# BAROREFLEX SENSITIVITY DURING THE GRAVITATIONAL STIMULUS: PHYSIOLOGY AND PATHOPHYSIOLOGY

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#### ABSTRACT

Baroreceptor mechanisms play a crucial role in healthy humans during a gravitational stimulus to maintain blood pressure and cerebral perfusion by providing proper orthostatic tolerance. In addition, they concur to synchronize central neural discharge activity and hemodynamic spontaneous fluctuations leading to an optimal interaction between the cardiovascular neural regulatory activity and the heart and vessel response.

In pathophysiological conditions as encountered before tilt induced neurally-mediated syncope, the gain of baroreflex control of heart rate and muscle sympathetic nerve activity (MSNA) is remarkably impaired, revealing a diminished capability to adapt in response to similar changes of blood pressure compared to healthy subjects. The loss of an organized post-ganglionic sympathetic discharge activity to the vessel leads to orthostatic intolerance in subjects with baroreceptor failure.

*Key words*: baroreflex sensitivity, muscle sympathetic nerve activity, cardiovascular sympathetic activity, gravitational stimulus

#### 1. PHYSIOLOGY

In healthy humans the change from rest to an orthostatic posture is followed by a blood pooling of about 800 ml into the high capacitance venous district below the heart leading to a drop of central venous pressure, a reduction of cardiac output and ultimately systemic hypotension (Mosqueda-Garcia 2000). The concomitant arterial baroreceptor and cardiopulmonary afferents unloading initiates a reflex neural sympathetic excitation and a concomitant vagal withdrawal that lead to arterial and venous vasoconstriction, an increase of heart rate and cardiac inotropism aimed at maintaining blood pressure and cerebral perfusion (Mosqueda-Garcia 2000). In addition, the overall increase of sympathetic activity is also sustained by positive feedback mechanisms induced by sympathetic afferents stimulation

generated by blood pooling in the low-pressure district attending the gravitational stress (Malliani 2000).

From a hemodynamic standpoint, during a 75° head-up tilt healthy humans manifest a mild increase of diastolic arterial pressure with a marked enhancement of heart rate, plasma norepinephrine levels and neural sympathetic discharge (muscle sympathetic nerve activity, MSNA), without major changes in systolic arterial pressure (Furlan 2000). Notably, beside changes in mean value under these conditions, everv single variable undergoes spontaneous fluctuations. In particular, the discharge activity of the sympathetic fibres is grouped after an oscillatory pattern characterized by a period of 10 seconds and is coupled with analogous rhythmic fluctuations of heart rate and blood pressure (Furlan 2000).

The quantification of the observed oscillatory phenomena is obtained by power spectrum analysis as 0.1 Hz (low frequency, LF) oscillatory component (Task Force ESC and NASPE 1996, Malliani 2000, Pagani 1986). During the sympathetic activation induced by tilt, the LF component of muscle sympathetic nerve activity (MSNA) variability is prevalent in the spectrum, resembling the changes observed in the same oscillatory components of RR and systolic arterial pressure variability (Furlan 2000). In addition, the linear coupling between LF fluctuation of MSNA and heart rate, and of MSNA and systolic arterial pressure, assessed by the coherence function, was found to increase during the gravitational stimulus suggesting the onset of a common oscillatory pattern based on prevailing 0.1 Hz fluctuation (Furlan 2000).

It must be pointed out that sympathetic neurons located in areas within the central nervous system involved in cardiovascular regulation were found to be characterized by a 0.1 Hz rhythmical discharge activity linked to low frequency spontaneous fluctuations of RR interval and blood pressure (Kaminski 1970, Montano 1996, Preiss and Polosa 1974). Interestingly, these fluctuations persist following the removal of baroreflex afferents by a stabilizer device connected to the arterial system of the animal or after bilateral vagal denervation in spinal dogs (Kaminski 1970, Preiss and Polosa 1974).

In patients with intractable heart failure, the suppression of spontaneous blood pressure fluctuations by a left ventricle assist evice is associated with a persistent LF component of RR variability (Cooley 1998). These observations cumulatively suggest that baroreflex activity is not necessary to the genesis of LF fluctuations that seem to be the result of the activity of a central oscillator. However, the inhibitory role of human baroreflex activity on tonic MSNA is established and may concur to organize the sympathetic neural activity after a discharge pattern with a period of 10 seconds (i.e. low frequency fluctuation). Analogous phenomena may arise in heart rate spontaneous variability during both increase and decrease of arterial blood pressure as the result of baroreflex modulation of heart period (Pagani 1997). Indeed, a blood pressure decrease is associated with the increase of heart rate and sympathetic nerve discharge (Furlan 1998a). Conversely, arterial pressure enhancement is attended by neural silence and a drop of heart rate (Furlan 1998a).

