**Inappropriate sinus tachycardia in post-covid-19 Syndrome**

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**Background:** Persistent symptoms after the acute phase of SARS-CoV-2 infection are referred to as "post-COVID-19 syndrome" (PCS), with a reported incidence ranging between 35% and 87%. Fatigue, palpitations and exercise intolerance are common complaints among PCS patients in whom unexplained sinus tachycardia, occasionally exacerbated by postural changes, is a frequent observation that remains poorly characterized.

**Purpose:** We sought to characterize the prevalence of inappropriate sinus tachycardia (IST) and postural orthostatic tachycardia (POTS) in a consecutive and prospective population of patients with PCS.

**Methods:** Consecutive patients with persistent symptoms 3 months after an acute SARS-CoV-2 infection were prospectively evaluated at a multi-disciplinary PCS unit. All patients were screened for IST or POTS and those with confirmed criteria underwent comprehensive cardiovascular examination including echocardiography, 24-hour Holter, Minnesota Living with Heart Failure Questionnaire (MLHFQ), six-minute walking test (6MWT) and inflammation and myocardial biomarkers. Two control patients, matched by age and gender, were assigned to each case: one with previous SARS-CoV-2 infection without PCS (group 2) and one without prior SARS-CoV-2 infection (group 3).

**Results:** IST or POTS criteria were met in 34 out of the 200 PCS patients (17%). The mean age was 39 ± 10 years, with 29 women (91%). The interval from the index COVID-19 disease to the PCS diagnosis was 71 ± 17 days, with a majority of patients (n = 29,85%) not requiring hospital admission during the acute phase. At physical examination, the mean heart rate was 96 ± 3bpm at supine and 112 ± 17bpm at the upright position, with 8 patients fulfilling diagnostic criteria of POTS. No underlying structural heart disease, pro-inflammatory state, myocyte injury or hypoxia were identified among our patient population. The 6MWT showed a significantly diminished exercise capacity with a 59% of the estimated distance after adjustment by age, sex and body mass index; an impaired quality of life was also identified, as suggested by a median MLFHQ total score of 67 out of 105 points. The 24-hour Holter showed an increase in HR predominantly during daytime in group 1 (mean daytime HR of 94 ± 3bpm), an altered heart rate variability with a decrease in time domain parameters [PNN50 4 ± 4 in group 1 (vs. 11 ± 9 in group 2 and 18 ± 9 in group 3; p < 0.002) respectively; SD 100 ± 20 (vs. 127 ± 38 and 136 ± 13; p = 0.009) and a decrease in frequency domain parameters [LF 751 ± 450 (vs. 1721 ± 1009 and 2199 ± 920; p = 0.01), HF 336 ± 280 (vs. 823 ± 1200 and 1229 ± 630; p = 0.01)].

**Conclusions:** IST and its POTS variant are a prevalent condition among PCS patients and may at least partially explain the common symptoms of fatigue, impaired exercise and palpitations that characterize the PCS. Cardiac autonomic nervous system imbalance may account as a plausible pathophysiological mechanism of IST in PCS patients.