Supplemental Material

Supplemental Material SM1. Postprandial hypotension and post-exertional hypotension as examples of distinct patterns of hypotension.

Supplemental Material SM2. Detailed recommendation for further research on orthostatic hypotension.

Supplemental Figure. Threshold effects and resting blood pressure.

Supplemental Material SM1. Postprandial hypotension and post-exercise hypotension as examples of the importance of characterizing patterns of hypotension.

An important example illustrating the importance of characterizing patterns, triggers, and etiology of orthostatic hypotension is postprandial hypotension (PPH), characterized by dramatic drops in BP within two hours after high-carbohydrate meals.[1] Less dramatic but significant PPH, with falls in BP averaging 10-20 mmHg have been reported in several studies of patients with essential HTN with a prevalence of ~20-40%.[2,3] Moreover, 20-40% of adults with diabetes also experience postprandial hypotension,[4,5] a significant risk factor for injurious falls and syncope.[6–9] In fact, hypotensive disorders are even more frequent among adults with both diabetes and HTN,[10–12] representing a major challenge for HTN treatment.

It is important to recognize this problem because it can affect BP control decisions if measurements are taken in the postprandial period. Moreover, PPH can worsen orthostatic symptoms, but also be prevented with acarbose, which delays the absorption of glucose by impairing the breakdown of complex carbohydrates in the gut and hence the release of insulin and vasodilating incretins.[13] This is arguably the only form of hypotension that can be treated without the use of pressor agents that would worsen HTN.

Another important example is post-exercise hypotension (PEH), a drop in BP after exercise that can persist for up to 24 hours compared to the immediate pre-exercise period or non-exercise control day.[14] PEH is more common in patients with hypertension than in normotensive individuals.[15] The magnitude of BP decline can vary between 8/9 mmHg to 10/7 mmHg in normotensive and hypertensive patients respectively. Type, intensity, and duration of exercise may influence the magnitude of PEH. During exercise, there is an increase in sympathetic activity and a decrease in parasympathetic activity.[15] Subsequently, the cardiac

output increases, the venous vasculature constricts in the non-exercising vascular bed, regional vasodilation occurs in the exercising muscles thus SBP increases, but there is minimal increase in DBP. For endurance/aerobic exercises, BP rapidly returns to baseline and a transient sudden BP decrease occurs. SBP increases more sharply with resistance exercise due to sympathetic vasoconstriction in the non-exercising muscles and BP declines to levels below normal following completion with a more pronounced transient sudden BP decrease beforehand. However, studies that compared the hemodynamic response to endurance and resistance exercises show that magnitude and duration of hypotension does not differ.[16,17] Additionally, there is conflicting evidence regarding the effect of intensity of exercise on PEH occurrence with most studies showing that exercise intensity does not affect the hypotensive response. Even 10 minutes of exercise has been shown to result in PEH. If hypotension is preserved following PEH then this could have clinical implications both in the short-term (i.e., complications and side effect of sudden drop in BP) and long-term (exercise as a non-pharmacological treatment for hypertension), however further studies are needed to understand the variability in time to return to baseline BP.[18]

For patients with orthostatic hypotension or orthostatic intolerance, aerobic training might benefit these individuals. In moderately and not highly fit individuals, improving aerobic capacity, increases plasma volume and subsequently orthostatic tolerance.[19,20] In highly endurance-trained individuals, improvement in orthostatic intolerance might not be observed due to the attenuated increase in carotid baroreflex response.[21] However, a randomized clinical trial among 31 military recruits with orthostatic hypotension showed that training (3 months of jogging, i.e., endurance training) compared to control resulted in improvement in symptoms of patients with orthostatic intolerance.[22] Overall, it is still unclear what amount of fitness to target

among patients with OH, though exercise generally seems to be helpful.[19] On the other hand, simple leg resistance training and tensing muscles could help in reducing orthostatic hypotension as they reduce venous pooling by increasing muscle tone and attenuate postural reduction in cerebral perfusion.[23–25]

Supplemental Material SM2. Detailed recommendations for further research among adults with orthostatic hypotension and hypertension.

There are a number of areas representing research priorities for OH among adults with hypertension.

