⁵⁷ An unresolved issue is how much harm results from supine hypertension in

Figure 3 Severe supine hypertension, transient OH, late cardioinhibitory reaction.

autonomic failure and whether hypertension should be treated in these patients.⁶³⁻⁶⁵

There are no accepted guidelines for the treatment of essential hypertension associated with sustained hypotensive reactions. Generally, hypertensive patients with no pre-treatment OH are at low risk of developing OH with use of antihypertensive drugs. Antihypertensive drugs typically only exacerbate pre-existing OH.⁶⁴ Generally, tighter control of the BP decreases the prevalence of OH.³¹ On the other hand, antihypertensive drugs themselves may increase OH,³⁶ particularly peripheral vasodilators such as α receptor antagonists and nondihydropyridine calcium channel antagonists. On the other hand, ACE inhibitors, angiotensin-receptor antagonists and β adrenoceptor antagonists with intrinsic sympathomimetic activity are less likely to worsen OH.³³ Recently, large studies have shown improvement of the postural baroreflex by long term β blocker treatment, but not with ACE inhibitors, calcium channel antagonists, diuretics, and angiotensin II receptor antagonists.⁴⁵ In this respect, in elderly patients β blockers may, therefore, be the most appropriate antihypertensive agents as they protect the elderly from orthostatic impairment.²⁴ In addition, careful management of electrolyte disturbances has been shown to decrease the risk of OH with diuretic use.¹⁻⁵⁷

SUMMARY

The SH-OH syndrome may have multiple aetiologies, variable course, and diverse outcomes. In the most typical cases the diagnosis is straightforward and the responsible mechanism evident. In those patients with mild or non-specific symptoms, the diagnosis is more demanding and the examination may benefit from results of bedside autonomic tests, the tilt test, as well as haemodynamic assessment. Discrete patterns of SH-OH may be recognisable. Future studies will show whether treatment tailored at particular SH-OH patterns may improve the BP control and patient symptoms.

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