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Case Report

The Challenging Syndrome of Supine Hypertension Associated with Orthostatic Hypotension

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Abstract

A 72-year-old man with basilar artery stroke was underwent successful angioplasty. Bilateral infarctions in the cerebellum, basal ganglia and capsula interna left the patient with central ataxia. His longstanding arterial hypertension (HT) had deteriorated. Orthostatic hypotension (OH) along with supine HT evolved, being indicators of efferent baroreflex failure. Managing the patient's blood pressure (BP) became challenging, more so under repeated changes of the clinical scenario during a 6 weeks period. There was a reminder to the numerous faces of syndrome of supine HT associated with OH: 1. longstanding HT phenotype had acutely changed under a cerebrovascular involving the midbrain; 2. new-onset OH, supine HT and highly variable BP not influenced by mental challenge were consistent with efferent baroreflex failure; 3. BP management under efferent baroreflex failure was difficult and there was a need to compromise, giving priority for avoiding orthostatic symptoms; 4. intercurrent sepsis caused an persistent alteration of the patient's BP status requiring discontinuation of antihypertensive medications.

INTRODUCTION

Blood pressure homeostasis refers to compensatory adjustments aimed at buffering changes the blood pressure (BP) in response to physiological stressors. The tight control of the central circulation is maintained through changes in cardiac output and vascular tone. Such changes are mediated by the autonomic nervous system. The sympathetic nervous system plays the predominant role in determining the level of the arterial BP and the distribution of the cardiac output. Central regulatory mechanisms control the sympathetic outflow to the cardiovascular system. Short-term reflex control of the sympathetic vasomotor activity is regulated by baroreceptor and chemoreceptor reflexes [1-3]. The loss of the normal baroreflex function in patients with autonomic failure causes a deep perturbance of BP control, with the patients often being hypertensive when supine and becoming hypotensive when upright. Orthostatic hypotension (OH), with or without supine HT, is common in patients with neurodegenerative disorders such as Parkinson's disease, multiple system atrophy, pure autonomic failure, dementia with Lewy bodies, and peripheral neuropathies. OH may provoke signs and symptoms of cerebral hypoperfusion, including nausea, fatigue, lightheadedness, dizziness, visual blurring, and eventually syncope. Supine hypertension (HT) may complicate with stroke, heart failure, and coronary events [1-3]. Because OH and supine HT typically coexist, are associated with wide swings in BP, may experience abnormal responses to pharmacological or physiological challenges, their management is problematic. Treatment of one aspect of the condition may worsen the other [2,4]. Even more challenging may be the condition under changing clinical scenarios, as shown in the case history below.

CASE PRESENTATION

A 74-year-old man was admitted for rehabilitation, recently having suffered a cerebrovascular event. During the preceding ten years he was treated for arterial hypertension. Recently, the BP came out of control with incidental 226/105 mmHg measured. Two weeks afterward the patient began to complain of headache, nausea, and unsteady gait. Deterioration to ataxia and impaired consciousness resulted in his referral in emergency to hospital. At arrival he was unresponsive. Cerebral CT and MRI revealed bilateral cerebellar infarctions, along with infarctions in the basal ganglia and capsula interna. The basilar artery was occluded. Selective angioplasty and stenting achieved complete opening of the basilar artery. The patient recovered consciousness. There was residual cerebellar ataxia, mild dysarthria, mild left central facialis palsy, and arterial HT. Six days later he was transferred to our institution for rehabilitation. At the time of admission, he was alert; fully conscient, the BP, heart rate, respiration, and SpO2 were within the normal range. His daily medications were prasugrel 10 mg, aspirin 100 mg, enoxaparin 40 mg, clonidine 0.45 mg, amlodipine10 mg, ramipril 5 mg, simvastatin 20 mg, esomeprazole 20 mg and tamsulosin 0.4 mg. Physiotherapy was scheduled, but a succession of unforeseen spells put a new challenge.

