# Great Arteries Contribution in Orthostasis Cardiovascular Adaptation

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The capacity of adopting an orthostatic posture is, undoubtedly, a milestone in the evolution of the human species and has motivated extensive research in the physiological and anthropological areas. The physiological mechanisms involved in adopting and maintaining an orthostatic posture and its complications have been investigated through the centuries. The anatomists do not consider the postural adaptation of the human being a peculiar transformation that occurred to mankind, but the culmination of a series of evolutionary phases that might have started in the body of the primate ancestors[1].

It is believed that the human cardiovascular system is adapted to maintain cerebral perfusion during the orthostatic posture. Although the gravitational force creates a gradient of pressure at the level of the circulatory system, the human being is capable of maintaining an upright posture because the gravitational pressure is partially neutralized by mechanisms that prevent the accumulation of fluids in the lower limbs[2].

Despite that, syncope, defined as a transient loss of consciousness and postural tonus due to cerebral hypoperfusion, has a considerable medical, social and economical impact. This clinical syndrome can be the consequence of not only reflex mechanisms[3], but also a clinical manifestation of a broad range of distinct clinical conditions[4].

A perspective of the cardiovascular adaptation to orthostatism is presented herein, in an attempt to assess evolutionary and physiological issues regarding the maintenance of circulatory homeostasis during orthostasis, stressing the role of the great arteries.

## Orthostatic posture and gravitational stress

Years of experiments carried out in quadrupeds or models constructed in the horizontal plane have helped researchers of the cardiovascular system to develop a type of "horizontal" idea about the cardiovascular system, completely neglecting the effects of gravity because the "vertical" gravity force exerts a minimal effect on circulation in the horizontal plane. However, the human cardiovascular system works in the orthostatic posture two-thirds of the time, in which the classical experiments conducted by the Guyton group, for the study of cardiovascular hemodynamics, present large limitations[5].

The change from a quadrupedal posture to a bipedal one created difficulties that can be interpreted through several signs, which are representative of an inadequate adaptation to orthostatic stress[6]. Bipedism presupposes a complete reorganization of the orthodynamics of the human body when compared to other mammals. This implicates in a different reorganization of the energetic supply for the body (oxygen and nutrients). As oxygen and the nutrients are carried by the blood, a complete reorganization and rearrangement of the blood supply between the different parts of the body is expected when there is a change from the quadrupedal posture to the bipedal one[7]. Thus, the hemodynamics must also be different.

The control of blood flow distribution in man is more complex due to the fact that the human brain has larger proportions compared to the other species. The brain represents 2% of the total body weight in man, demands 15% of the cardiac output at rest and requires the maintenance of a stable output regardless of posture or locomotion[8]. The change from a supine posture to the orthostatic one results in a displacement of blood at the thorax level to the subdiaphragmatic venous system, a phenomenon usually called venous pooling[9]. If compensatory adjustments do not occur promptly after the change in posture, the arterial pressure decreases, and the individual can present from milder symptoms related to orthostatic intolerance to the sudden loss of consciousness[10].

Although gravity has long[11] been recognized as the main deforming force that acts against the human body through changes in posture, its implications in the cardiovascular system, with possible influences in the development, morbidity and mortality of cardiovascular diseases are yet to be well defined[12-15]. Nonetheless, it is clear at this point that, despite all the benefits inherent to the orthostatic posture, gravitational stress has become accepted as a primary

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*Received on 05/14/05 • Accepted on 12/08/05*

variable capable of affecting circulatory homeostasis. It is gravity (+Gz), acting at a mean velocity of 9.8 m/s$^2$, the variable responsible for the blood redistribution present through the adoption of orthostasis.

The hydrostatic opposition to the venous return, the third-space loss of fluid, venous return decrease and cardiac output reduction, all of which are hemodynamic alterations secondary to the gravitational effect, act as multiple stimuli, generating a variety of compensatory mechanisms[16,17]. Additionally, the gravitational stress can be aggravated by the level of physical activity, environmental temperature, and drug use and by several physiopathological processes, all capable of augmenting the disparity between the vascular volumetric capacity and blood flow volume [18-20].

## Man and microgravity

If gravity did not exist, man would not need such a complex cardiovascular system, particularly the presence of protection mechanisms to maintain a circulatory homeostasis during orthostatism. In general, the adaptation to gravity is, in part, acquired, and needs to be continuously trained.

For astronauts, the possibility of absence of weight due to microgravity causes major alterations in the cardiovascular system. The new pattern of blood distribution is interpreted as a volemia increase and compensatory mechanisms are promptly initiated (increase of natriuretic hormone secretion, inhibition of the rennin-angiotensin-aldosterone system), leading to a plasmatic volume decrease. A decrease in the sensitivity of the baroreflex and vestibulosympathetic reflex, as well as alterations in the autonomic nervous system, increase of vessel compliance in the lower limbs and disorders of arteriolar vasoconstriction are also observed[21-23].

All these alterations can be considered as a cardiovascular "deconditioning" capable of generating intolerance to orthostatism when astronauts return to the Earth's environment. Similar cardiovascular system alterations have been observed after long periods of bed rest (a situation that simulates microgravity), indicating that the orthostatic posture has a fundamental role in gravitational stress. The studies that seek the functional "understanding" of the organism in space are extended to high-prevalence clinical situations in the Earth's environment, such as arterial hypertension, orthostatic hypotension, and finally, syncope.

## The force of gravity and gravitational stress – General Aspects

The effect of the Earth's gravitational field on the human cardiovascular system is similar to the effect of an electric field in a conduit. Similarly to an electric field that moves free electrons along a conduit, the gravitational field moves blood (free particles) along the cardiovascular system. The effect of the gravitational field is measured by the gradient of the gravitational potential ($U_{gr}$), which is equal to the work performed by the field to move the mass of blood unit through the system towards Earth ($U_{gr}$=gz x r). The direction of the Earth's gravitational field close to the surface is vertical, and the distance r is equal to the system height: $U_{gr}$=gz x h. That explains why the effect of gravity is significant only in the orthostatic posture. In the horizontal posture, the height of the human body, h, is too little, making $U_{gr}$ negligible, but it increases several fold during orthostasis[24].

