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EDITORIAL

The quest for biomarkers in postural tachycardia syndrome and other updates on recent autonomic research

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The quest for cardiovascular biomarkers in POTS

Despite the fact that postural tachycardia syndrome (POTS) was first described nearly 150 years ago and given its diagnostic criteria in 1993, we are no closer to identifying a biomarker to predict prognosis. This is largely due to the fact that POTS is a heterogenous syndrome with many potential etiologies, creating significant challenges for physicians striving to provide targeted treatment options for patients. In a recent study, Spahic and colleagues aimed to isolate POTS-specific proteomic markers from 994 consecutive patients of their syncope unit in Malmö, Sweden [1]. Patients were referred for either unexplained syncope or symptoms of orthostatic intolerance, and all patients underwent head-up tilt testing (HUT). From this cohort, the authors selected patients 15–50 years old with available proteomics data and either a diagnosis of POTS or a normal cardiovascular response during HUT. This left 113 patients with a diagnosis of POTS and 283 patients without a diagnosis, but a normal HUT for a comparison group (i.e. without vasovagal syncope, OH, or exaggerated postural tachycardia, and without cardiovascular disease or hypertension). The mean age of the POTS group was 26.3 ± 8.4 years, while the non-POTS group was slightly older at 31.5 ± 9.8 years ($p < 0.001$). Non-POTS patients had higher body mass indices (BMI 24.3 ± 4.1 vs. 22.7 ± 3.5 kg/m^2, $p < 0.001$). Gender was similar between groups.

Blood was drawn from an intravenous canula prior to HUT, and the plasma from these samples was analyzed by a multiplex immunoassay that measured 92 cardiovascular disease-related human proteins. Oligonucleotide-labeled antibody probes were used to detect the corresponding target proteins in the plasma sample. When two of these antibodies were detected in close proximity, a new polymerase chain reaction (PCR) target sequence formed, which was subsequently detected and quantified by standard real-time PCR.

The authors discovered two proteomic results of note. Their principle finding was that plasma levels of growth hormone (GH) were significantly higher in women with POTS compared to men with POTS, and higher than both male and female controls. Their second finding was that plasma levels of myoglobin (MB) were significantly lower in men with POTS compared to male controls. In multivariate regression analysis adjusted for age and BMI stratified by sex, both POTS diagnosis and maximum orthostatic ΔHR were significantly associated with lower MB levels in men and higher GH levels in women.

The authors provide several hypotheses for their GH findings, including the possibility of (a) proinflammatory cytokines increasing plasma GH concentrations, (b) G-protein-coupled receptor (GPCR) autoantibody destruction of GH receptors in the anterior pituitary gland, and (c) lower BMI of POTS patients leading to an increase in lipolysis and higher GH levels. These findings are interesting in light of prior evidence suggesting that octreotide might be useful to reduce some of the symptoms of POTS [2]. Octreotide inhibits GH secretion; however, it also acts as a potent splanchnic vasoconstrictor, thus inducing a vasopressor effect. This is even more interesting considering that patients with POTS have been shown to have greater splanchnic blood pooling while upright [3]. Insulin-like growth factor-1, synthesized in the liver, is secreted into the blood under the control of GH, and is known to induce peripheral vasodilation via nitric oxide synthase and/or potassium channel activity. This may provide a mechanistic link connecting the elevated GH levels seen in this study with prior observations of splanchnic

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pooling and octreotide efficacy in reducing symptoms in POTS patients. In terms of the MB findings, the authors hypothesize that lower MB levels might be the result of deconditioning, though they are admittedly uncertain why this association was seen in the male POTS group only.

The primary limitation of this study is that the control group consisted of symptomatic individuals. The authors relied on a negative HUT result to dichotomize their groups. The sensitivity of HUT may be problematic, especially for episodic conditions such as vasovagal syncope. Other limitations include unequal age and BMI between groups, which may have influenced cardiovascular profiles. The authors also failed to control for menstrual cycle variation as well as oral contraceptive use, which may have influenced GH secretion. Nonetheless, this study is notable as it highlights an important technology that represents further steps in the direction of personalized medicine.

REM sleep behavior disorder in MSA: does timing matter?

