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Blood pressure

Orthostatic hypotension: A review

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ABSTRACT

Orthostatic hypotension, defined by a drop in blood pressure of at least 20 mmHg for systolic blood pressure and at least 10 mmHg for diastolic blood pressure within 3 minutes of standing up, is a frequent finding, particularly in elderly patients. It is associated with a significant increase in morbidity and mortality. Although it is often multifactorial, the first favoring factor is medications. Other etiologies are divided in neurogenic orthostatic hypotension, characterized by autonomic failure due to central or peripheral nervous system disorders, and non-neurogenic orthostatic hypotension, mainly favoured by hypovolemia. Treatment always requires education of the patient regarding triggering situations and physiological countermanoeuvers. Pharmacological treatment may sometimes be necessary and mainly relies on volume expansion by fludrocortisone and/or a vasopressor agents such as midodrine. There is no predefined blood pressure target, the goal of therapy being the relief of symptoms and fall prevention.

1. Introduction

Orthostatic hypotension is defined as a decrease in blood pressure of at least 20 mmHg for systolic blood pressure or 10 mmHg for diastolic blood pressure within 3 minutes of standing up. This physical finding may vary greatly with time in the same patient, and may be symptomatic or not [1,2]. As opposed to hypertension, which is most often asymptomatic but must be treated to avoid long-term complications, management of orthostatic hypotension is mainly guided by its symptoms, to improve immediate quality of life of the patient.

Prevalence of orthostatic hypotension is approximately 6% in the general population, but increases exponentially with age, ranging from 10 to 30% or even 55% in studies carried out on older populations [3–13]. Risk factors for orthostatic hypotension include age, multiple medications, smoking status, low body mass index, hypertension (treated or not), and diabetes, with a prevalence of 20% in middle-aged diabetic patients [4,10,12,14–16]. More than 30% of the patients with Parkinson's disease or dementia with Lewy's bodies have orthostatic hypotension, which can precede diagnosis of the neurological disorder by up to 5 years [17–20].

Orthostatic hypotension is significantly associated with increased mortality and morbidity [8]. The number of hospital admissions directly related to orthostatic hypotension in the United States was estimated to be over 80,000 per year in 2004, and is continuously increasing given ageing of the population [21]. Orthostatic hypotension is thus a significant burden for healthcare systems and a major public health challenge. Its appropriate diagnosis and management are daily issues for most healthcare professionals.

In this review, we will describe the diagnosis, aetiologies, treatment and prognosis of orthostatic hypotension in light of the physiological mechanisms involved in maintenance of postural normotension.

2. Physiological background: the normal orthostatic response

A clear understanding of mechanisms involved in maintenance of blood pressure upon standing up is key to decipher causes and treatment of orthostatic hypotension. The act of standing up is a challenge for human physiology: due to the effect of gravity, within a few seconds, 500 to 700 mL of blood translocate from the upper body to venous capacitance vessels of the lower limbs and splanchnic circulation [22]. In addition, because of the increased hydrostatic pressure, approximately 10% of the intravascular plasma shifts towards the interstitial compartment within 10 to 30 minutes of upright posture [23,24]. This results in a decrease of

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venous return, right ventricle filling pressure, and ultimately cardiac output by approximately 20%, hence the ensuing drop in blood pressure which may compromise perfusion of organs above heart level in the absence of compensatory mechanisms. With evolution, humans developed adaptive mechanisms to overcome this gravitational stress, and thus became the only animals capable of maintaining the erect posture for prolonged periods of time.

2.1. Muscle pump

First, this shift in blood volume towards the lower part of the body is counteracted by muscle contractions, which are necessary to stand up and maintain upright posture. Muscle contractions not only increase venous return by compressing capacitance vessels and preventing excessive pooling in the lower body, but also increase vascular resistance.

2.2. Baroreflex

The main physiological system involved in homeostasis maintenance upon standing up is the autonomic nervous system, integrated in the feedback loops of the cardiac and arterial baroreflex (Fig. 1) [25]. In brief, any modification in blood pressure is detected immediately by the baroreceptors, and integrated in the medulla, which then triggers compensatory modifications in the heart and vessels through the parasympathetic and sympathetic nervous systems (Fig. 1).

Baroreceptors are mechanosensitive nerve endings located within the wall of vessels, which detect small reductions in arterial pressure or central blood volume, through deformations of the vessel wall. Arterial or high-pressure baroreceptors are located in the carotid sinuses and aortic arch and play the most important part in the acute adaptation to the upright posture [26,27]. Low-pressure baroreceptors (or voloreceptors) are mainly located in major cardiopulmonary vessels and detect a reduction in central blood volume. They are involved in particular in the control of renal sympathetic nerves [28].