The gravitational stress can be defined as follows: gravity causes a significant displacement of blood to the infradiaphragmatic territory when the cardiovascular system is in the orthostatic posture. For the adequate maintenance of circulation to the supradiaphragmatic territory during orthostasis, the cardiovascular system must perform an additional work to return blood to the heart and neutralize the effect of gravity. The sum of this work (W), equal to the product of the gradient of the gravitational potential and the displaced mass of blood (M) represents the gravitational stress on the cardiovascular system: GS = W = $U_{gr}$ x M. It is unnecessary to mention that this additional overload on the cardiovascular system during orthostasis remains unknown in the traditional studies on the human circulatory hemodynamics. Nonetheless, the gravitational stress can increase with no gravity force augmentation. The natural action of the gravitational stress is to generate a redistribution of blood to the lower limbs in the cardiovascular system.

Contrary to water in a glass, the blood contained in an elastic and complex vascular system is redistributed slowly, and the change of blood does not happen instantly, but increases proportionally to the time the individual remains in orthostasis. Thus, based on the equation established for the gravitational stress, the mass of blood displaced by influence of gravity, M, is a function of time, GS=$U_{gr}$ x M (t) = g x h x M (t). This means that gravitational stress can increase not only through the gravity force increase, but also depending on the duration of the orthostatic posture period[24]. Hence, remaining an excessive period of time in orthostasis requires a more advanced stage of anti-gravitational response with higher sympathetic hyperactivity, hypervolemia and arterial pressure increment, similarly to what would occur with an increment of the gravitation force.

## Dynamic cardiovascular response to the orthostatic posture

During bipedal posture, gravity causes gradients of pressure in all of the body fluid compartments, including veins and arteries. In the arterial system, there is a change in the hydrostatic indifferent point, defined as the axial

reference in which the pressure of the venous blood column is not altered by the postural rearrangement, located at the level of the right atrium in supine decubitus, going to the infradiaphragmatic aortic territory in orthostasis[25]. However, due to higher vessel compliance, the main effect is the redistribution of the venous volume, which thus interferes with the global blood pressure. The accumulation of blood in the venous territory starts immediately during orthostasis and is completed in 3 to 5 minutes[26]. The venous volume of the lower members increases in approximately 500 to 700 ml[27]. Around 200 to 300 ml of blood is transferred to the veins below the abdomen. This translocation of blood volume is mainly derived from the intrathoracic compartment and results in the decrease of cardiac filling pressure and systolic volume[28-31].

In addition to the blood transference from the thoracic compartment, the central blood volume is affected by the transcapillary filtration of fluid into the interstitial space in some body parts, in response to the high capillary pressure associated to the low contraposition of the interstitial pressure. Additionally, the continuous filtration into the interstitial space further reduces the circulating volume[32]. The loss of transcapillary fluid is stabilized after approximately 20 to 30 minutes, with a plasmatic volume decrease of around 15%, although this process remains present with the maintenance of orthostasis[33]. Therefore, the distribution of blood volume is carried out through a complex system, by the intrinsic characteristics of the venous system, to the pumping effect of the skeletal musculature of the lower limbs (antigravity musculature) and, as mentioned previously, to the displacement of the hydrostatic indifferent point[12].

The capacity to maintain the cardiac output and the mean arterial pressure during the orthostatic "challenge" can be influenced by the behavior of the venous return. Amongst other factors, the venous return decrease can be the result of a combination of the decrease of the total blood volume with the accumulation of blood in the lower limbs, which subsequently may cause a subnormal ventricular filling pressure and deviate the curve of Frank-Starling to a segment in which the capacity of compensating for the orthostatic hypotension is limited[14,34,35]. Nonetheless, the human cardiovascular system has such a powerful "built-in" defense mechanism against the gravitational stress that it can completely neutralize the gravity-induced blood redistribution imposed by the orthostatic posture. The mechanism is the peripheral pumping.

The lower limbs are equipped with a specific system of blood pumping, the calf musculature, which is many times called "the peripheral venous heart". The deep veins of the calf, which are found inside a compartmented musculature, present valves that, similar to the cardiac valves, prevent blood reflux and are able to resist to pressures of several hundreds of mmHg. The compression of the venous segment during muscular contraction increases the pressure inside the muscular compartment, which leads to the closing of the valves and causes an ascendant blood flow. Through the regular contraction of the calf muscles during the orthostasis, the venous blood is pumped out of the lower limbs against gravity, reversing the gravitational action in blood distribution. Thus, the incapacity of the heart in "drawing" blood from the venous segment of the cardiovascular circuit is compensated by the presence of the additional pump in the venous system. This system, which consists of the calves, generates an effective pumping action that is not dependent on the filling pressure, helping to successfully maintain circulation during orthostasis.

Therefore, the final equation of gravitational stress can be expressed as follows: $GS = g \times h \times M(t) / R_{p} \times H_{per}$, where $R_p$ is the peripheral resistance and $H_{per}$ is the work of the "peripheral venous heart"[24].

Although initial studies have demonstrated a decrease in the brain blood flow during the orthostatic posture[36], it is currently known that cerebral perfusion in humans is maintained by a cerebrovascular self-regulation, which allows an effective cerebral functioning and a satisfactory distribution of regional flow within a broad variation of perfusion pressure[37]. In comparison to what occurs with quadrupeds, human beings present a more constant distribution of total blood flow in the several body segments during the orthostatic posture, including for the great arteries, suggesting a better functional adaptability to gravitational stress[8].

The redistribution of blood volume, flow and pressure, caused by the upright posture, can endanger pre-load, arterial pressure and organic perfusion, and it is compensated by a compensatory sequence of interconnected neurohumoral mechanisms that are opposed to the continuous circulatory caudal direction imposed by the hydrostatic pressure[15]. As early as 1904, Erlanger and Hooker observed, using the passive inclination test (IT), that the acceleration of the cardiac frequency and the decrease of the pulse pressure occurred in the upright posture. They considered this pattern of behavior similar to that observed during a hemorrhagic event and concluded it was the normal response of the human being to postural stress[1]. Turner emphasized that the circulatory adjustment would be specific for each individual, according to his own personal pattern, and that some patterns of individual response would be higher than others[1].