(1) Epidemiology & pathophysiology:

a. *Older adults.* Older adults with HTN often take multiple medications and are at greater risk of complications from hypotension. ABPM data would be useful to characterize BP lability in this population to identify patterns amenable for therapy to reduce adverse health outcomes.

b. *Diurnal BP variation/ABPM and OH.* There is a need for research on supine/nocturnal hypertension due to its role in aggravating daytime orthostatic intolerance and its contribution to adverse clinical outcomes.

c. *Definition and phenotypes.* The term OH itself may be a misnomer because it implies the presence of hypotension while standing,[26] whereas, especially in hypertensive patients, upright BP can be normal and occasionally high. In this regard, it is not clear if the determinant of poor outcomes linked to OH is the magnitude of the drop in BP or the absolute standing BP. There may even be differences in cardiovascular outcomes between OH defined by SBP or DBP criteria.[27]

d. *Pathophysiology.* Emerging evidence implicates vascular stiffness as an independent risk factor of OH that may be due to alterations in vascular smooth muscle cells caused by dysfunction of the baroreflex pathway.[28] Arterial stiffness may attenuate baroreceptor sensitivity of the large elastic arteries, thereby possibly triggering

orthostatic BP changes.[29] The mechanistic underpinnings by which OH predicts future CVD events is postulated as the result of a long-term increase in arterial stiffness fostering functional changes of both the central and peripheral arteries, however, further testing of this hypothesis is warranted.[30] Noninvasive central pressure assessment could be a useful tool for elucidating these pathways.

(2) HTN Treatment & OH:

a. *Symptomatic OH.* Recent large clinical trials indicate that intensive BP control can be achieved in most hypertensive patients without triggering OH. However, more research is needed to determine if this approach applies to patients with symptomatic OH who were usually excluded from clinical trials.

b. *Antihypertensive class and OH.* Similarly, there are few systematic studies to guide the selection of antihypertensive class among patients with symptomatic OH. It would be informative to understand the hemodynamic correlates of antihypertensive classes (i.e., non-invasively measured systemic vascular resistance, stroke volume, cardiac output, and central blood pressure, etc) in adults with OH compared to adults without OH; and the effect of posture on these measures.

(3) Screening & Diagnosis:

a. *Measurement timing.* The most common definition of OH, a drop in SBP >20 mm Hg or DBP >10 mm Hg from supine to standing BP within 3 minutes, has been used in large epidemiological studies linking OH with cardiovascular outcomes.[31] Upright BP was measured at different times in these studies (1, 2, or 3 min) and research is needed to reach consensus as to the optimal timing.[32] A negative finding (no significant differences between time points) would be equally important.

b. *Diagnostic threshold.* Some consensus guidelines recommend a larger threshold of >30 mm Hg drop in SBP to define OH in patients with HTN. It is not clear if it offers any advantage in population studies. All of the studies linking OH to cardiovascular outcomes have used the threshold of >20 mm Hg without correcting for the presence of HTN. A few but important large clinical trials have used seated-to-standing instead of supine-to-standing measurements while maintaining the same orthostatic threshold. At least one found a correlation between "seated OH" and heart failure and overall mortality,[33] highlighting the strength of this association despite the loss of sensitivity. Determining an adequate threshold that defines OH from the seated position is arguably the area of research that may provide the greatest return on investment.

c. *Screening.* Orthostatic BPs are rarely measured in clinical practice, even among patients admitted for syncope despite its documented cost effectiveness.[34] Defining criteria for "seated OH" would reduce the burden of screening for OH. Likewise, we need data to guide the decision of who should be screened routinely for OH. Age, history of postural symptoms or falls, and presence of comorbidities are factors to consider.

