Abstract

Orthostatic intolerance (OI) is a confusing topic. Some of the confusion originates from recent appreciation of the condition's clinical variants, some originates from the emerging understanding of its diverse underlying pathophysiologies, and some originates from its nomenclature, which seems to change at least every year.

The term orthostasis literally means standing upright.

OI may be defined as "*the development of symptoms during upright standing relieved by recumbency.*" Although the use of a term such as OI logically implies the presence of findings when upright, typically, variations in heart rate, blood flow and blood pressure (BP) regulation are also found when supine or sitting, but these may require special equipment to detect and therefore may not be easily apparent requiring orthostatic stress to become evident.

Standing successfully requires interplay of blood volume, physical, neurologic, humoral, and vascular factors which compensate for the effects of gravity on venous pooling. Under ordinary conditions, acute humoral alterations have little to do with the initial response to standing upright but they play an important role in chronic OI or relatively late during upright standing. Also, changes in such factors may affect resting or tonic responses and thus may influence overall vascular regulation through background effects. OI is not always due to autonomic or other compensatory dysfunction and can be due to inadequate responses of compensatory mechanisms to environmental stressors. For example, someone who is dehydrated may be unable to stand up without dire consequences, but no dysautonomia is noted; instead, the autonomic and other compensatory systems cannot adequately compensate for the loss of circulating blood volume. On the other hand, a true dysautonomic cause of OI, in which compensatory factors are inadequate, is pure autonomic failure; patients with this condition not only cannot easily stand and have clearly detectable autonomic abnormalities in all physical positions. Therefore, OI encompasses any condition with blood flow, heart rate, and BP regulation inadequacy that are most easily demonstrable during orthostatic stress but may be present in all positions. Under such circumstances, OI may be the most obvious manifestation of a more widespread impairment in integrative neurovascular physiology.

To clarify this issues we studied during four years the prevalence and clinical picture of patients referred to our Autonomic Unit with some sort of OI and thereafter in some special groups (normal controls, patients with autonomic dysfunction, asymptomatic patients with Familial Amyloidotic Polyneuropathy TTR met30+, patients with Postural Tachycardia Syndrome, subjects with neurocardiogenic syncope with positive tilt table test (TTT), patients with syncope and with negative TTT and a group of healthy old subjects). We used an extensive protocol, including hemodynamic, autonomic, humoral, cardiac and cerebrovascular parameters, between several others, with the objective to clarify different OI syndromes.

We conclude that OI syndromes are very prevalent and observed among all ages. Several patients are misdiagnosed, particularly with epilepsy, before their referral to a syncope clinic. In addition OI before treatment had significant repercussion in quality of life. In patients with heart disease a cardiac etiology for syncope must be excluded, but neuro-mediated syncope in younger patients, orthostatic hypotension (OH) and carotid sinus hypersensitive in older patients, are not rare causes of loss of consciousness in this group of patients.

Neurocardiogenic syncope is the most frequent cause of OI, particularly in the young and female gender. Carotid sinus hypersensitivity is a cause of syncope prevalent in aged men. OH seems to be more rare than previously assumed cause of OI, especially if no vasodepressor drugs are involved or the patients does not have dysautonomia. In young people OH as a cause of OI was not observed. Postural tachycardia syndrome is also a rare cause of OI and almost only seen in females. Psychiatric pseudo-syncope can be triggered by tilt test and is also more prevalent in females.

Tilt table test is the gold standard for the diagnosis of neurocardiogenic reflex and other OI syndromes if the symptoms are reproduced during the test. In the almost one thousand patients evaluated the mean time for the positivity of the tilt test was 21 min (range from 3 to 40 minutes) and pharmacologic challenge, particularly sublingual nitrates, raise the sensitivity of the test by near 30%.

The massage of the carotid sinus should also be performed in the orthostatic position since the sensitivity of the test rise almost 100%. The massage should be performed with continuous monitoring of the ECG and blood pressure, to diagnosis vasodepression associated to cardio-inhibition.

Female sex and young age are risk factors for the positivity of tilt test result, however cardio-inhibition as a result of neurocardiogenic reflex during tilt test is more prevalent in males. After adjustment for age and sex, it appears that blurred vision and excessive sweating when preceding the loss of consciousness are suggestive for neurocardiogenic syncope. Moreover, experience of palpitations by the patients suggests that syncope has a cardiac etiology. In syncope, fatigue and pallor after recovery of consciousness suggests a neurocardiogenic cause, whereas the existence of trauma point to another cause of syncope.

