We take the ability to cope with hemodynamic challenges elicited by many daily activities, including eating, taking a hot shower, enjoying an alcoholic beverage, or standing for granted. In contrast, in patients with severe autonomic failure, these activities produce hypotension and disabling symptoms. Eating, heat exposure, and alcohol ingestion elicit vasodilation in specific vascular beds. However, the hemodynamic stresses imposed by standing are particularly severe. With assumption of the upright posture, approximately 500–1000 ml blood is pooled below the diaphragm. Venous capacitance vessels in the splanchic area are particularly important in this regard. Moreover, hydrostatic pressure changes in capillaries force approximately 15% of plasma volume from the vascular to the interstitial space within 10–15 min of standing. Together, these mechanisms reduce venous return and cardiac preload. Therefore, even perfectly healthy people exhibit transient blood pressure (BP) reductions as they stand up and may briefly feel dizzy (Fig. 1 – left panel). Buffering reflexes, particularly arterial baroreflexes, efficiently adjust sympathetic and parasympathetic efferent activity such that BP is rapidly restored. Thus, supine and upright BP measurements differ little or not at all in a healthy younger person.

In patients with autonomic failure, efferent autonomic nerves are damaged or dysfunctional such that BP cannot be maintained with standing (Fig. 1 – right panel). Excess venous pooling or decreased cardiac and vascular responsiveness to adrenergic stimuli may also limit orthostatic tolerance. Orthostatic hypotension is usually defined as a sustained reduction of at least 20 mmHg in SBP or 10 mmHg in DBP within 3 min of standing [1]. The prevalence of orthostatic hypotension increases with age and heralds increased morbidity and mortality. In a recent meta-analysis, presence of orthostatic hypotension was associated with relative risks of 1.50 for overall mortality, 1.41 for coronary artery disease, 2.25 for heart failure, and 1.64 for stroke [2]. Therefore, supine and upright BP and heart rate measurements should be routinely assessed. Although we encourage our students and young doctors to do so, we rarely find orthostatic vital signs in a patient’s chart. No doubt, there is much room for improvement.

In most cases, orthostatic hypotension is mild to moderate and – while indicating increased risk – does not produce symptoms. Indeed, cerebral autoregulation maintains blood flow across a wide range of BPs. Asymptomatic patients should be regularly monitored but do not require treatment for their orthostatic hypotension. Orthostatic symptoms ensue when the orthostatic BP reduction exceeds the brain’s autoregulatory capacity. Severely affected patients may not be able to stand for more than a few seconds or minutes before disabling symptoms occur. From a hypertension specialist’s point of view, it is important to recognize that many patients with severe orthostatic hypotension are hypertensive in the supine position [3].

Managing patients with severe orthostatic hypotension is challenging. Rare diseases, such as pure autonomic failure (Bradbury–Eggleston syndrome), multiple system atrophy, autoimmune autonomic ganglionopathy, or dopamine B12 deficiency may respond to vitamin B12 substitution [5].

As causal treatments are rare, most patients with severe orthostatic hypotension require symptomatic therapy, which can substantially improve their quality of life. Clinical trials guiding therapy are also rare. Instead, we often have to rely on physiological reasoning and observations in small case series. Successful therapy requires education of patients as well as their families and their local physicians. Many apparently ‘trivial’ issues can make a difference in daily life. For example, we explain how to recognize orthostatic symptoms and demonstrate maneuvers ameliorating upright BP, such as leg crossing [6]. The impairment in baroreflex BP buffering explains substantial BP...
reductions following a meal, with alcohol ingestion, during exercise, or with heat exposure. Hyperventilation elicits a depressor response in these patients [7]. These responses have to be considered when planning the day. Finally, these patients are exquisitely sensitive to vasodilators and diuretics and we avoid these drugs as much as possible.

Nonpharmacological treatments are a cornerstone of orthostatic hypotension management. Because supine BP is elevated in these patients, urine volume and sodium excretion are much increased during the night [8]. In addition to causing nocturia, the resulting volume loss worsens orthostatic symptoms when arising. Sleeping with the whole bed tilted head-up lowers nocturnal BP and volume excretion while improving orthostatic hypotension the next morning. Patients should avoid a low-sodium diet and increases in dietary sodium intake can be considered, provided that there are no contraindications. In many patients with severe orthostatic hypotension, drinking water produces a profound pressor response within minutes that is sustained for more than an hour. This pressor response appears to be a spinal reflex, engaging residual sympathetic efferent nerves [9] and can be exploited to improve orthostatic and postprandial hypotension [10]. We recommend that patients drink a glass of water before arising in the morning and before meals. However, water ingestion should not exceed 2–3 l/day. Finally, compression garments may improve orthostatic symptoms by reducing venous pooling. Abdominal compression may be more effective than leg compression [11]; however, individual responses vary from patient to patient.

