The pathophysiology and diagnosis of orthostatic hypotension

D. Robertson, MD
Autonomic Dysfunction Center
Depts. of Medicine and Pharmacology
Vanderbilt University
AA 3228 Medical Center North
1161 21st Avenue South
Nashville (TN) 37232-2195, USA
Tel.: +1-615/343-8633
Fax: +1-615/343-8649
E-Mail: david.robertson@vanderbilt.edu

Abstract Orthostatic Hypotension (OH) is a common manifestation of blood pressure dysregulation. OH takes a heavy toll on quality of life. It has many potential etiologies, and many effects of aging can increase susceptibility to OH. Neurological disorders are especially likely to cause severe OH. In this brief review, the pathogenesis of OH is considered, particularly in terms of autonomic neuropathy, multiple system atrophy (MSA), pure autonomic failure, baroreflex failure, and dopamine beta hydroxylase deficiency. While OH is difficult to treat, its control greatly enhances the quality of life.

Key words orthostatic hypotension · orthostatic hypertension · autonomic · syncope · fainting

Cardiovascular dysregulation

Disorders of cardiovascular dysregulation encompass a broad spectrum all the way from very low pressures to very high pressures. Some of these disorders are depicted in Fig. 1, where the broad middle group includes the great majority of individuals, those with normal blood pressures. On the right, hypertension includes approximately 10% of the population; these patients have blood pressures that are elevated while they are lying, while they are standing and while they are upright. Separating the hypertensive patients from normal are the labile hypertensive patients, who occupy the controversial and ill-defined borderland of pressures ranging from 120/80 to 140/90. Conversely, on the left extreme, are patients with low blood pressure when standing, usually normal blood pressure while seated, and sometimes high blood pressure while lying down. These are individuals with orthostatic hypotension (OH). Between this group and normal subjects are patients with the milder dyssautonomias, postural tachycardia syndrome [13; 24] (POTS) and neurally mediated syncope (NMS). POTS patients have orthostatic tachycardia and symptoms of sympathetic activation on standing, while NMS patients usually have normal pressures in all postures, but occasionally have “fainting” associated with a brief, usually less than 1 min, hypotension and/or bradycardia. POTS and NMS patients do not usually have OH, and that is why their disorders are often classified as “milder dysautonomias”; patients with
these disorders do not usually consider them mild in a general sense.

There is one very important difference between approaches to treatment at the right and left ends of this spectrum. On the right, the blood pressure perturbation usually has no associated symptoms. We do not treat these patients to make them feel better. We treat them to try to prevent complications of hypertension perhaps 20 or more years down the line. On the other hand, people on the left extreme have symptoms that are often quite devastating. Such patients need help today. So, our strategy in these patients is to improve their functional capacity today, make them feel better, keep them active, and our focus is one of quality of life today. Many of the same medicines used to treat OH are also used in an effort to treat POTS and NMS. Beta blockers have sometimes been used in all categories of cardiovascular dysregulation depicted in Fig. 1, though the rationale for their use in NMS and OH is questioned.

**Orthostatic hypotension**

Orthostatic hypotension is defined as a fall of systolic blood pressure of at least 20 mmHg or a fall of diastolic blood pressure of at least 10 mmHg within 3 minutes of standing [20]. It is a physical finding and not a diagnosis; so it may be symptomatic or asymptomatic. Most people who are symptomatic from OH have a much greater fall in pressure on standing. Thus this is a very broad definition, and perhaps 50% of elderly patients might occasionally meet these criteria [3]. Evaluation and therapy are therefore primarily driven by symptoms.

When we stand, there is about 500–1,000 ml of blood that goes from the upper body to the lower body, primarily the lower abdomen, buttocks, and legs. In response to this, there are compensatory effects from activation of the sympathetic nervous system, the renin-angiotensin system, and consequent aldosterone release. These come into play to help maintain cardiac output during the stress of upright posture. Because upright posture is a relatively late evolutionary development, our mechanisms for maintenance of upright posture may still be under considerable genetic pressure.