Several regulatory mechanisms occur instantly in response to the effects of gravity. The initial adjustment to orthostasis is mediated by the regulatory neural system[30,31]. The main receptors involved in these adjustments are the cardiopulmonary mechanoreceptors, located at the level of the right atrium and the pulmonary veins, and the sinoaortic receptors, located in the carotid sinus and aortic arch[38]. In addition to responding, in an isolated form, for the alterations in circulatory volume, these baroreceptors

present a complex inhibitory interaction between the cardiopulmonary and the sinoaortic baroreflexes, which causes the reduction in the cardiopulmonary afferent input to increase the gain of sinoaortic baroreflex[39]. Finally, the decrease in the activation of the cardiopulmonary receptors produces a peripheral vasoconstriction for normotension maintenance, due to the decrease of the central venous pressure and cardiac output[40].

The primary objective of the arterial baroreflex is to maintain the arterial pressure close to a point of reference for a relatively short period of time. The rapid regulation of the arterial baroreceptors, regardless of the new pressure level, is due to the fact that this reflex acts as a "buffer" system, which is effective on the arterial pressure fluctuations that occur in everyday life. The arterial baroreceptors also play a smaller role in the long-term control of the arterial pressure level[41].

These aorticocarotid baroreceptors tonically inhibit the vasomotor centers of the brainstem. A decrease in the blood pressure removes this inhibitory stimulus, resulting in an increase of the sympathetic tonus and decrease of the parasympathetic tonus[42]. From a functional point of view, the two components of the arterial baroreflex (carotid and aortic) are not equivalent. It has been suggested that the aortic baroreflex has a higher threshold and lower sensitivity than the carotid one[38]. The information of the baroreceptors is transmitted through several pathways that accompany the route of the ninth and tenth cranial pairs until the brainstem centers. These two nerves are the afferent pathway of the reflex, whereas the efferent pathway consists of the vagus nerve and the sympathetic pathways that run at the level of the intermediolateral spinal cord[6]. The changes in the neural discharge can result in changes of vasomotor tonus, systolic volume and cardiac frequency.

The vestibular system also seems to contribute to the sympathetic activation through the recruiting of otolytic organs. This is achieved through the vestibulosympathetic reflex. This reflex is a feedback neural system that regulates the sympathetic neural discharge through nerve afferences from the vestibular system[43].

During a prolonged orthostatic period, in addition to the baroreceptors and the vestibular system, delayed-action regulatory mechanisms based on additional reflexes of the humoral system that include the natriuretic hormone secretion, rennin and aldosterone, are also involved with the maintenance of arterial pressure[15,27,44].

Regarding the hemodynamic parameters, orthostatism causes, in the individual chronically adapted to gravitational stress, a slight decrease in the systolic arterial pressure, in general lower than 20 mmHg. The diastolic arterial pressure remains stable or is slightly elevated, and the mean arterial pressure is not significantly altered. The telediastolic pressure in the right ventricle diminishes, the cardiac output decreases around 20%, and the cardiac frequency and peripheral vascular resistance increase 10% to 30% of the initial value[6].

When, however, the head-lower limb acceleration vector +Gz is chronically diminished, such as during long supine rest periods, human beings demonstrate a reduction in the orthostatic tolerance, associated to a compromised regulation of the arterial pressure. These observations include an increase in the compliance of the lower limbs, alteration of the cardiovagal reflex response, contraction of the circulating blood volume and decrease of the systolic volume[14].

On the other hand, Muenter et al observed that, individuals submitted to sleep restriction periods (approximately 4 hrs/night for 4 consecutive days), showed a better blood pressure regulation in an orthostatic situation[45]. The individuals presented an increase in systolic arterial pressure and a decrease in cardiac frequency during orthostatic stress, simulated through the use of sub-atmospheric pressures applied to the lower part of the body, called "lower body negative pressure" (LBNP), reinforcing the hypothesis that, in normal individuals, the continuous exposition to gravitational stress triggers a better circulatory adaptation. The same can be said of patients with neuromediated syncope, who, when submitted to daily orthostatic training through a technique called "tilt training", presented remission of clinical symptoms, even when the drug therapy was ineffective[47]. Newman et al (1998) used IT to assess plane pilots, routinely exposed to high levels of gravity (+Gz) and normal individuals[47]. These authors observed that the pilots presented a significant increase in the systolic arterial pressure, mean arterial pressure and pulse pressure during the IT with 75º, when compared to the control group ($p < 0.05$). No significant alterations were observed between the two subgroups of this study regarding the response of cardiac frequency to orthostatic stress.

When analyzed at a systemic level, cardiac output, more than cardiac frequency, represents the final organic reflex response to the stimulation of the baroreceptors by orthostatic stress[33]. Based on this fact, Convertino[14] analyzed cardiac output alterations that could occur in response to arterial pressure and cardiac frequency variation in individuals repeatedly exposed to high levels of gravitational acceleration. This author observed the importance of not only cardiac frequency analysis but also of the systolic volume, in the assessment of the effective gain of cardiac baroreflex integrity in maintaining arterial pressure during the orthostatic hypotensive "challenge". The better orthostatic performance observed in these individuals supports the hypothesis that a repeated exposition to gravitational acceleration is associated to changes in blood volume and autonomic function, in opposition to what occurs with bedridden individuals[14].

The physiological mechanisms that administrate arterial pressure regulation in the human being (example: baroreflex, vascular volume control) have to constantly adapt to the daily stimulation of gravity; in other words,

to the postural variations. The analysis of the response of the blood volume and the carotid-cardiac baroreflex in adapting to changes caused by the gravitational stimulation can have significant importance, because the blood volume and the responsiveness of the carotid-cardiac reflex are two primary factors (in addition to height) when predicting the evolution for arterial hypotension and syncope[48].