We only consider the use of pressor drugs in patients with severe orthostatic hypertension who are symptomatic on maximal nonpharmacological therapy. In fact, suboptimal nonpharmacological therapy is a common cause for pressor agents to fail in controlling orthostatic symptoms. Several shorter or longer acting drugs have been proposed for the treatment of orthostatic hypotension [12]. Of those, many are not well studied and are not approved for this indication. The systematic review and meta-analysis by Strassheim et al. [13] in this issue evaluates the use of droxidopa in the treatment of orthostatic hypertension. In the body, droxidopa is converted to norepinephrine through dihydroxyphenylalanin decarboxylase. In patients with dopamine β-hydroxylase deficiency who are unable to convert dopamine to norepinephrine, the drug replenishes endogenous norepinephrine and relieves excess dopamine virtually curing the orthostatic hypotension [14]. In other patient groups with orthostatic hypotension, droxidopa acts more like a regular adrenergic agonist.

Strassheim et al. [13] included randomized controlled clinical trials testing droxidopa in patients with orthostatic hypotension in their analysis. Studies had to include at least one measure of symptoms, BP, activity of daily living, or adverse events. The investigators identified four trials meeting these criteria with a total of 494 patients. The good news is that droxidopa ameliorated orthostatic symptoms and upright BP. Similar to all other pressor agents known to man, droxidopa also tended to increase supine BP. However, the analysis also highlights the limitations of current clinical studies in the treatment of orthostatic hypotension. First, the study endpoints are heterogeneous and may not always relate to symptom burden in real life. Second, patients included in these studies may not represent patients actually requiring pharmacotherapy. In fact, in three out of four studies, average upright SBP was well above 90 mmHg. It is also unclear whether or not patients received optimal nonpharmacological therapy. Finally, drug dosing may not be optimal. In particular, dosing pressor agents routinely thrice daily as in trials with droxidopa [13] or with the direct α-adrenoreceptor agonist midodrine [15] does not make much sense. Because orthostatic symptoms often gradually improve during the day, we commonly dose such drugs in the morning and if needed around noon. Pressor agents taken later in the day are rarely required and will worsen supine hypertension during the night. Furthermore, because some patients are exceedingly
hypersensitive to pressor drugs, we recommend that drug
doses are individually titrated to avoid potentially danger-
ous BP surges. Obviously, a meta-analysis cannot mitigate
limitations of the included trials. The importance of the
study by Strassheim et al. [13] is that it provides an unbiased
overview of the data regarding the use of droxidopa in
patients with orthostatic hypotension.

The incentives for industry to develop new drugs for the
treatment of orthostatic hypotension are rather limited.
Therefore, we may not see larger scale trials with ideal
patients being evaluated for ideal clinical endpoints. The
state of affairs is not better when it comes to nonpharma-
cological therapies. Limited data should not lead to thera-
petic nihilism. Instead, we should apply the available data
with the goal to help our patients to live a better life with
their orthostatic hypotension. Finally, regulatory authorities
should recognize the need to approve drugs for the treat-
ment of symptomatic severe orthostatic hypotension
not controlled by nonpharmacological means and the
difficulties of conducting clinical trials in this population.

ACKNOWLEDGEMENTS

J.J. served as advisor for Boehringer-Ingelheim, Janssen-
Cilag, Novartis, Novo, Orexigen, Vivus, and receives
research support from Boehringer-Ingelheim and Boston
Scientific. J.T. receives research support from Boston
Scientific. G.G. reports no disclosure.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

3. Shannon JR, Jordan J, Costa F, Robertson RM, Biaggioni I. The hyper-
tension of autonomic failure and its treatment. Hypertension 1997;
50:1062–1067.
7. Oront J, Bernard GR, Biaggioni I, Hollister AS, Robertson D. Direct vasodilator effect of hyperventilation-induced hypocapnia in auto-
11. Denq JC, Opfer GT, Giuliani M, Felten J, Convertino VA, Low PA. Efficacy of compression of different capacitance beds in the amelio-