**Orthostatic blood volume shift**

While an individual is lying down, blood volume is distributed throughout the body as depicted in Fig. 2. The second frame in the figure shows that same distribution in a theoretical instantaneously upright transition. But in the third frame, it can be seen that by 1 min of upright posture, the shift of perhaps 500 ml of blood to the lower part of the body is well advanced. The next phenomenon, depicted in the fourth frame, is perhaps even more important in the real world of OH management. It illustrates that after the pooling of blood, there is a period of 20–30 min during which substantial loss of plasma volume from the blood into the tissues occurs. This produces at least as great a challenge to the cardiovascular system as the more widely appreciated pooling of blood depicted in frame 3. Indeed, in healthy subjects, there is a 14% fall in plasma volume within 20 min after assumption of the upright posture, most of which occurs within the first 10 min. That 14% translates into about 430 ml of blood, close to the amount taken in a blood donation. Since the cellular component of the blood remains in the circulation, even the hematocrit, if you measure it carefully, changes, perhaps rising from 37 to 41 (Fig. 3). The lower hematocrit of the supine posture occasionally puts
otherwise healthy persons into the usually accepted “anemia” range of hematocrit, and has therefore been called “postural pseudoanemia [9]” for that reason. Thus, much of the “noise” in hematocrit measurement in clinical practice is actually not noise but reflective of changes in blood related to patient’s posture in the time leading up to the sampling.

This volume shift is reflected in BP during continuous blood pressure monitoring in a patient with OH. You can see in Fig. 4 that during monitoring after a patient with OH stands for about 20 min, the blood pressure does not so much plummet immediately, but rather transitions downward over a few minutes as the pooling first and then the plasma volume shift become sequentially engaged. It is noteworthy that many patients with chronic OH tolerate degrees of hypotension that are quite low, at least for a few minutes.

**Types of orthostatic hypotension**

The interaction between the brain and the cardiovascular system in blood pressure control is paramount, and this has lead to an expansion of our understanding of the different kinds of abnormalities which occur on standing. First we now recognize that in addition to the OH we commonly recognize between 1 min and 3 min of standing, there is both an earlier form of OH (“initial orthostatic hypotension”, IOH [26] and a later form developing between 5 min and 45 min (“delayed orthostatic hypotension” [5], DOH). IOH occurs immediately upon standing and is detectable only by beat-to-beat blood pressure monitoring [12]. This occurs at a time when many normal subjects, on arising from overnight sleep, may have a transient sense of impaired cerebral blood flow, but this typically goes away in a few seconds. However, falls of 40/20 mmHg in the first 15 s of standing are sometimes seen, and this period is associated fairly commonly with syncope in susceptible individuals. It is due to a mismatch based on an initial increase in venous return, increase in right atrial pressure, and overcompensation, accompanied by the muscle-derived late dilatation in the legs due to the act of standing. Delayed orthostatic hypotension (DOH) has recently been systematically studied by Freeman and his collaborators [6]. They found that among 230 people who ultimately had OH; either on standing or on the tilt table, 46% had OH within 3 min, but another 15% had OH in the 3–10 min interval, and then over the next half hour or so, an additional 39% manifested orthostatic pressures. The latter tended to be younger patients, and many fell into the category of POTS.

**Orthostatic hypertension**

Perhaps surprisingly, some patients have orthostatic increases rather than decreases in blood pressure when they stand. These individuals display orthostatic hypertension [2; 23]. The more severely affected patients have relatively rare disorders such as baroreflex failure [11], mast cell activation disorder (mastocytosis) [22], hyperadrenergic POTS, or pheochromocytoma.

**Signal amplification in dysautonomias**

Patients with OH due to autonomic impairment have a range of remarkable clinical characteristics. Many of these derive from the loss of buffering reflexes. The baroreflex keeps blood pressures from having excessively large excursions; preventing pressure from getting too high when there is a pressor stimulus and preventing pressure from getting too low when there is a depressor stimulus. When the baroreflexes fail,
Stimuli that would not do very much in healthy persons may have a big impact on blood pressure in a patient with OH due to autonomic failure. There is thus huge signal amplification in going from normal individuals to individuals with autonomic dysfunction. There are a number of interesting consequences of this. For example; food lowers blood pressure in healthy individuals by only 1 mmHg, but in people with autonomic dysfunction, food may lower blood pressure by 40 mmHg [14; 19], and they may pass out when they try to stand after finishing a meal. Conversely 16 ounces of water can raise blood pressure about 40 mmHg in the hour or so after it is ingested [21]. This effect and that of food can sometimes be harnessed by patients to benefit blood pressure control. Some drugs such as clonidine, which are used to lower blood pressure in hypertension, may display a pressor effect in autonomic failure as there is both hypersensitivity of vascular alpha adrenoreceptors and loss of baroreflex buffering. Likewise, the tachycardic (beta-1) effect of isoproterenol (Isuprel) is 6-fold elevated in the OH of autonomic failure. The depressor (beta-2) effect of isoproterenol is 17-fold elevated in this disorder [18]. Just half of a 5 mg oral terbutaline tablet, such as is used in asthma without notable depressor effect, is capable of reducing supine blood pressure by half in a patient with autonomic failure.