Early in the morning, while the patient was moved from his

bed to the bathroom, he lost consciousness and exhibited jerking movements of the arms and legs. Brought back to bed the jerks ceased instantly and he recovered consciousness. A physician called in emergency found the patient alert and the spell had terminated; there were no observable differences on physical and mental examination. The electrocardiogram was unchanged, in sinus tachycardia. The next morning the patient experienced a similar spell under similar circumstances. In suspecting OH, a supine-to-standing postural test was performed at bedside. The supine BP was just about 130/85 mmHg. When the patient was brought to stand, the BP dropped immediately to 86/64 mmHg. OH was diagnosed and measures were prescribed to mitigate BP instability. When a third similar event occurred, the patient was referred to hospital. In the emergency department the BP was 178/102, measured with the patient supine. Neurology examination was unrewarding. Cerebral CT showed no evidence of an acute insult; the basilar artery was patent. Anticonvulsive treatment with levetiracetam was prescribed and the patient was returned to our ward. The ensuing morning, the patient being seated on a wheelchair after breakfast, he was at ease and free of symptoms. His sitting BP was 120/66 mmHg. Brought to bed, the BP rose to 174/106 within 3 minutes. On repeating the supine-to-standing measurement the BP instantly dropped to 87/35 mmHg (Figure 1) with the patient appearing disturbed. Back to bed the malaise vanished.

Obviously, there were wide swings in BP: supine HT despite maximal antihypertensive treatment and severe symptomatic OH. Supine HT and severe OH were replicated on repeating the test a few days later (Figure 2).

Application of elastic compression by an abdominal binder increased the supine BP but did not prevent OH. Remarkably, during OH the ratio of orthostatic heart rate change / systolic BP change was <0.5, which is consistent with baroreflex failure [4]. The reduced heart rate response to hypotension was constantly noticed during hospitalization on sitting-to-supine, supine-to-standing, and sitting-to-standing transitions. On further evaluation, neither emotional nor emotional challenging induces a notable change of BP and heart rate. The patient's responses to postural and emotional challenges were consistent with efferent baroreflex failure. Efferent baroreflex failure is characterized by

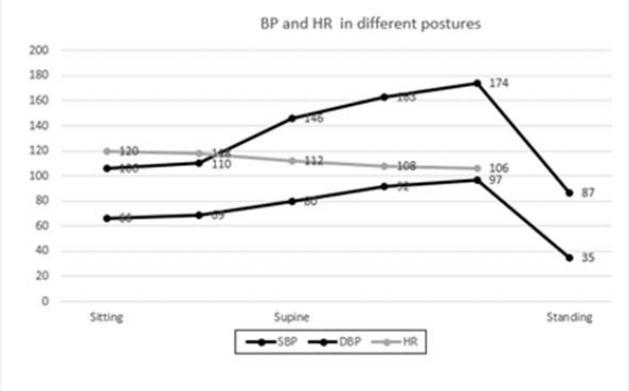

Figure 1 Supine hypertension associated with orthostatic hypotension.

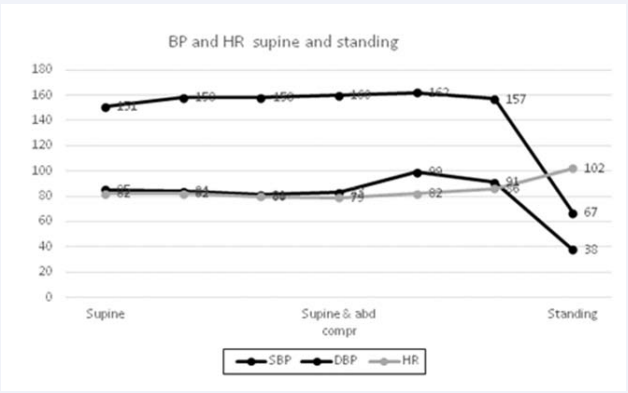

Figure 2 Moderate supine HT enhanced by application of abdominal elastic compression. On standing the BP dropped instantly. The ration of supine to standing HR change/systolic BP change was 0.18.

BP in the hypertensive range when the patient is supine and an immediate fall in BP when the patient is upright, with minimal acceleration of the heart rate; the BP returns to baseline as soon as the patient returns to the supine position. Emotional arousal has no significant effect on heart rate or BP [4].