The comparison of the cardiocirculatory functional behavior when facing gravitational oscillations allows two conclusions: 1) the human being is capable of undergoing continuous adaptation to gravitational stress; 2) the mechanisms that allow us to tolerate the gravitational effect are highly malleable and trainable, or acquirable through training[14]. Therefore, it has been established that an autonomic nervous system, capable of maintaining a dynamic adaptive behavior that allows an adequate cardiac output in response to the blood volume oscillations caused by the orthostatic posture, is fundamental[39,49]. Thus, clinical conditions that interfere in the responsiveness of the baroreflex system can somehow interfere in the circulatory homeostasis[50-53].

## Factors that influence the baroreflex sensitivity

It is known that alterations at activity and/or balance level of the several branches of the autonomic nervous system can be considered one of the main factors responsible for the development of essential chronic arterial hypertension. The hypertensive individuals present an increase in the variability of arterial pressure fluctuation and a decreased sensitivity of the baroreceptors[9,54]. The hypertensive patient's gender also seems to be an important determinant in baroreflex sensitivity, as the autonomic function shows to be more compromised in the female sex[54].

Hypertensive individuals are less responsive to induced sympathetic stimulation[55,56]. In fact, the analysis of the autonomic response of hypertensive individuals to postural change, when compared to that of normal individuals, shows that, although there is a basal increase of sympathetic activity during the orthostatic posture, the sympathetic response is significantly decreased, suggesting an impairment of the mean arterial pressure control by the baroreflex in these individuals[9].

The reflex hemodynamic responses to orthostatic stress are also attenuated by aging. When a young healthy individual rises from a sitting or supine posture, there is a variable change in the systolic arterial pressure of around 10 mmHg, an increase in the diastolic arterial pressure of 10 to 15 mmHg and an increase in the cardiac frequency of 25 to 30 bpm. This response occurs within approximately 30 seconds. In contrast, when an elderly healthy individual rises, a trend towards a decrease in the systolic arterial pressure (0 to 5 mmHg), as well as the maintenance of the diastolic arterial pressure and the absence or attenuation of the cardiac frequency positive response (10 to 15 bpm) are observed. Around 6% to 30% of elderly individuals present orthostatic hypotension (decrease in the systolic arterial pressure $\geq$ 20 mmHg, or in the diastolic arterial pressure $\geq$ 10 mmHg), when standing upright[58,59]. Contrarily to what could be predicted, the majority of elderly individuals who present inadaptation to orthostatic stress do not have well-defined pathological alterations, such as central or peripheral degeneration of the autonomic pathways or adrenal failure. These individuals possibly represent an extreme condition of the distribution of age-related physiological changes to posture[27].

The best-known biological change in arterial pressure control that occurs with age is an attenuation of the baroreceptor responsiveness, which is represented by the baroreceptor-heart reflex[3,60,61]. This finding is commonly considered as indicative of an age-related primary abnormality in cardiovascular control, as the baroreflex is the main factor that influences a rapid adaptive response to orthostasis[53].

There are, however, many other age-related alterations in the cardiovascular function, which can contribute significantly to an inadequate response to orthostasis, such as reduction in arterial[27,62] and myocardial[63] compliance, in the activation of the rennin-angiotensin-aldosterone system[64], in renal sodium retention[65], a defect in the brain self-regulation and the presence of systolic arterial hypertension[27].

The location of arterial baroreceptors in the compliant great arteries means that changes in the natural compliance, which can be caused simply by aging, disease or physical activity, also have the potential of influencing the afferent activities of the baroreceptors and consequently affect the autonomic reflex activity[66].

The arterial compliance has a fundamental role in the cardiac energy demand, in maintaining the diastolic arterial pressure and the coronary blood flow[66,67]. Probably, the least evident is the influence of the vascular mechanical properties on the autonomic function by alterations in the afferent activity of the baroreceptors. Although it is difficult to investigate the extension to which these two phenomena are interconnected, Kingwell et al, analyzing arterial compliance and its possible influence on the baroreflex in hypertensive individuals and athletes, observed not only a direct relation between arterial compliance and higher blood pressure due to reflex activation in athletes, but also a baroreflex deficit in hypertensive individuals[66]. Nevertheless, basal assessments of vascular stiffness might not represent the mechanical stress that affects the great arteries with barosensory function during dynamic changes in pressure that characterize the baroreflex role[68,69]. Additionally, a compromised neuronal function can participate with an outstanding role, causing the

reduction of the baroreflex gain with the decrease of the vascular mechanical function[70].

Through the measurements of the integrated gain of the cardiovagal baroreflex and its mechanical and neural components, analyzed dynamically (during parenteral administration of sodium nitroprussiate and phenylephrine), Hunt et al observed that the integrated gain in sedentary male elderly individuals was lower than half of that found in young, equally sedentary, individuals[70]. This finding was derived from a decrease in the mechanical as well as neural transduction. Another significant observation of this study was that physical activity was able to compensate these results, making the physically active elderly individual to present duplicated baroreflex gain values in relation to sedentary individuals of the same age and comparable to that of young sedentary individuals. A low neural transduction in sedentary elderly individuals is compatible with the evidence of an altered central autonomic integration[40,71], of a decreased vagal output[72] and a lower density of muscarinic receptors in the sinus node[73], which occur with aging. The strong relation between the cardiovagal baroreflex gain and the neural component can reflect some of these declines.

Considering that age not only decreases the baroreflex gain[53,60,61], but also causes a hardening of the great arteries[67], it is possible to establish that the dynamic function of the arteries with a barosensory role is important in the age-related cardiovagal baroreflex decline. Another fundamental aspect is that the analysis of the behavior of the great arteries and the baroreflex in a supine resting position can provide limited information regarding the age-related difference in vascular mechanisms during changes in the arterial pressure, which characterize the baroreflex role[70]. The importance of the interference of the arterial pressure dynamic behavior on the baroreflex sensitization in the hypertensive patient was confirmed by Siché et al, who observed that the major determinant of the baroreflex sensitivity was the 24-hour arterial pressure level, and that the latter was not significantly determined by age[41].

