Value of ^{123}I-MIBG SPECT for the assessment of dysautonomia in patients with long COVID

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1. Introduction

Long coronavirus disease (COVID) can affect the autonomic nervous system (ANS), resulting in symptoms of dysautonomia including orthostatic intolerance and abnormal heart rate variability [1]. The assessment of dysautonomia in patients with long COVID is challenging, and can be performed using various diagnostic autonomic function tests [2]. One method used to investigate autonomic disorders is iodine-123-metaiodobenzylguanidine (MIBG) single-photon emission computed tomography (SPECT) imaging, but its usefulness in patients with long COVID has not been systematically reported. A better understanding of long COVID–related ANS dysfunction is crucial for the development of effective diagnostic and therapeutic strategies for affected individuals. Fig. 1.

2. Methods

Patients included in this cross-sectional study were selected prospectively from consecutive patients attending outpatient clinics of arrhythmia specialists in Rio de Janeiro, Brazil, between June 2021 and August 2022. The inclusion criteria were previous severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection confirmed by real-time reverse-transcription polymerase chain reaction of nasopharyngeal and/or oropharyngeal swab samples, and new or exacerbated symptoms of dysautonomia. The exclusion criteria were a history of coronary artery disease, congestive heart failure, or severe valvular heart disease and Parkinson's disease. Trained investigators collected demographic, clinical, and laboratory data. The patients underwent myocardial sympathetic innervation scintigraphy with MIBG and resting myocardial perfusion SPECT imaging with 99mTc-sestamibi (MIBI).

The MIBG scintigraphy protocol was initiated with the ingestion of 20 mL of a 10 % potassium iodide solution, followed by 185 MBq MIBG administered intravenously. Images were captured using a hybrid SPECT/CT dual-head gamma camera (Symbia 16 T; Siemens Healthineers). CT examinations were performed after SPECT imaging. Each patient underwent myocardial perfusion scintigraphy at rest with the injection of 555 MBq MIBI. Gated SPECT images were captured 30 min after radiotracer administration.

MIBI and MIBG uptake were evaluated using a semi-quantitative scoring system ranging from 0 to 4 in each of the 17 left ventricular segments. Summed scores were calculated to determine the extent of perfusion and sympathetic innervation defects. The mismatch between innervation and perfusion, indicating viable but denervated myocardium, was calculated.

Statistical analyses were performed using SPSS software (version 29.0; IBM Corporation, Armonk, NY, USA).

3. Results

Of 18 patients with symptoms of dysautonomia, 2 were excluded due to previous myocardial infarction. Ten (62.5 %) of the remaining 16 patients included were female, and the mean patient age was 42.7 $\pm$

15.5 years. The patients' clinical data are summarized in Table 1. The main symptoms were syncope ($n = 9$) and near-syncope ($n = 5$). Patients had no other neurological or cognitive complications. Main comorbidities were hypertension (25 %), obesity (18.7 %), and dyslipidemia (31.2 %).

During SARS-CoV-2 infection most cases were mild and did not require hospitalization. Two (12.5 %) patients reported thromboembolic phenomena and two (12.5 %) patients were hospitalized and received oxygen therapy, with one requiring non-invasive ventilatory support.

All patients underwent complete imaging examinations. On MIBG SPECT myocardial scintigraphy, the radiotracer distribution was heterogeneous in 8 (50 %) patients and radiotracer uptake was abnormal in 12 (75 %) patients. The mean early and late H/M ratios were 1.77 ± 0.11 and 1.85 ± 0.15, respectively. The mean WR was 21.88 % ± 6.6 %/hour and the mean summed uptake defect score was 4.06 ± 3.5. The basal, mid-inferolateral, and apical-lateral segments and the apex were most commonly affected. On MIBI SPECT examination, perfusion was normal in all but one case, which showed reduced perfusion in the apex and apical-anterior segment.

Twelve patients underwent the tilt table test, which led to the reproduction of previous clinical symptoms in eight (66.7 %) cases. Three patients had vasodepressor responses, three had mixed responses, one presented orthostatic tachycardia, and one had a cardioinhibitory response.

MIBG was abnormal in 75 % (12/16) of the cases and tilt table test was positive in 66.7 % (8/12). Of the 12 patients with abnormal MIBG uptake, 5 (41.7 %) had positive tilt table test results, 4 (33.3 %) had negative tilt table test results, and 3 (25 %) did not undergo the tilt table test. Three patients had positive tilt table test results but no MIBG uptake.

4. Discussion

In this study, a large proportion (75 %) of patients with symptoms of dysautonomia related to long COVID had reduced MIBG uptake, suggesting the presence of myocardial sympathetic denervation, in the absence of perfusion abnormalities. In addition, most (66.7 %) patients' symptoms were reproduced during tilt table tests, with vasodepressor and mixed responses.

Although symptoms of dysautonomia related to long COVID have been reported consistently [3], MIBG SPECT has not, to our knowledge, been used systematically in this context. Reduced sympathetic innervation in the myocardium has been associated with arrhythmia, reduced myocardial contractility, impaired cardiovascular reserve, and reduced cardiovascular capacity to adapt to physiological changes [4]. Our group recently detected peripheral sympathetic overactivation associated with vascular dysfunction and reduced exercise capacity in COVID-19 survivors [4]. Whether this sympathetic overdrive is caused by the involvement of the carotid body by direct virus invasion, is a consequence of immune response exacerbation, or a compensatory mechanism related to myocardial denervation with reduced contractility, heart rate variability, and stress response remains unclear [5].