Several times the patient had convulsive spells early in the morning when he was quickly raised by caregivers from the bed to the bathroom. The convulsions were instantly relived when he was brought to bed along with the immediate recovery of the consciousness. These spells occurred exclusively in the context of OH and not under other circumstances. The likely diagnosis was convulsive syncope [5]. Syncope and convulsions were afterwards prevented by avoiding brisk transitions from supine to upright posture and did not recur after discontinuation of levetiracetam. Improved orthostatic tolerance was attained by elastic compression applied to the legs and abdomen before rising from the bed, while maintaining the three-drug antihypertensive regimen. For the better control of supine HT transdermal nitroglycerine was applied during the night and removed before the patient was rising from bed. The supine and sitting BP were fairly controlled, syncope and convulsions were avoided, but OH could not be eliminated. Measurements recorded during physiotherapy are shown in Figure 3, when the patient exercised rising from a chair by supporting himself with the hands against a Swedish ladder. Standing for two minutes caused discomfort and presyncope, standing for less than one minute was not associated with symptoms though OH was severe. Further improvement was noticed a week later when the patient was able to stand four minutes (Figure 4).

Unexpected deterioration of orthostatic tolerance occurred after removal of a temporary bladder catheter, the patient now being unable to sit on the edge of the bed (Figure 5). Possible causes were considered: dehydration, bleeding, sepsis, heart failure, inadvertent use of medications. There was no evidence of either, no change in medication, no loss of fluids (neither vomiting, diarrhea, sweats, bleeding), the rectal temperature and the electrocardiogram were normal. Blood and urine cultures were taken. All antihypertensive medications were discontinued. It was only 16 hours later that fever emerged rising to 39.30C.

In the context of urinary catheter manipulation urosepsis was suspected. Treatment with amikacin was started followed by prompt remission of the fever and improvement of the patient's general state as well as the orthostatic tolerance. E. coli was cultured in the urine.

The sitting BP remained normal 9 days after discontinuation of antihypertensive medications. Though recurrence of supine HT was expected after remission of sepsis this did not occur and six weeks later there was no further change in the patient's BP condition: the supine and sitting BP were normal, OH occurred immediately on standing but permitted transitions in comfort (Figure 6).

DISCUSSION

When a normal individual stands a gravitational shift of nearly 500 ml of blood occurs almost instantly away from the chest to the veins below the diaphragm, thereby diminishing the venous return, with the resultant drop of cardiac output and BP. Stretch receptors located within the adventitia of the carotid artery and aortic arch sense the changes in arterial BP and initiate the afferent limb of the baroreflex, the excitation moving through the vagus and glossopharyngeal nerves to the nucleus tractus solitarii in the brainstem. So triggered, neurons in the nucleus tractus solitarii give input to the rostral ventrolateral medulla where sympathetic activity originates. From these centers the sympathetic stimuli are carried through preganglionic efferent fibers in the intermediolateral column of the spinal cord and through the postganglionic efferent fibers that innervate the heart and blood vessels. Sympathetic stimulation causes vasoconstriction, tachycardia and increased cardiac contractility [1].

The sympathetic nervous system plays the predominant role in determining the level of arterial BP and the distribution of cardiac output. Upon standing from a supine or seated position, healthy, volume-replete individuals will typically experience a modest decline in systolic BP of less than 10 mmHg, a slight increase in diastolic BP of about 2.5 mmHg, and a modest increase in heart rate by 10-20 beats per minute. These compensatory changes are induced primarily by augmentation of norepinephrine output from sympathetic peripheral nerve endings. Failure of the

Figure 3 Minute-to-minute BP change under changing posture from sitting to standing.

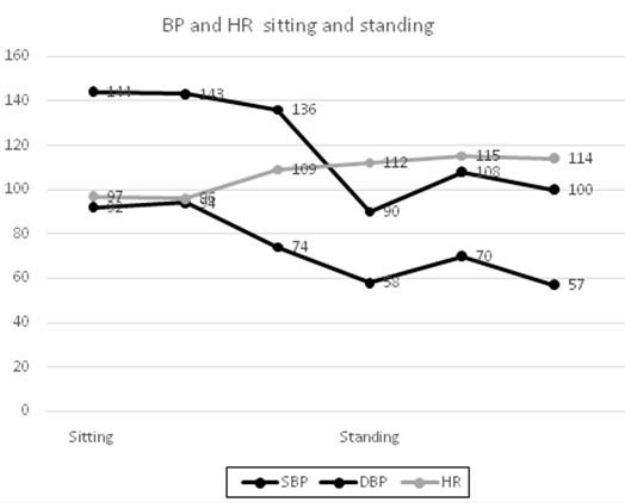

Figure 4 Asymptomatic orthostatic hypotension. The ratio of HR change/SBP change 0.43 is consistent with baroreflex failure.