A decrease in the carotid arterial compliance can be an important mechanism responsible for the age-related cardiovagal baroreflex reduction. However, it has been suggested that the association between cardiovagal baroreflex/arterial compliance is not simply due to a co-linearity with aging[74]. It is known that the vascular structure of the carotid and aortic sinus area determines the distortion and tension at the level of the arterial baroreceptors during acute changes in the blood arterial pressure[75]. In this context, an age-related decrease in the compliance of the carotid artery can restrict the capacity of its sensitive mechanical segments to adequately identify and translate changes in the intravascular pressure into afferent nervous signals to the central nervous system[76,77].

Among the several theories proposed for the physiopathology of the vasovagal syncope, one of the most studied is the baroreflex dysfunction[44]. Mosqueda-Garcia et al investigated the baroreflex sensitivity in individuals with vasovagal syncope and positive IT and observed a decreased response of the baroreflex cardiovagal and sympathetic components when compared to the control group[78]. Some authors have suggested that the function of the baroreflex is preserved, but it undergoes a sudden suppression due to a depressor reflex that originates from the heart[79]. In general, all studies that deal with this issue report some type of baroreflex dysfunction that results in the incapacity to feel or compensate the hemodynamic alterations triggered by the gravity force in patients with neuromediated syncope[44].

Thus, it is possible to consider that the analysis of the influence of aortic compliance on the baroreflex can allow a further elucidation of the adaptation to orthostatism and the physiopathology of neuromediated syncope.

## Great arteries and adaptation to orthostatism

A typical characteristic of living tissues is their capacity to respond to overload changes, altering their geometry, structure and/or mechanical properties[80].

As previously established, the increase of stiffness of the great arteries, caused by arterial hypertension and aging, for instance, also results in a compromised sensitivity of the baroreflex, which can interfere in the adequacy of the cardiocirculatory response to orthostatic stress[42,81].

Kingwell et al evaluated the influence of arterial compliance in the baroreflex function in normotense athlete and hypertensive individuals. These authors suggested that, due to the decreased arterial compliance in hypertensive patients, broad arterial pressure variations do not cause adequate changes in vascular circumference, thus interfering with the baroreceptor firing[66]. A decreased arterial compliance can thus explain the behavior of in *plateau* bradycardia in hypertensive subjects.

Siché et al utilized the measurement of the carotid-femoral pulse wave velocity (PWV) in individuals with slight to moderate systemic arterial hypertension (SAH), measured by out-patient monitoring of arterial pressure, to evaluate the baroreflex sensitivity in relation to the hardening of the great arteries. In this study, the increase of PWV was significantly associated with an alteration in the baroreflex sensitivity. The development of an arterial distensibility alteration was related to a deficit in the baroreflex sensitivity, predominating over the vagal control loop[41]. The baroreflex sensitivity alteration would then translate the degree of severity of the vascular distensibility alteration, with a consequent prognostic interest. The vascular structure of the carotid sinus area and aorta determines the tension and the distortion in the arterial

baroreceptors during acute changes in arterial pressure. In this context, a decrease in arterial compliance[76] can be expected to restrict the capacity of its sensitive mechanical segments to identify and adequately translate changes in the intravascular pressure into afferent nervous signals to the central nervous system[74].

As it can be observed, most data regarding the central circulatory hemodynamics in human beings were formulated based on hydraulic models, which are predominantly known in the supine posture, due to technical and ethical issues.

The first studies performed with the objective of assessing the effects of gravitational stress on hemodynamic parameters and its influence on the contour of the aortic pulse wave were carried out in primates[82-84]. It was observed that the central hemodynamics presented a pattern of response to gravitational stress that had well-defined phases. Immediately after the start of gravitational stress, there would not be a baroreflex yet, due to a delay in the physiological response time. In this phase, in comparison to what was observed in the basal phase, a later systolic peak would not occur in the contour of the ascending aorta pulse wave, resulting from a reflected pulse wave returning to the heart. Therefore, the reflected wave would later appear in the diastole, suggesting a decrease in the pulse wave velocity, likely due to an increase of aortic compliance together with a mean pressure decrease.

Immediately after that, the so-called compensatory phase would ensue, in which the baroreflex response would be present. In this new phase, the pulse wave contour would return to the basal patterns, with an increase in the mean arterial pressure. The reflected wave would appear prematurely, suggesting a stiffer aorta at this phase, compared to the anterior one. An increase in the systolic volume and peripheral vascular resistance could also contribute to an increase in wave reflection. According to the authors, the aim of this response would be to maintain the efficiency of the ventricular/vascular coupling, in opposition to the gravitational effect[83].

In spite of the importance of using experimental models that utilize animals that are phylogenetically close to humans, such as baboons, it is also important to bear in mind the specific characteristics of the circulatory system architecture, which depend on postural body habits and affect the pulse wave contour due to the variation of amplitude, the summation and/or cancellation of arterial reflexions[84].

The analysis of the characteristics of pulse transmission and pulse wave shape in baboons was performed by Lathan et al[84]. These authors observed that the wave shape, the aortic impedance and the PWV in these primates were different when compared to those of humans[84]. A significant difference demonstrated in this study was that the dimension of the abdominal aorta was only slightly smaller than that of the thoracic aorta in comparison with those of humans, in whom the aorta presents a cuneiform aspect, with its abdominal segment, located below the renal arteries, presenting a markedly decreased diameter when compared to that of the lower portion of the thoracic aorta[85,86]. This finding would be responsible for a low coefficient of aortic reflection at the level of the renal arteries in baboons, a finding that could be accountable for the differences observed in humans.

The current evidence points out to the arterial stiffening, calculated by the PWV measurement, as an important risk factor for cardiovascular morbidity and mortality, and emphasize its influence in the adaptive control of arterial pressure[87-89]. Thus, the measurement of PWV might contribute to a better understanding of the dynamic behavior of the great arteries against the gravitational stress.

## A NEW HYPOTHESIS FOR THE UNDERSTANDING OF CARDIOVASCULAR ADAPTATION TO ORTHOSTATISM — THE ROLE OF THE GREAT ARTERIES

Recent studies demonstrate that the great arteries are no longer seen merely as passive blood conduits that have the function of transporting and distributing blood, but are now seen as having a fundamental and complex role in maintaining the circulatory physiology, as well as in the origin of cardiovascular disease[66,87,90,91].