(4) OH Treatment

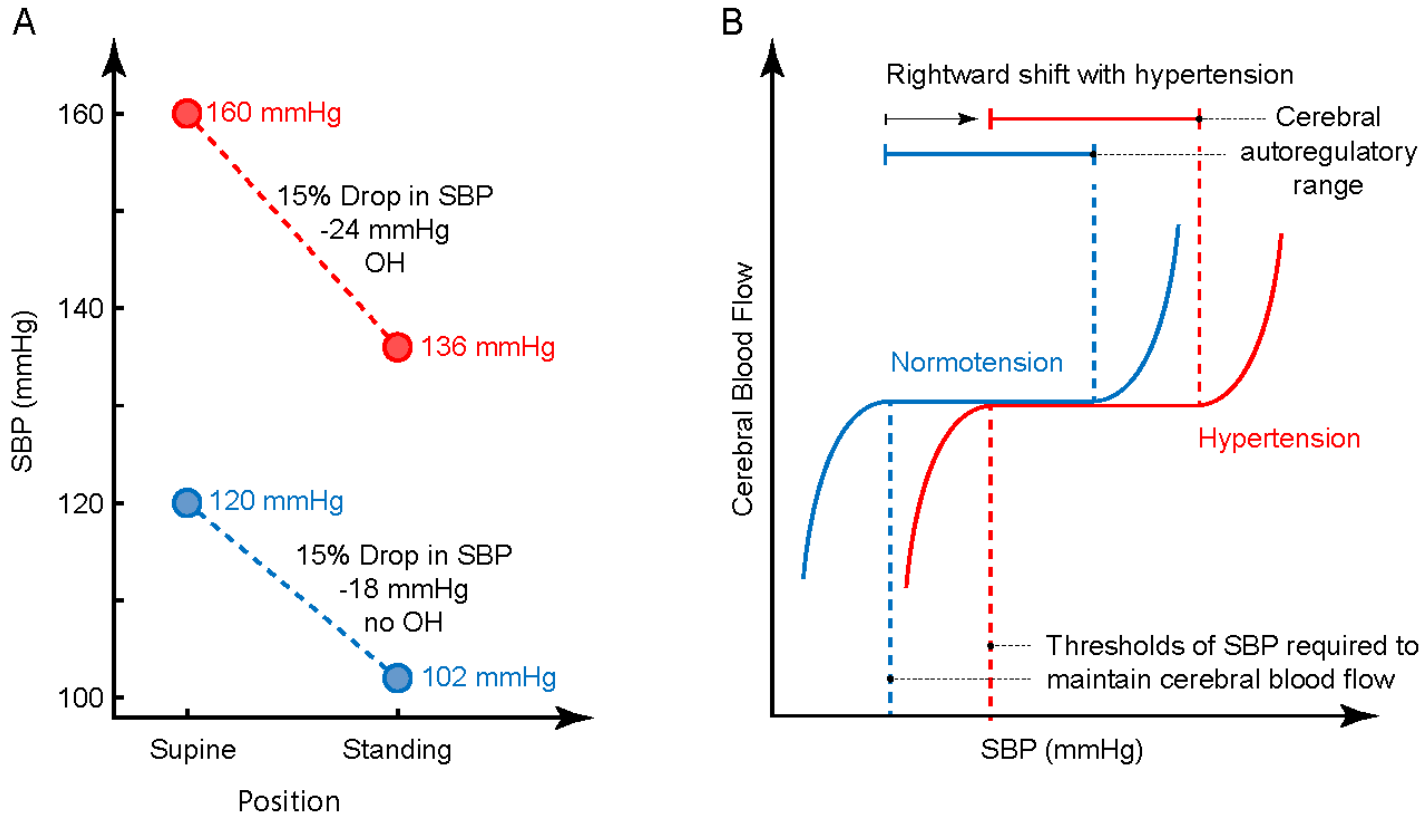
a. *Neurogenic OH.* Only two medications have been approved for the treatment of neurogenic OH, based on clinical trials that excluded patients with the most common causes of OH.

b. *Postprandial hypotension.* More work is needed on the role of modulating gastrointestinal hormone secretion/splanchnic blood pooling to improve BP control.

c. *Nocturnal HTN.* While timed antihypertensive medications (morning versus evening) do not seem to improve cardiovascular disease outcomes in the general population,[35] there may be a role for short-acting antihypertensive interventions at night for adults with supine HTN and morning OH.

d. *HTN treatments.* OH disproportionately affects older adults. More work is needed evaluating HTN classes and its impact on nocturnal HTN, pressure natriuresis, and orthostatic tolerance.

Supplemental Figure. (A) The same percent change among a patient with a normal resting systolic blood pressure (**SBP, blue**) will result in a larger absolute decline in blood pressure among patients with a higher resting SBP (**red**) that meets the definition of orthostatic hypotension (**OH**). (**B**) These changes may be asymptomatic as the blood pressure threshold required to maintain cerebral blood flow increases among adults with hypertension.



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