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REVIEW TOPIC OF THE WEEK

Orthostatic Hypotension

Epidemiology, Prognosis, and Treatment

Fabrizio Ricci, MD,* Raffaele De Caterina, MD, PhD,* Artur Fedorowski, MD, PhD†‡

ABSTRACT

Orthostatic hypotension (OH) is a common cardiovascular disorder, with or without signs of underlying neurodegenerative disease. OH is diagnosed on the basis of an orthostatic challenge and implies a persistent systolic/diastolic blood pressure decrease of at least 20/10 mm Hg upon standing. Its prevalence is age dependent, ranging from 5% in patients <50 years of age to 30% in those >70 years of age. OH may complicate treatment of hypertension, heart failure, and coronary heart disease; cause disabling symptoms, faints, and traumatic injuries; and substantially reduce quality of life. Despite being largely asymptomatic or with minimal symptoms, the presence of OH independently increases mortality and the incidence of myocardial infarction, stroke, heart failure, and atrial fibrillation. In this review, we outline the etiology and prevalence of OH in the general population, summarize its relationship with morbidity and mortality, propose a diagnostic and therapeutic algorithm, and delineate current challenges and future perspectives.
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Orthostatic hypotension (OH) is a key manifestation of autonomic dysfunction, typically observed when cardiovascular adaptive mechanisms fail to compensate for the reduction in venous return that normally occurs on assuming the upright position. It reflects a structural or functional sympathetic denervation or a deranged reflex regulation of sympathetic outflow (1). OH is the second most common etiology of syncope, occurring in approximately 15% of syncope presentations (2). It frequently affects older people and patients who have neurodegenerative disease, diabetes, or hypertension. Unfortunately, OH is often unrecognized or misdiagnosed and may be an overlooked factor associated with increased cardiovascular morbidity and all-cause mortality. Its management includes both pharmacological and nonpharmacological measures that are not always satisfactory and may lead to complications (3). In this review, we first outline the pathophysiology of OH; discuss its etiology, epidemiology, and prognosis; and propose a diagnostic and therapeutic algorithm.

THE HOMEOSTATIC REGULATION OF BLOOD PRESSURE

Cardiovascular blood pressure (BP) homeostasis refers to compensatory adjustments aimed at buffering changes in BP and opposing cardiovascular remodeling. Regulation of BP is a very complex physiological function that depends on a continuum of actions of the cardiovascular, neural, renal, and endocrine systems (4). In contrast to the local (peripheral) regulation of tissue BP, which primarily aims to achieve a tight matching of regional blood flow to local metabolic demands and occurs through locally produced mediators (autacoids), including eicosanoids, nitric oxide, endothelins, and tissue plasminogen activator, the central circulation maintains tight control of BP through changes in cardiac output and vascular tone.

From the *Institute of Cardiology "G. d'Annunzio" University and Center of Excellence on Aging, Chieti, Italy; †Department of Clinical Sciences, Lund University, Clinical Research Center, Skåne University Hospital, Malmö, Sweden; and the ‡Department of Cardiology, Skåne University Hospital, Malmö, Sweden. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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Such changes are mediated by the autonomic nervous system. The sympathetic and parasympathetic components of the autonomic nervous system play a crucial role in the fine-tuning of BP, enabling the body to respond to physiological stressors. The sympathetic nervous system plays the predominant role in determining the level of arterial BP and the distribution of cardiac output. Despite the existence of cholinergic vasodilation in some vascular beds, the overall contribution of the parasympathetic nervous system to the regulation of vascular tone is almost negligible, in contrast to the role of the parasympathetic nervous system in the regulation of cardiac functions via its negative chronotropic and inotropic effects.