The technical limitations, the structural complexity of the arterial wall and the dynamic behavior of the great arteries, however, have hindered the study of the arterial tree under very common situations, such as the response and accommodation to postural stress[92-94].

In a recent study, Elias[95] assessed for the first time, the influence of the orthostatic posture compared to the supine posture, over the aortic distensibility in normal and hypertensive individuals of both sexes, utilizing the carotid-femoral PWV measurement obtained during supine decubitus and during the IT as the aortic stiffness index. This study demonstrated the existence of an immediate significant elevation of the PWV associated to the adoption of the orthostatic posture (11.7%) (10.1 $\pm$ 2.3 *versus* 11.7 $\pm$ 2.5, for the supine posture and during the IT, respectively; $p < 0.001$). This vascular functional behavior pattern was observed in all study individuals, regardless of age, causing many young individuals to present PWV levels during the IT that were similar to those presented by elderly individuals during the supine decubitus. Another relevant aspect of this study was the observation of the dynamic characteristic of the PWV response, which promptly returned to the basal patterns when the supine decubitus was resumed. In this study, the systolic arterial pressure and age were the main variables responsible for the increase in PWV, in supine decubitus as well as during orthostatism. As there was no significant systolic arterial pressure increase

in the orthostatic posture, the author considered that the PWV increase was probably caused by alterations in the circulatory dynamics due to the gravitational action, in association to the structural and geometric characteristics of the aorta[95]. This hypothesis was supported by the knowledge that the PWV, based on the Moens-Korteweg formula, depends on the vascular radius and thickness, as well as on its elastic modulus.

It is known that, structurally, the ratio of elastic/collagen fibers varies from 3.1:1 in the proximal descending aorta, to 2.8:1 in the region of the middle thoracic aorta, and to 0.8:1 in the abdominal aorta[96]. The collagen elastic module is much superior to that of elastin, which means that, the farther from the heart, the stiffer the artery becomes, and also that its elastic module and its PWV increase. In other word, the vascular distension is limited by the collagen fibers, and by the elevated Young's elastic modulus[97,98]. The fact that PWV was obtained during the IT places the arterial segments differentially exposed to the gravitational action, somehow mimicking what happens during the active orthostatic posture. While the segment located between the aortic root and the aortic arch up to the level of the carotid artery is under the direct contraposition of gravity, the remaining aortic segments, up to the level of the femoral arteries, present the circulating blood flow going along with the vector of gravitational action. The immediate result of this is that gravity promotes a progressive increase in arterial pressure in the segments below the cardiac level in the orthostatic posture[15,30,99].

Given the hydrostatic pressure generated by the gravitational action and the consequent change in the hydrostatic indifferent point, there is a higher blood flow to the arterial segments with a bigger elastic modulus and smaller radius, disclosing the increment of the carotid-femoral PWV measured during orthostasis[100,101]. This PWV increase is responsible for the premature return of the reflected waves from the peripheral sites to the ascending aorta. These prematurely reflected waves (during the ventricular ejection period) are added to the reflected component of the pulse wave caused by the left ventricular ejection and influence the contour of the pressure and flow waves[102]. Hence, the early return of the reflected component that occurs during the systolic component of the pulse wave leads to a consequent increase in pulse pressure[103,104] (Fig. 1). It is likely that this increase, caused by the reflected wave in the initial portion of the arterial pulse wave, is due to a complex evolutional functional adaptation of the vascular system with the objective of maintaining an effective blood flow to the brain in response to bipedism[95].

The role of the wave reflection in the circulatory homeostasis during orthostasis is reinforced by the observation that, when nitroglycerin, utilized in the sublingual route for IT sensitization, generates a peripheral vasodilation, it leads to a delay in the reflected component of the pulse wave and the consequent reduction in the proximal systolic pressure, resulting in symptoms of low brain flow in patients with neuromediated syncope[105,106]. In fact, although a decrease in the coefficient of reflection is verified with the use of nitroglycerin, paradoxically, an increment in aortic stiffness is also observed. Soma et al[107] ascribe this secondary aortic stiffness to a possible reflex activation of the sympathetic nervous system. These authors state that the cardiac frequency increase, which is a consequence of sympathetic activation, can be unfavorable as it reduces ventricular ejection time, time for the aortic root peak flow, the systolic volume and the cardiac output[107].

Other aspects that deserve to be analyzed are the cardiac frequency behavior associated to postural change and the potential role of the alterations in the hemodynamics and structure of the great arterial vessels in their response patterns[97]. Initial experimental studies of humans in supine decubitus showed a positive correlation between the cardiac frequency increase and an augmented aortic stiffness[108-111]. By observing that the effect of the cardiac frequency increase, causing the stiffening of the elastic arteries, occurred independently from the sympathetic modulation, Mircoli et al[112] suggested that the decrease of frequency-dependent arterial distensibility would primarily occur because of the viscous characteristic of the vascular wall and its response inertia to the intravascular pressure changes[112]. However, Wilkinson et al[113], in a study that assessed the behavior of PWV in healthy individuals submitted to atrial stimulation, did not observe significant alterations in aortic distensibility in the face of cardiac frequency increase.

In opposition to the findings obtained in supine decubitus, Elias[95] observed a negative correlation between cardiac frequency and PWV in orthostatic posture ($r = -0.37$, $P < 0.001$). Age was the main variable responsible for the cardiac frequency behavior in the orthostatic posture ($r = -0.52$, $P < 0.001$). In search for a better understanding of this finding, the author also analyzed the correlation between the cardiac frequency, obtained during orthostatic stress, and the basal measurement of the PWV, having observed a negative correlation between the cardiac frequency and the basal PWV ($r = -0.30$, $P < 0.01$). These results showed the possibility of an association of the basal pattern of arterial compliance with the cardiac frequency response level, during orthostasis[95].