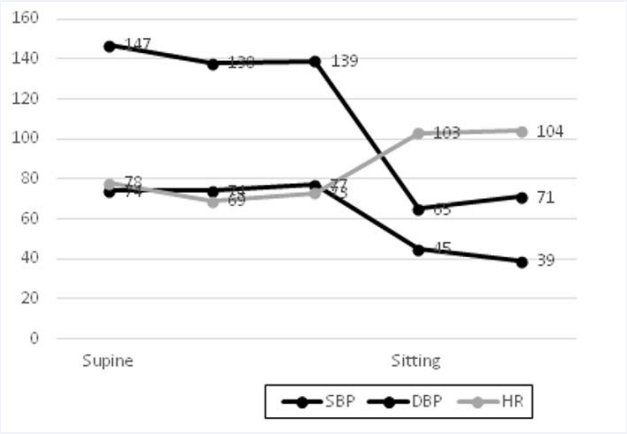

Figure 5 Worsening of postural tolerance..

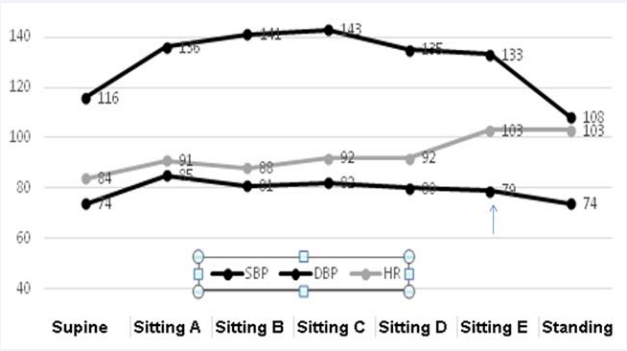

Figure 6 BP and HR under changing in close succession conditions: supine, A. sitting before breakfast, B. sitting & mental challenge, C. sitting postprandial, D. sitting & exercise of upper limbs, E. sitting & exercise of lower limbs, at last standing for one minute.

responsible homeostatic mechanisms causes OH, i.e. an excessive fall in BP occurring early after standing up. Efferent baroreflex failure is defined by a sustained fall in BP of at least 20/10 mm Hg within 3 minutes after assumption of an upright posture and return to baseline as soon as the patient returns to the supine position. Emotional arousal has no significant effect on heart rate or BP in the patient with efferent baroreflex failure [4]. Supine HT (>140/90 mm Hg) develops in 50% of patients with efferent baroreflex failure, probably because of the activation of residual sympathetic fibers and denervation supersensitivity. In the proposito, having bilateral cerebellar infarctions, as well as infarctions in the basal ganglia and in the capsula interna, the neurogenic etiology of the new-onset OH was readily apparent. The responses to postural and emotional challenges were consistent with efferent baroreflex failure. On supine-to-standing postural test, the ratio of heart rate increase (beats per minute) to the decrease in systolic BP (millimeters of mercury) provides distinction between neurogenic OH and OH of other origins. Since the heart rate response to hypotension is blunted in patients with efferent baroreflex failure, a ratio < 0.5 indicates baroreflex failure and provides a sensitive and specific cutoff value [4]. This heart rate response is distinctive from non-neurogenic OH where acceleration of the heart rate is prominent. In the proposito the ratio was repeatedly <0.5, on sitting-to-supine, supine-to-standing, sitting-to-standing transitions.

Several times the patient had convulsive spells early in the morning, when he was quickly raised by caregivers from the bed to the bathroom: he lost consciousness along with convulsions of the upper and lower limbs. The convulsions were instantly relived when he was brought to bed along with the immediate recovery of the consciousness. The spells occurred in the context of OH and not in other circumstances. The diagnosis of convulsive syncope is familiar to physicians specialized in passive tilt examination. Seizure-like activities were observed in about 66% of patients during head-up tilt induced syncope [5]. Induction of syncope with tonic-clonic seizure-like activity under tilt was reported in patients with recurrent, unexplained seizure-like episodes unresponsive to antiepileptic medication. On electroencephalograms non-epileptiform theta and delta wave were seen dissimilar to epileptic seizure [5].