**Predisposing factors for orthostatic hypotension**

There are a number of predisposing factors for OH, including dehydration, deconditioning, poor nutrition or the bodily changes that occur with aging (Table 1). The latter factors lead to more vulnerability to OH in the aging population. There are drugs administered for other conditions that may concomitantly cause OH. The tricyclic antidepressants in chronic use have long been recognized as a cause of OH, and of course antihypertensive agents and diuretics can do this as well. Vasodilators like nitroglycerin, hydralazine, and calcium channel blockers can also cause OH. A commonly unrecognized cause of OH nowadays is tizanidine (Zanaflex). This problem arises simply because people are not expecting this side effect. Tizanidine is used as a muscle relaxant in fibromyalgia. Patients generally say it helps their condition, but it also is an alpha-2 agonist and therefore has clonidine-like effects, and so may cause episodic OH at the time of the major effects of the drug.

### Causes of orthostatic hypotension

Several neurological conditions (Table 2) give rise to OH. Autonomic neuropathy [25] may sometimes occur in relatively pure form, and is recognized by its spectrum of autonomic manifestations (Table 3). It encompasses what used to be called acute pandysautonomia, but also includes many cases of what is termed pure autonomic failure, owing to early conflation of the two pathophysiologies. Typically, it has an onset over days to weeks. There is sympathetic failure with OH and anhidrosis, which may be very severe and then characteristically parasympathetic failure is pronounced. Gastrointestinal, urological, and sicca changes are usually a hint that autonomic neuropathy may be the cause of the patient’s OH. Although there probably are many causes for this, some patients have an antibody to a component of nicotinic receptor at the critical ganglion synapse where autonomic function is transduced. It may account for up to 50% of these patients; so assessing that antibody in the paraneoplastic panel identifies these individuals. Pure autonomic failure was described in the classical paper of Bradbury and Eggleston in 1925. It is characterized by severe OH; insidious onset, slow progression, modest gastrointestinal impairment, marked supine hypertension,

### Table 1 Orthostatic hypotension: Causes I

<table>
<thead>
<tr>
<th>Predisposing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Deconditioning</td>
</tr>
<tr>
<td>Nutritional</td>
</tr>
<tr>
<td>Aging</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Tricyclic antidepressants (chronic)</td>
</tr>
<tr>
<td>Antihypertensives and diuretics</td>
</tr>
<tr>
<td>Vasodilators</td>
</tr>
<tr>
<td>Tizanidine (Zanaflex)</td>
</tr>
</tbody>
</table>

### Table 2 Orthostatic hypotension: Causes II

<table>
<thead>
<tr>
<th>Autonomic neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure autonomic failure</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies</td>
</tr>
<tr>
<td>Dopamine β hydroxylase deficiency</td>
</tr>
<tr>
<td>Brainstem lesions</td>
</tr>
<tr>
<td>Spinal cord injury</td>
</tr>
</tbody>
</table>

### Table 3 Mainfestations of dysautonomia

| Impaired papillary function; dry eyes |
| Orthostatic hypotension and supine hypertension |
| Reduced gastrointestinal motility, gastroparesis, constipation or diarrhea |
| Bladder dysfunction |
| Male erectile dysfunction |
| Impaired sweating |
and often very low plasma norepinephrine levels [10]. Other neurological systems are not involved. These people have a very good prognosis and often live decades, and we have several patients who have lived into their 90s with this. Parkinson’s disease with autonomic failure is associated with sympathetic neuropathy, and OH occurs in some, but not all Parkinson’s disease patients [8]. The hypotension in a few of them can be quite severe and MIBG or PET studies may help detect that, although we do not have good benchmarking for these tests yet. Dementia with Lewy Bodies is important to recognize in individuals with some Parkinsonian features, but progressive cognitive decline in these people may be more dramatic, and include visual hallucinations. The autonomic failure and some of the cognitive aspects can improve with cholinesterase inhibition. Multiple system atrophy (MSA) is very difficult problem because it involves not only the autonomic but also cerebellar and extrapyramidal systems [17]. MSA has the severest outlook of any dysautonomia. Sleep apnea also occurs commonly in MSA.