MIBG SPECT can be useful for the evaluation of the extent of myocardial sympathetic denervation; it provides quantitative data that aid the diagnosis of dysautonomia, determination of its prognosis, and evaluation of treatment effects. Although the tilt table test can be used to dynamically assess ANS integrity and identify different forms of autonomic dysfunction, its results were inconclusive for some patients in our series who had reduced MIBG uptake. Previous studies have reported false negative results in the tilt table test in up to 30 % of patients with dysautonomia [6]. In addition, the tilt table test does not provide information about the mechanisms underlying autonomic dysfunction or the anatomical location of denervation.

This study has some limitations, including the small sample size and lack of a control group. In addition, four patients had no tilt table test available.

Our findings suggest that MIBG SPECT can be a useful adjunct method for the investigation of dysautonomia symptoms in patients with long COVID. Future studies would be relevant to assess the value of the method for monitoring the progression and treatment of long COVID.
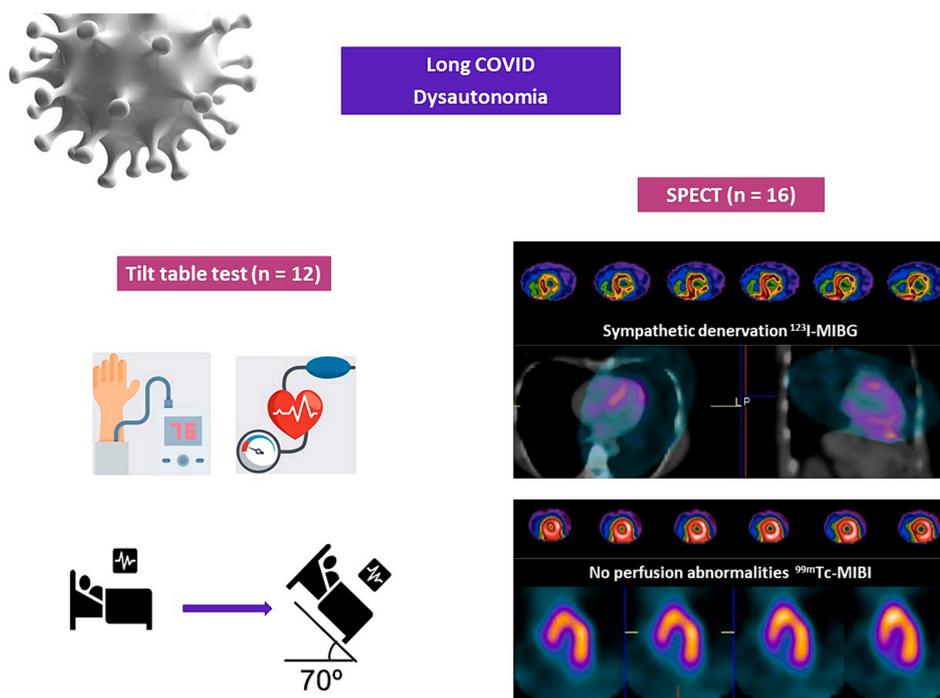

Fig. 1. Graphical abstract illustrating the use of tilt table-test and MIBG and MIBI SPECT imaging to investigate patients with symptoms of dysautonomia related to long COVID. ^{123}I-MIBG and ^{99m}Tc-MIBI SPECT images show myocardial innervation defects with normal MIBI uptake indicating sympathetic denervation/preserved myocardial perfusion mismatch.

Table 1
Patient characteristics.

Patient #	Age (years)	Sex	Symptoms	Perfusion (MIBI)	SS score (MIBG)[b]	Tilt table test
#1	48	Male	Syncope	normal	7	Mixed response
#2	20	Female	Syncope	normal	0	Vasodepressor response
#5	38	Male	Orthostatic hypotension	normal	6	N/A
#6	21	Female	Near-syncope	normal	3	Mixed response
#7	39	Female	Near-syncope	normal	0	N/A
#8	39	Female	Near-syncope	normal	6	N/A
#9	43	Male	Syncope	normal	4	Negative
#10	22	Female	Near-syncope	normal	0	Orthostatic tachycardia
#11	46	Female	Syncope	normal	5	Mixed response
#12	56	Female	Syncope	abnormal	2	Cardio inhibitory response
#13	46	Female	Syncope	normal	6	Negative
#14	31	Female	Near-syncope	normal	6	N/A
#15	45	Male	Orthostatic hypotension	normal	0	Vasodepressor response
#16	81	Male	Syncope	normal	9	Negative
#17	59	Male	Syncope	normal	2	Negative
#18	49	Female	Syncope	normal	12	Vasodepressor response

Patients #3 and #4 were excluded.

N/A, not available.

[a] 99mTc-sestamibi single-photon emission computed tomography.

[b] Iodine-123-metaiodobenzylguanidine summed uptake defect score from 0 to 68. The SS score was calculated considering 0 (normal uptake) to 4 (no uptake) in each of the 17 left ventricular segments.

5. Sources of funding

6. Disclosures

The other authors have declared no conflicts of interest.

7. Ethics approval statement

The institutional review boards and ethics committees of the participating institutions approved the study protocol (CAAE#34035120.1.0000.5249). All patients provided written informed consent before enrollment.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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