"Transversal" studies have shown that the basal cardiac frequency does not differ between young and elderly individuals in the supine posture[114-115]. However, the analysis of cardiac frequency in healthy individuals in the sitting posture has shown that cardiac frequency decreases with age in both sexes[116,117]. The studies utilizing the IT to assess the cardiovascular adaptation to orthostatic stress also reported a significantly lower cardiac frequency in elderly individuals[17,117,118]. We know

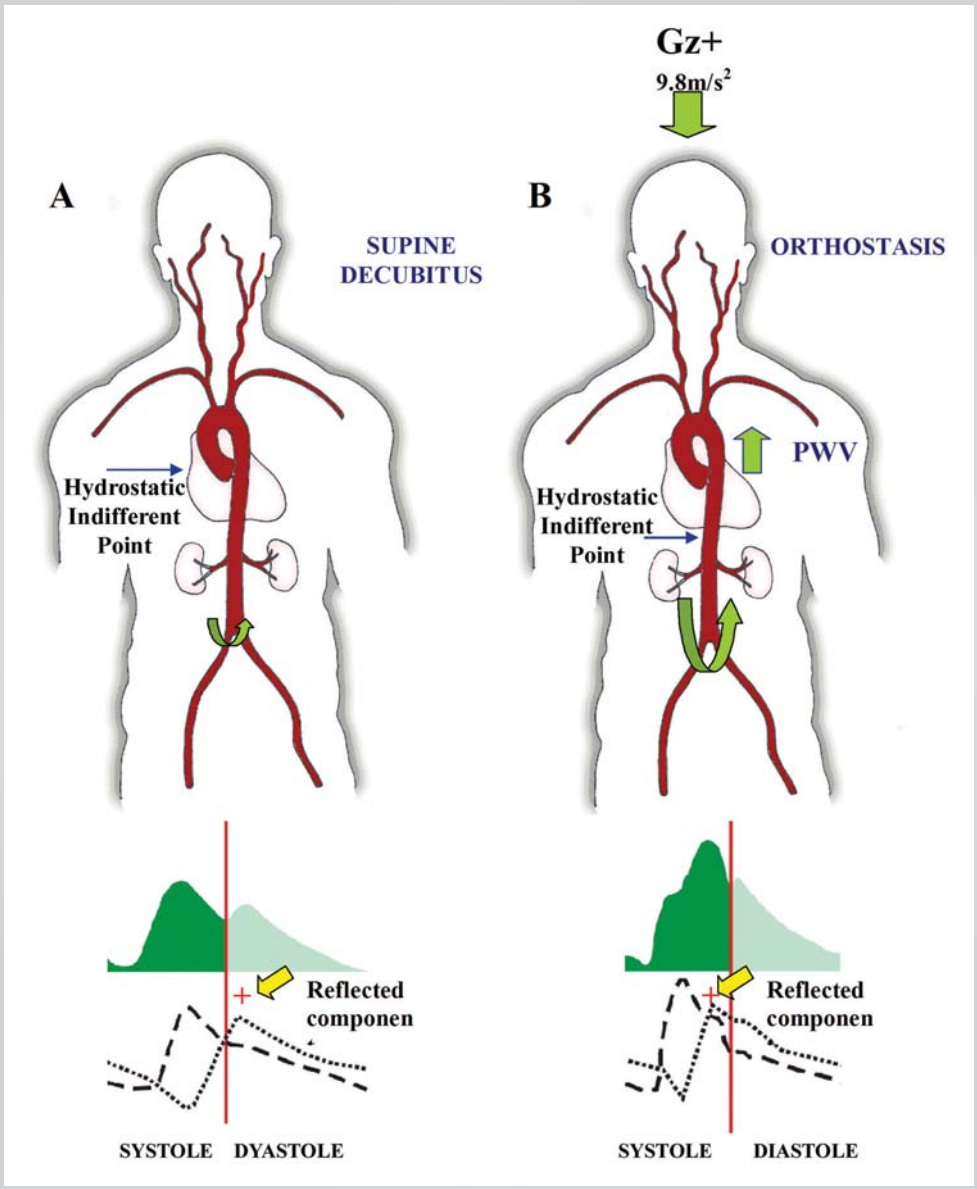


*Fig. 1 - Schematic mechanism proposed for the behavior of the pulse wave length in a normal young individual. **A)** In supine decubitus, the reflected component occurs during the diastole due to a smaller PWV. **B)** In the orthostatic position, due to the gravitational force, the indifferent hydrostatic point changes to the subdiaphragmatic aorta, which has a smaller radius and a greater elastic modulus; therefore, PWV increases, leading to an earlier return of the reflected component of the pulse wave, which then occurs with a systolic "pulse summation". Thus, pulse wave morphology is altered.*

that the resting cardiac frequency is modulated, in part, by the equilibrium between the sympathetic and the parasympathetic tonus, with a predominance of the latter. The intervention of age and posture on cardiac frequency suggest that age-related alterations occur in the regulatory mechanisms of cardiac frequency[101]. The acute cardiac frequency increase in response to the rapid change into the orthostatic posture, in general occurring within the first seconds after standing upright, although present in all individuals, decreases in magnitude with age, and can be delayed[118]. This decrease in the variability of the cardiac frequency observed in elderly patients, when compared to young individuals in the orthostatic *versus* the supine posture, has been attributed to a decrease in the recruitment of baroreceptor activity when the upright position is adopted[17,117,118].

As the autonomous nervous system is the main intermediator between the nervous and cardiovascular systems, the understanding of its participation in the modulation of the cardiac frequency response during postural change is essential[103]. It has been established that the sensitivity of the baroreceptor is negatively correlated with aging, the increment of basal arterial pressure and the PWV[39,64,75,119], being such alterations partly caused by cyclic dynamic arterial alterations[68,72]. Although the cardiac frequency increases less during

postural stress in elderly individuals when compared to young ones, the systolic volume reduction tends to be smaller in the healthy elderly individual than in the young one; consequently, the cardiac output does not significantly vary with age, as the smaller increment of cardiac frequency is compensated by a smaller systolic volume reduction[101].

Considering the dynamic behavior of the aortic compliance when facing postural change, one could presume that a higher systolic volume decrease would lead to a decrease in the aortic pulsatile deformation, with a subsequent decrease of baroreceptor stimulation and cardiac frequency increase.