Dopamine beta-hydroxylase (DBH) deficiency is an extremely rare but instructive disorder, because it is a notable success story in terms of both diagnosis and therapy. The specific gene defect is in the DBH enzyme which produces norepinephrine from dopamine. Patients with this have severe OH, exercise intolerance, and usually ptosis of the eyelids. Erectile function (primarily parasympathetic) is not prevented but retrograde ejaculation (due to sympathetic failure) occurs. These patients have no norepinephrine in their neurons and instead they have stoichiometric replacement of norepinephrine by its precursor dopamine. DBH deficiency is interesting to us because it is one example where we get almost a “Lazarus” effect in response to droxidopa. Droxidopa is essentially a norepinephrine molecule to which a carboxyl group is attached [7]. This enables it to be absorbed orally, get past the liver and into the circulation where it is a substrate for the norepinephrine transporter and gets pumped into the sympathetic neuron. Within the neuron, and at other sites, droxidopa is decarboxylated to endogenous neurotransmitter norepinephrine, restoring sympathetic function. We reported a DBH deficiency patient in 2005 who, in her early 20s, was only able to stand erect for about 2 min before therapy, but after she was placed on droxidopa she rapidly began to be able to do many more things, and took up running, first tentatively but ultimately in an increasingly athletic fashion. After about a year of training she successfully completed the 26 mile New Orleans Marathon [4]. Completion of this benchmark reflected both the drug and this patient’s determination.

The alien landscape of orthostatic hypotension

Orthostatic regulation of drug levels

Liver blood flow (LBF) in humans is posture dependent. In healthy subjects, LBF is 5% less in the seated posture than in the supine posture, but in patients with OH that LBF decrement is a whopping 30%. A consequence of this is that drugs like lidocaine which are removed from the blood by first pass hepatic clearance will display dramatically posture-dependent plasma levels. When orthostatic hypotensive patients are receiving intravenous lidocaine, levels of the drug are almost twice as high when they are seated as when they are supine. Sitting up can so elevate plasma lidocaine levels that seizures may occasionally be provoked when patients with autonomic failure sit up [1].

Garden hose “therapy” of orthostatic hypotension

In OH due to autonomic failure, hyperventilation reduces blood carbon dioxide and this is attended by rapid fall in blood pressure in subjects with OH, sometimes 40 mHg within 60 s. Since hyperventilation may occur with physical exertion, this effect contributes to the depressor effect of exercise. Conversely, breathing through a dead space increases carbon dioxide concentration in inspired air, and the effect of this is to raise blood pressure 20 mHg or more. Some patients are so sensitive to this effect that they can stand longer while breathing through a short length of garden hose [15].

Afebrile hypotension as presentation of infection

Patients with severe autonomic failure have impaired capacity to manifest a fever in response to infection. Instead they present with an acute fall in blood pressure and a greatly reduced functional capacity. Such infections tend to be in the urinary tract or the lung. When patients note a substantial acute decrement in their functional capacity, they should have urinalysis and a chest examination to rule out infection [16].

Wet shirt therapy in hot weather

When the hypohidrosis in autonomic failure is severe, the inability to perspire can lead to temperature elevation in patients exposed to hot weather (>90°F). This increase in temperature leads to a fall in blood
pressure and the patient feels greatly fatigued, and may only be able to tolerate this temperature for a few minutes. Providing “artificial perspiration” in the form of a wet shirt will help speed heat dissipation and allow more tolerance of hot weather with maintenance of a higher blood pressure. Usually the wet shirt will provide benefit for about an hour before it must be re-wetted [16].

Acknowledgements The help of my colleagues in Vanderbilt’s Autonomic Dysfunction Center is acknowledged. I thank Ms Ella Henderson for help in the preparation of this manuscript. Supported in part by the U.S. Public Health Service: P01-HL56693, RO1 HL71784, and RR 00095.

Disclosure Dr. Robertson has served as a consultant for Chelsea Therapeutics.

References