Afferent pathways [glossopharyngeal (IX) and vagus (X) nerves for carotid and aortic baroreceptors, respectively, and non-myelinated vagal nerve fibers for low-pressure baroreceptors]

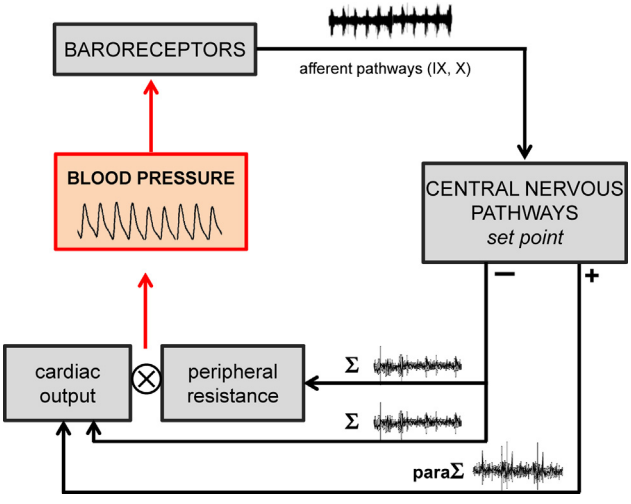

Fig. 1. Arterial and cardiac baroreflex feedback loops. Any variation in the regulated variable (blood pressure) is detected by sensors (baroreceptors) and communicated to the integrating center (central nervous pathways in the medulla), where the value of the regulated variable is compared to the set point. Efferent pathways then convey the information to the effectors (heart and vessels), thus correcting the variation of blood pressure. Σ: sympathetic system; paraΣ: parasympathetic system.

synapse in the central nervous system, especially in the *nucleus of the tractus solitarius* [29,30]. Central neuronal circuits then involve the caudal ventrolateral medulla and the rostral ventrolateral medulla, which control sympathetic output to the arteries, veins, and heart through the intermediolateral column of the thoracic spinal cord, and the *nucleus ambiguous*, which controls parasympathetic output to the sinoatrial node of the heart.

A decrease in blood pressure results in a decreased activity of the afferent nerves, causing an increase in sympathetic outflow (negative feedback loop) and a decrease in parasympathetic outflow (positive feedback loop), which result in:

- arterial and venous constriction, leading to increased peripheral arterial resistance and venous return;
- increased cardiac inotropism and chronotropism, leading to increased cardiac output;
- increased renal sympathetic activity, leading to renal vasoconstriction, renin synthesis, decreased glomerular filtration rate and increased tubular sodium reabsorption.

2.3. Renin–angiotensin system

While the baroreflex is a very short-acting feedback loop, activated within seconds, other systems involved in orthostatic homeostasis act with minutes and hours, the main one being the renin–angiotensin aldosterone system [31]. Standing up results in the production of renin by the juxtaglomerular apparatus, in response to a transient drop in afferent arteriole perfusion pressure. Increased renin promotes cleavage of angiotensin from liver-produced angiotensinogen to angiotensin I, transformed into angiotensin II by the angiotensin-converting-enzyme. Angiotensin II is a potent vasoconstrictor and also increases tubular reabsorption of sodium. In addition, it stimulates the secretion of aldosterone from the adrenal cortex, which also causes reabsorption of water and sodium. Angiotensin also acts centrally to increase sympathetic outflow [32].

A decrease in right atrial pressure upon standing up reduces the synthesis of atrial natriuretic peptide, which has actions opposite to those of the renin–angiotensin aldosterone system. Furthermore, afferent inputs from the vestibular system stimulate sympathetic neural outflow [33] and thus contribute to maintenance of blood pressure upon standing up. Other local vasoactive systems such as nitric oxide, vasopressin, venoarteriolar reflex and myogenic response are believed to play a minor role in the pathophysiology of orthostatic hypotension.

2.4. From physiology to pathology

Hence, homeostatic ability to maintain blood pressure while standing relies on adequate blood volume and on the integrity of the nervous system, heart, vessels, and muscle pump. Overall, in healthy individuals, the assumption of upright posture does not result in major changes in blood pressure: close monitoring by beat-to-beat blood pressure measurement usually shows a small decrease in systolic and diastolic blood pressure (≈ 5 mmHg) and an increase in heart rate (15 to 30%, < 30 bpm) during the first 10 seconds, then followed by a return to baseline value (or slightly above) for systolic blood pressure and typically a small increase in diastolic blood pressure, resulting in a decrease in pulse pressure (5–10%) [34].

Any dysfunction of the autonomic nervous system (functional or lesional, chronic or transient, due to central or peripheral alterations) defines neurogenic orthostatic hypotension, whereas orthostatic hypotension in the presence of a fully preserved