Patients with OH are more symptomatic than the other OI patients, in part because they have more episodes in their lives and a more reduced orthostatic tolerance (for instance mean duration of tilt test was 6 min in our patients with OH due do autonomic failure). OH patients and the older subjects were selected after exclusion of cardiac involvement, nevertheless they had more ectopic beats (ventricular and supraventricular) on Holter monitoring than any other groups.

Patients with autonomic dysfunction and HO, as expected, had markedly reduced heart rate variability values on 24-hour ECG monitoring. Interestingly, patients with familial

amyloidotic polyneuropathy TTR met30+ had already reduced levels of the time domain vagal parameter on Holter recordings (pNN50) when still asymptomatic. This can be used in the future for early detection of vagal function involvement in this incapacitating disease. Heart rate variability is also reduced in the elderly healthy subjects using Holter and 24-hour blood pressure monitoring (ABPM), indicating that ageing affects cardiac autonomic control.

Using Holter and ABPM recordings, POTS patients had a high maximum heart rate during day time, but similar values during the night when asleep in the supine position as compared to controls.

Using ABMP, patients with HO and autonomic dysfunction had lower values of systolic blood pressure (SBP) during the day and inverted dipping during the night, suggesting that this simple non-invasive tool is useful in studying patients with autonomic dysfunction.

We observed good correlations with HR and blood pressure measurements obtained by Holter and ABPM with the values observed in the laboratory with the Finapres® device that measures blood pressure in the finger. The supine values correlated well with night values and the orthostatic values with day time values.

Inferior vena cava diameter was decreased in patients with POTS, suggesting hypovolemia.

POTS patients, old subjects and patients with dysautonomia had lower levels of urinary sodium concentration that probably points to a less salt intake. Conversely, dysautonomic patients had reduced urinary osmolarity. An inverse correlation between urinary osmolarity and natriuretic peptides (ANP and BNP) was observed.

The simple Ewing autonomic maneuvers like Valsalva and deep breathing test with beat-by-beat BP and HR monitoring were reasonable accurate to discriminate between patients with symptomatic and asymptomatic TTR met30+ and also older subjects.

POTS patients (as compared to other groups) had very low levels of ANP and BNP, suggesting a normal or hypercontractile left ventricular function and possibly hypovolemia. Symptomatic FAP patients and older subjects had normal values of BNP, but higher than the other groups, suggesting subtle subclinical cardiac dysfunction, not yet detectable by other measures of cardiac evolution like LVE function assessed by echocardiogram.

Prolonged tilting reduced plasma ANP levels in each group, compatible with a reduction in venous return and perhaps also by progressive hypovolemia, due to increased capillary transudation to the extravascular space in the lower part of the body due to gravidity. No change in plasma BNP with prolonged tilting was observed, compatible with the knowledge that this parameter is more dependent on left ventricular function than on circulating volume.

Neurocardiogenic syncope patients had a huge rise of adrenaline levels, several minutes before the development of the Bezold-Jarish reflex, which could played a role in the trigger of the reflex. Even patients with syncope, but with negative tilt test (before pharmacological challenge) already had higher plasma adrenaline levels as compared to healthy control subjects, suggesting that if the tilt test was more prolonged they will also had a positive response even without drugs administration.

Baseline plasma noradrenaline is low in dysautonomic patients and the response during tilt is blunted. This fact is also seen in asymptomatic FAP TTR met 30+ patients. POTS patients had normal values of noradrenaline during supine position, but experienced a huge rise during the initial tilting phase. This observation has impact on the therapeutic assessment of this group of patients.

Old patients were the only group that had higher dopamine levels, regardless their position, reflecting the age-dependency of this hormone with ageing.

Cardiac output and stroke volume decreased with orthostatic stress and continue to drop with prolonged tilting. After tilting, POTS patients had a similar decreased of cardiac output compared with other groups, because the larger reduction in stroke volume was compensated with an exaggerated rise in heart rate.

Orthostatic stress induced by tilting was associated with an increase in peripherical vascular resistances (PVR) and heart rate (HR) in all groups, but this increase was less pronounced in patients with dysautonomia.

Ageing was associated with a reduction in heart rate in both supine and tilting position. POTS patients had a huge rise in HR with tilting without a reduction in left ventricular ejection time (LVET), so the diastolic time interval is significantly reduced in these patients, which could result in a reduction in coronary flow during orthostasis in this group of patients. Dysautonomic patients had a blunted HR rise with orthostatic stress.

After tilting, the elderly and patients with dysautonomia, had higher values of LVET in relation to healthy controls, for a similar heart rate. This suggests the existence of subclinical left ventricular systolic dysfunction with orthostasis, pointing that a preserved sympathetic tone maybe necessary to maintain cardiovascular hemodynamics upon orthostatic stimulus.