Rapid eye movement sleep behavior disorder (RBD) is a well-defined prodromal marker of the alpha-synucleinopathies including multiple system atrophy (MSA), where it is present in over 80% of patients [4], however how the presence or timing of RBD influences prognosis and survival in these diseases is less clear. In their publication "Progression and prognosis in multiple system atrophy presenting with REM behavior disorder" [5], Giannini et al. attempted to better answer this question. The authors retrospectively reviewed the records of all patients evaluated yearly at the University of Bologna between 1991 and 2018 with a clinical diagnosis of MSA. Patients were categorized as probable, possible, or definite MSA-Parkinsonian subtype (MSA-P) or MSA-Cerebellar subtype (MSA-C). Onset of disease was defined as the first reported sign or symptom of motor or autonomic dysfunction that could be related to MSA. Occurrence of other signs or symptoms (such as orthostatic hypotension and stridor), latency from disease onset, and timing and latency of disease milestones (i.e. frequent falls, urinary catheterization) were noted. Disease duration was defined as the interval from the onset of the first symptom to death or to the end of the study, and survival data were defined as the interval from the onset of the first symptom to death. The authors defined pre-RBD or post-RBD according to its occurrence before or after MSA onset.

A total of 158 patients were included for analysis (79 MSA-P and 79 MSA-C). Most were probable MSA (126) and the remainder possible (29) and definite (3). Pre-RBD occurred in 42 patients (27%), while post-RBD occurred in 65 patients (41%). The median duration before the first autonomic or motor sign or symptom was 3 (2–5) years. Among the pre-RBD group, 29 patients presented with a history of autonomic failure (25 urinary symptoms and 6 symptomatic OH), 17 with a cerebellar syndrome, and 6 with Parkinsonism. Compared to the post-RBD group, patients with pre-RBD showed a more frequent autonomic onset of MSA (69% vs. 45%) and less frequent Parkinsonism at disease onset. Pre-RBD patients were also more likely to present with signs of more aggressive disease including earlier stridor, shorter latency to urinary catheterization, severe dysphagia, and wheelchair dependency. Finally, pre-RBD patients had a more aggressive disease course, as measured by reduced survival times. The authors concluded that it is not the presence of RBD alone, but instead the onset of RBD as the first manifestation of disease that is correlated with more aggressive features, perhaps by nature of the anatomical deposition of alpha-synuclein in the brainstem structures involved in both sleep and autonomic control.

The primary limitation of this study is its retrospective nature, thus limiting the specificity of diagnosis. This is especially problematic in MSA, a notoriously difficult disease to diagnose with certainty. Longitudinal studies in RBD are needed, and are currently being designed, to better answer these questions with greater certainty.

Wearable sympathetic measures from heart rate variability and electrodermal activity

Heart rate variability (HRV) obtained from electrocardiogram data has been used as a measure of cardiac autonomic function for several decades. Spectral analysis of HRV is traditionally divided into high frequency (0.15–0.4 Hz) and low frequency (0.04–0.15 Hz) bands. The high frequency (HF) band is accepted as a measure of vagal tone, and the low frequency (LF) band is likely an interplay between sympathetic and parasympathetic drivers of autonomic function. Based on these variables, a ratio of LF/HF can be used as a measure of sympathovagal balance. Previous attempts to obtain a more reliable and consistent measure of sympathetic tone from HRV analysis have failed to produce a clinically viable metric. Electrodermal activity, otherwise known as the galvanic skin response, is another technique used to measure sympathetic function, and relies on skin conductance as an indirect measure of sweat production. These two measures—HRV and electrodermal activity—have the potential to evolve as dynamic measure of autonomic tone outside of traditional autonomic testing labs, as both HRV data and electrodermal activity can be obtained from a single wearable device such as a wristwatch.

In their recent publication "Assessing autonomic function from electrodermal activity and heart rate variability during cold-pressor test and emotional challenge", Ghiasi et al. reported their analysis of spectral and bispectral analysis

of HRV variability [6]. The authors recruited 26 healthy subjects and monitored HRV and electrodermal activity at a signaling rate of 500 Hz through a commercially available device. Subjects completed an experimental protocol that included cold pressor testing and affective stimulation through various videos (emotional challenge), interspersed with rest. Subjects were randomized to different series of experimental protocols, and all the testing was completed in one session.

The authors used previously developed mathematical and statistical models [7] to obtain both vagal measures from HRV and new indices of sympathovagal balance from the electrodermal activity and HRV parasympathetic metrics. These new indices combining spectral analysis of both HRV and electrodermal activity provided a statistically significant difference between the subjects' resting state and their response to cold pressor testing, thus providing an improved measure of sympathovagal balance than HRV alone.

This study, while scientifically rigorous, is limited by the small sample size. However, we suspect these sensitive indices might have utility in detecting very early autonomic syndromes or mild degrees of autonomic instability in established syndromes. In the future, our patients with wearable devices that are able to obtain both HR and electrodermal activity (though not at the frequency used in this study) will be able to obtain these autonomic metrics. How these metrics change in disease states, and if these metrics are responsive to therapeutic intervention is unknown, but they may prove to be more sensitive than currently available autonomic tests in the autonomic testing lab.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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