Central regulatory mechanisms control the sympathetic outflow to the cardiovascular system in both the short and long term (5). Short-term reflex control of the sympathetic vasomotor activity is regulated by homeostatic feedback mechanisms, such as the baroreceptor and chemoreceptor reflexes. Central mechanisms also produce specific patterns of sympathetic activity according to different external stimuli or stresses (6,7). In the long term, cardiovascular homeostasis depends on a more complex interplay of several mechanisms, including changes in the sympathetic vasomotor outflow, renal control of extracellular volume, pressure natriuresis, and the activity of antagonistic "push-pull" systems (8), such as the kallikrein-kinin and renin-angiotensin-aldosterone systems (5,6,9–12).

PHYSIOLOGY OF UPRIGHT POSTURE. Orthostatic stress is a common daily challenge for humans when posture changes from lying to standing or during prolonged quiet standing. Almost immediately, with the transition from the supine (recumbent) to the upright (erect) position, a gravitational shift of nearly 500 ml of blood away from the chest to the distensible venous capacitance system below the diaphragm (venous pooling) occurs. This results in a rapid decrease in central blood volume and a subsequent reduction of ventricular preload, stroke volume, and mean BP (13). In the vascular system, a reference quantitative determinant of these changes is the venous hydrostatic indifference point (HIP), when pressure is independent of posture (14). In humans, the venous HIP is approximately at the diaphragmatic level, whereas the arterial HIP lies close to the level of the left ventricle (14). The venous HIP is dynamic and is significantly affected by venous compliance and muscular activity.

Upon standing, contractions of lower limb muscles, along with the presence of venous valves, provide an intermittent unidirectional flow, moving the venous HIP toward the right atrium (15). Respiration may also increase venous return because deep inspiration results in both a decline in thoracic pressure and an increase in intra-abdominal pressure, which lowers retrograde flow due to compression of both the iliac and femoral veins (14). To provide an appropriate perfusion pressure to critical organs, an effective set of the neural regulatory system is promptly activated upon standing (6). The sympathetic nervous system is fast acting and primarily modulated by mechanoreceptors and, to a smaller degree, by chemoreceptors. Arterial baroreceptors (high-pressure receptors) are located in the carotid sinus and the aortic arch and—by conveying baroceptive impulses via carotid sinus and aortic depressor nerves to the brainstem, notably in the nucleus of the solitary tract—determine tonic inhibition of vasomotor centers (16) (**Figure 1**). In contrast, cardiopulmonary baroreceptors (volume receptors) are located in the great veins and the cardiac chambers and detect changes in the filling of the central venous circulation but are not essential for orthostatic cardiovascular homeostasis (16). A sudden drop in BP in the carotid sinus and the aortic arch triggers baroreceptor-mediated compensatory mechanisms within seconds, resulting in increased heart rate, myocardial contractility, and peripheral vasoconstriction (17). An additional local axon reflex, the veno-arteriolar axon reflex, results in constriction of arterial flow to the muscles, skin, and adipose tissue, leading to almost one-half of the increase in vascular resistance in the limbs upon standing (14,18,19). Ultimately, orthostatic stabilization is normally achieved in roughly 1 min or less. During prolonged quiet standing, in addition to venous pooling, transcapillary filtration in the subdiaphragmatic space further reduces both central blood volume and cardiac output by approximately 15% to 20% (20,21). This transcapillary shift equilibrates after approximately 30 min of upright posture, which can result in a net fall in plasma volume of up to 10% over this time. Continued upright posture also results in activation of neuroendocrine mechanisms, such as the renin-angiotensin-aldosterone system, which may vary in intensity depending on the volume status of the patient (18). Still, the most important homeostatic response to prolonged orthostatic stress appears to be the carotid baroreflex-mediated increase of peripheral vascular resistance. The inability of any one of these factors to perform adequately or coordinately may result in a failure of the system to compensate for an initial or sustained postural challenge. This may produce a transient or persistent state of hypotension, which, in turn, can lead to

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

ECG = electrocardiogram

HIP = hydrostatic indifference point

HUT = head-up tilt test

OH = orthostatic hypotension

SBP = systolic blood pressure