All groups had similar BP values during supine rest. Tilting induced hypotension in dysautonomic patients. Systolic BP remained unchanged even in patients with neurocardiogenic syncope until the beginning of the reflex, which contrast with the earlier changes observed in the cerebrovascular dynamics.

Dysautonomic patients as expected had only residual autonomic activity (tonic or reflex). Elderly healthy patients had a decline in autonomic function, either in supine rest or after orthostatic stress compared with young controls.

POTS patients had normal autonomic function while in supine position but suffered a huge rise of sympathetic activity and a profound reduction in vagal activity during orthostatic stress.

Patients with neurocardiogenic mediated syncope had normal autonomic function in supine rest and initial tilting, but a few minutes before the neurocardiogenic response started, an abrupt fall in baroreceptor gain (vagal reflex activity) was observed and could be one of the triggers of this complex reflex.

Asymptomatic FAP patients had reduced vagal activity compared to normal controls, indicating that tonic vagal activity is affected first in the disease.

Sympathetic function, estimated by the low frequency component of systolic blood pressure variability, is marked reduced in dysautonomic patients. Elderly patients had preserved sympathetic vasomotor function while supine but had a blunted response to orthostatic stress. POTS patients had normal sympathetic activity while in supine rest but experienced a huge and sharp rise during the initial phase of tilting. Patients with neurocardiogenic syncope had a small rise in sympathetic activity in the first minutes of tilt, like normal controls, but a few moments before the neurocardiogenic reflex we observed a further significant rise not observed during prolonged orthostatic challenge in the normal controls.

Low frequency component (LF_RR) of heart rate variability is not a safe measure of sympathetic activity, neither their normalization (LF_nu).

The normalized components of heart rate variability (LF_nu and HF_nu) as the Italian researchers suggest are in our opinion insufficient to quantify the autonomic function, particular when this activity is very diminished, like in patients with dysautonomia.

In conclusion, our findings in this thesis suggest that the parameter best correlating with tonic vagal activity is the high frequency component of HRV (HF_RR), with vagal reflex activity was the baroreceptor gain (BRG) and with the sympathetic activity, the low frequency component of systolic blood pressure variability (LF_SBP).

The most relevant conclusions in the substudy using Transcranial Doppler (TCD) of the behavior of cerebral hemodynamics in chronic orthostatic intolerance were as follows:

In patients with disautonomia, there was the expected compensatory cerebral vasodilator response when the fall in systemic blood pressure occurred. This indicates that notwithstanding the severe autonomic nervous system dysfunction, the regulatory cerebrovascular mechanisms in adaptation to the orthostatic stress which help to offset the occurrence of cerebral hypoperfusion are still intact. Nevertheless, excessive reduction of systemic blood pressure values beyond the critical closing pressure may quickly lead to vascular collapse and consequently to the occurrence of syncope. In the early phases of autonomic dysfunction, the cerebrovascular response to orthostatic stress

appears to be broadly maintained, which was consistent with the lack of symptoms. In these individuals, in the recumbent position, however, seem to demonstrate already a failure of cerebral vasoconstriction, suggesting that cerebral autoregulation (CA) is defective considering the high levels of BP in this position. This unexpected result lead us to believe that the autonomic nervous system has a role in the performance of cerebral vascular tone regulation, but this role is complex and interrelated with other mechanisms that control vascular tone.

Patients with Postural Tachycardia Syndrome (POTS) showed an excessive cerebral vasoconstriction during orthostatic stress and this is probably one of the most important factors in explaining their characteristic symptoms during standing. The findings are in line with the hyperadrenergic state reported in the literature and confirmed in this thesis.

In the group of neurocardiogenic syncope patients, cerebral autoregulation (CA) seemed to be already compromised even in the supine position, but with a greater impact during prolonged standing. Cerebral vascular resistance did not changed after the orthostatic stress, which suggest the existence of cerebrovascular dysfunction in these individuals. There seemed to be a more gradual response to tilt, which could be detected already in the early stages. However, in the last minutes before the neurocardiogenic reflex that induced syncope, and even when there is still stable values of systemic blood pressure, a rapid decrease in cerebral blood flow occurs, suggesting the existence of cerebrovascular dysfunction of which the etiology is unclear, helping to trigger these individuals to neurocardiogenic syncope.

In the group of healthy elderly patients, although asymptomatic, there seems to be a decrease in cerebral vascular reserve during prolonged standing, particularly when compared to the supine position, which could make elderly to be more likely to experience syncope during prolonged periods of standing, along with the decline in autonomic function already observed and stated.