This patient was treated many years long for arterial HT. After the recent stroke the BP came out of control and high doses of antihypertensive medications were required, without however achieving adequate control of the supine BP. Lately, when severe OH came in focus along with supine HT, the management BP became still more demanding. Supine HT associated with OH constitutes a therapeutic challenge since treatment of one aspect of the condition may worsen the other [1-4]. Supine HT may predispose to cardiovascular and renal disease. This is the rationale for treating supine HT. Yet, treatment of supine HT may exacerbate OH. There is no agreement among clinicians, when, or how vigorously to treat supine HT [5-7]. At the very minimum, all patients with neurogenic OH and supine HT should be advised to avoid supine posture during the day and elevate the head of the bed during the night. Expert recommendations suggest that supine HT requires intervention if the systolic BP exceeds 180 mmHg or diastolic BP exceeds 110 mmHg [2].

A time restricted hypotensive effect during the hours the patient lies in bed may be obtained with transdermal nitroglycerin 0.1-0.2 mg/hour, to be removed before standing up [8]. The vasodilator effect of nitroglycerin may provide a clinically significant lowering of the BP. The plasma concentration of nitroglycerin reaches plateau within 2 hours, which is maintained over the time the nitroglycerin patch is left on the patient's skin. The nitroglycerin plasma concentration falls rapidly after patch removal, so the patient may be allowed to sit watchfully a short time afterward. In the proposito, under application of a Nitroderm TTS 10 mg patch the BP at 6 a.m. was in the range 127-118/74-60 mmHg. Should HT treatment be tempered in the presence of OH? An analysis originating in the SPRINT study concluded that there is no need to adopt higher BP targets if OH is symptomless [9]. The situation differs in symptomatic OH. Interventions that are effective in treating hypotension in other forms of low sympathetic tone can be tried, but none has been rigorously tested in patients with baroreflex failure. These include 500 mL oral water bolus, abdominal binder compression, midodrine and droxidopa [1-4]. Droxidopa may be less likely than midodrine to exacerbate supine HT according to a meta-analysis [10]. Some patients may require the addition of fludrocortisone, however, this has not been rigorously tested and carries the risk of exacerbating underlying hypertension and augment long-term cardiovascular damage [2]. Treating neurogenic OH in patients with cardiovascular conditions requires a balance between symptom relief and minimizing adverse outcomes. A fair result is considered avoidance of orthostatic symptoms that not necessarily is averting OH.

Numerous factors may affect the BP homeostasis to a change in posture, including functioning of the autonomic nervous system, the intravascular volume, the anatomic and functional integrity of the heart and blood vessels, duration of the upright posture, the postprandial state and the ambient temperature. Elevation in body temperature causes peripheral vasodilation. Patients with OH should avoid situations that could increase core body temperature, such as exercise when ambient temperature and humidity are high, utilization of hot tubs, spas, or prolonged hot showers [2]. Febrile states are often associated with a remarkable decrease of BP in hypertensive subjects and the need to taper off antihypertensive medications. This occurrence is ascribed to the effect of proinflammatory cytokines (a topic not extensively studied). In the proposito, aggravation of OH under sepsis lasted a week after fever had remitted. Awareness is warranted to hypotension emerging during an acute febrile illness, when antihypertensive medications need to be tapered down, and to expect BP overshoot after recovery from the acute illness, when up-titration of antihypertensive medications may be required [11,12]. In managing this patient, a four-fold message emerged: First, the longstanding hypertensive phenotype may change due to a cerebrovascular event. Second, new-onset OH along with supine HT and a highly variable BP which is not affected by mental challenge is consistent with efferent baroreflex failure. Third, BP management under efferent baroreflex failure is challenging, needing compromise, and giving priority to avoid orthostatic symptoms. Fourth, intercurrent sepsis may cause a persistent alteration of the patient's BP status requiring tapering down or discontinuing antihypertensive medications.

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