The maintenance of the systolic volume in elderly individuals is attributed to a lower venous compliance in this group, which would allow the preservation of the cardiac filling volume, and consequently, of the systolic volume[101]. However, an age-related lower cardiac frequency could also mean an adaptation mechanism of man to bipedism[95]. It is known that the cardiac frequency affects pre-load through its effect on the diastolic filling time. The cardiac frequency also modulates the state of myocardial contractility through its effect, by altering the myocardial concentration of $Ca^{2+}$ and $Na^{+}$. As a consequence of the increase of myocardial contractility, the cardiac frequency also modulates the final systolic volume, the systolic volume and the ejection fraction[101]. Thus, a lower cardiac frequency could, at first, allow a better cardiac performance when facing a stiffer arterial system. Further large-scale longitudinal studies will define whether this recent observation in the cardiac frequency behavior is caused by structural alterations of the great arteries, which are inherent to the aging process, and to some degree of interference in the mechanical component of the baroreflex.

## Functional behavior of the great arteries – Possible clinical implications

Considering what was presented here, the following hypothesis can be formulated: the return of the reflected component of the pulse wave is essential for the immediate adaptation to orthostatism, as well as in the activation, at an adequate degree, of the baroreceptors. Assuming that such hypothesis is correct, it is possible to consider the participation of these recent findings in some very common clinical conditions associated to the orthostatic posture. The more frequent occurrence of neuromediated syncope in young individuals is well established[120]. Another aspect is that such events occur more commonly with taller individuals. As the aortic length is related to body height, the arterial reflection wave occurs later in taller individuals[121], and it would not be incongruous to suppose that, in young individuals, especially females, those who present lower basal levels of arterial pressure, the presence of a more elongated aorta could interfere with the return of the reflected component to the proximal aortic portions in an optimized way, which could result in the activation of reflexes related to the genesis of the syncope (for instance, the Bezold-Jarisch reflex). Another aspect that supports this hypothesis is, as previously discussed, the importance of height (h) in gravitational stress[24]. Therefore, in young individuals, the premature return of the reflected component of the pulse wave caused by the increment of the PWV during orthostasis would act together with the baroreflex and other regulatory mechanisms of the arterial pressure, allowing an immediate adaptation to orthostatism[95].

Based on the recent data, the hypothesis of the participation of the great arteries in the maintenance of circulatory homeostasis as well as in the syncope-triggering mechanism must be taken into account, aiming at a new theory, to be incorporated to the several existing ones, for the physiopathology of neuromediated syncope[44].

As for the analysis of the orthostatic adaptation in elderly individuals, who present higher susceptibility to morbid cardiovascular events and postural hypotension, the application of these recent findings is still questionable.

Literature data have shown a broad diurnal variation in the occurrence of cardiovascular events, with a peak incidence of myocardial infarction, sudden cardiac death and ischemic and hemorrhagic stroke occurring in the first hours of the morning[122-124]. A more detailed analysis of this circadian pattern has identified the hour that follows awakening, more than any other time of the day, as the one during which more cardiovascular events occur[122,123]. Although it has not been established whether the additional increase of PWV during orthostasis is just a structural adaptive process inducing mechanism or a marker of morbid events, this finding must be taken into account.

One must consider that, although a premature return of the reflected component of the pulse wave can contribute to a lower cardiac frequency during orthostatic stress, generating potential advantages in the postural adaptation of the elderly, chronic abnormalities in the aortic distensibility, such as those possibly generated by the orthostatic posture, create an incompatibility between the ventricular ejection and the aortic flow energy. Hence, a more premature return of wave reflection caused by the increase of the PWV can create an increase in the hydraulic load for the left ventricle[125].

Therefore, a combined ventricle-vascular stiffening can potentially have important consequences for the cardiac response to the variation of filling volume, as a stiffer heart-arterial system generates higher alterations in systolic pressure for a given change in ejected systolic volume or in the ventricular volume[126,127].

The overlapping of the known autonomic/baroreflex regulation abnormalities associated to aging[59,128,129], with the age-related arterial hardening, can aggravate

the arterial pressure fluctuations related to postural and postprandial stress[126,127]. This postural increase of PWV can add to the sympathetic nervous activity augmentation, particularly the adrenergic activity and other acute risk factors such as platelet hyperactivity, hypercoagulability and hypofibrinolysis, blood viscosity and vasospasm increase[130], contributing for the increase of cardiovascular morbidity and mortality in the morning period. Finally, the volemic oscillations caused by the upright posture are potentially more likely to be experienced by this population. This puts the elderly individual at higher risk, not only because a transient orthostatic hypotension generates the decompensation of a cardiac structural disease (for instance, coronary failure), but also because in situations of additional volemia decrease (for instance, infectious processes, use of vasodilator or diuretic agents, diarrhea and vomiting) there may be symptoms of orthostatic intolerance or even syncopal events[53,131].

Hence, a longitudinal investigation of a large, unselected population group is necessary, aiming at assessing the independent contribution of the postural variation of the PWV for the individual cardiovascular risk.

## Conclusion

The exact mechanisms responsible for the cardiovascular adaptation to orthostatism need further clarification. Several theories have been proposed as being fundamental in maintaining the circulatory homeostasis against the gravitational stress. However, a better understanding of the human adaptation to orthostasis must take into account the gravitational gradient generated by such posture.

Possibly, the hypothesis presented herein will contribute to the understanding of the participation of the great arteries in the cardiovascular adaptation to orthostasis and will enable a better analysis of the response of the great arteries to gravitational stress, of the physiopathology of neuromediated syncope and orthostatic hypotension.

Another aspect is how much the anti-gravitational adaptive phenomena can contribute to cardiovascular morbidity and mortality, when added to the inherent degenerative alterations such as arterial hypertension, aging and pre-determined genetic markers.

## Acknowledgements

To Prof. Dr. Roberto Sá Cunha, for the technical assistance and suggestions. To Prof. Dr. Dalton Vassalo and Dr. Márcio Augusto Silva, for text review.

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