Therefore, baroreflex mechanisms during tilt are more likely to play a role in *modulating* the amplitude and in synchronizing the LF fluctuations of heart rate, arterial pressure and MSNA (Furlan 2000). In keeping with this hypothesis is the observation of the absence of a LF component in both RR and systolic arterial pressure variability in subjects with pure autonomic failure (Furlan 1995) during a 45° head-up orthostatic challenge. In addition, we observed a remarkable orthostatic intolerance and hypotension in spite of high level of plasma catecholamine and MSNA in a patient with a baroreflex failure because of a rhinopharyngeal cancer who underwent neck radiotherapy (Furlan 2001). Notably, the post-ganglionic sympathetic discharge activity was completely disorganized suggesting that a proper neural frequency modulation (0.1 Hz) is required to induce a suitable vasoconstriction as already suggested in animal studies (Stauss 1998).

## 2. PATHOPHYSIOLOGY

In physiological conditions, the increase of the LF component of RR variability (LF<sub>RR</sub>, in normalized units) during a gravitational stimulus tends to be constant over time. Indeed, in a previous study, based on time variant spectrum analysis of RR variability, which enabled us to follow the beat by beat change in  $\mathrm{LF}_{RR}$  and  $\mathrm{HF}_{RR}$  amplitude , the two spectral components and RR interval were relatively stable during a 15 minute lasting tilt procedure in healthy subjects (Furlan 1998b). Conversely, in the pathophysiological condition of a neurally mediated syncope, we observed that the progression of tilt was often characterized by wide fluctuations of  $LF_{RR}$  and  $HF_{RR}$ , suggestive of a marked instability of the cardiac autonomic control up to the onset of syncope (Furlan 1998b). Interestingly, that pattern occurred without concomitant changes in mean RR value, which remained stable. Thisunderlies the discordance between modifications in the oscillatory components of heart rate variability and the absence of concordant changes in heart rate (Furlan 1998b). In general terms, heart rate results from pacemaker intrinsic discharge, sympathetic and vagal neural modulation and circulatory neurohormones (Malliani 2000). Conversely, heart rate variability reflects the autonomic modulation of the seno-atrial node activity. Therefore, heart rate and its variability are separated entities and the former may not follow the changes of the latter (i.e. of the spectral components of RR variability). In this context the analysis of heart rate variability may furnish additional information on the state of the cardiac neural control which might have remained hidden if considering the simple changes of heart rate.

In a different group of subjects with analogous clinical problems, that is a single spell of syncope during a tilt test without a clinical history of loss of consciousness, the gain of baroreflex control of heart rate and MSNA computed during a 15° step-wise head-up tilt, revealed a diminished capability to increase heart rate and MSNA in response to similar changes of blood pressure compared with controls (Mosqueda-Garcia 1997). In these subjects MSNA was abolished before syncope and this suggests the existence of a remarkable impairment of baroreflex control of heart rate and MSNA in the period preceding syncope (Mosqueda-Garcia 1997).

Preliminary experiments within the context of a European Space Agency research project have recently provided somehow different results. In healthy volunteers who underwent  $-6^{\circ}$  head-down bed rest for three weeks, the upright posture was associated, as expected, with an initial remarkable increase of the MSNA as assessed both in bursts per minute and in MSNA total activity, in heart rate whereas blood pressure was maintained. In addition, discharge pattern of the post-ganglionic the sympathetic fibres was grouped after a clear 0.1 Hz rhythm. However, in the subset of subjects who fainted, the minute preceding the loss of consciousness was characterized by a disruption of such rhythm. Thus, in spite of the fact that the sympathetic drive to the vessel was still present until the syncope, blood pressure progressively declined and heart rate was either maintained or dropped near zero. This observation confirms that the period preceding a syncope is characterized by an overall baroreceptor activity alteration. Importantly, it also points out that the presence of an organized sympathetic discharge at 0.1 Hz rhythm is mandatory in order to keep blood pressure and heart rate adequate during the gravitational stimulus.

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