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The performance of COMPASS-31 questionnaire with regards to the autonomic nervous system testing results and medication use: a prospective study in real-life setting

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Abstract

The aim of this study was to investigate the performance of the Composite Autonomic System Score-31 (COMPASS-31) questionnaire in a real-life setting in consecutive patients referred to the laboratory for objective testing of the autonomic nervous system (ANS), with the hypothesis that COMPASS-31 results differ depending on medications and findings of the tilt-table test results. 171 consecutive patients (125 females, mean age 41.5±19.3) referred for testing of the ANS were enrolled. Before testing, all patients completed the recently validated Croatian version of COMPASS-31. The following data was systematically collected for all patients: age, sex, diagnoses, and medications. Results of COMPASS-31 were significantly higher in patients taking medications with a known influence on the ANS ($p<0.001$). Patients with POTS had significantly higher orthostatic intolerance and vasomotor domains of the COMPASS-31 ($p=0.048$ and $p=0.022$, respectively). Patients with a cardiovagal score ≥1 had a significantly higher vasomotor domain of COMPASS-31 compared to the patients with normal results of ANS tests ($p=0.030$). These findings suggest the COMPASS-31 might be a valuable screening tool for autonomic dysfunctions, as it is associated with impaired ANS tests, but usage of medications that modify the ANS should always be taken into account.

Key words: autonomic nervous system, COMPASS-31,medications

Introduction

Function of the autonomic nervous system (ANS) may be impaired in different neurological disorders. The Composite Autonomic System Score-31 (COMPASS-31) is the most widely used questionnaire used to assess symptoms of ANS dysfunction. COMPASS-31, a refined and simplified version based on the original Autonomic Symptom Profile and the Composite Autonomic System Score, is a set of 31 questions divided into 6 domains of the ANS: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor (1). Having a simplified scoring scheme and improved internal consistency than its predecessors, COMPASS-31 might serve as a screening tool for various disorders that affect ANS. Its usefulness has already been demonstrated for the evaluation of ANS dysfunction in diseases such as multiple sclerosis, polyneuropathy, and fibromyalgia (2, 3, 4) and more importantly, in disorders in which the autonomic function is commonly impaired from an early stage, as is in multiple system atrophy or Parkinson's disease (5). Also, COMPASS-31 proved itself as a reliable tool with a fair diagnostic accuracy in patients with diabetes mellitus, common widespread disorder which interferes with the ANS function (6).
Another important aspect of ANS disorders are functional ANS disorders like syncope and postural orthostatic tachycardia (POTS), where investigation of symptoms is crucial in making the correct diagnosis. Rea et al. confirmed that COMPASS-31 allows the distinction of POTS not only from healthy controls through all the domains, but also from autonomic failure/neuropathy (AF/N) through certain domains: increased values in orthostatic intolerance and pupillomotor domains indicating POTS, while secretomotor, gastrointestinal (GI), bladder and vasomotor domains contributed to AF/N diagnosis (7). Lastly, symptoms of ANS dysfunction, reduce the quality of life and may be ameliorated by changing the therapy the patient is currently using. As medications may alter ANS function, it is reasonable to expect that they may also alter the COMPASS-31 questionnaire score, however, results of studies reporting this association are still ambiguous (8,9).
Therefore, the aim of this study was to investigate the performance of COMPASS-31 questionnaire in a real life setting in consecutive patients referred to the laboratory for objective testing of the ANS, with the hypothesis that COMPASS-31 results differ depending on medications and objective findings of the tilt table test results.

Methods

This was a prospective study which enrolled consecutive patients referred for the tilt table test or testing of cardiovascular reflexes together with the tilt table test from November 2017 until February 2018 in the Referral Center for Autonomic Nervous System Disorders.
Before testing, all patients completed the recently validated Croatian version of COMPASS-31 questionnaire (2).
In patients referred for tilt table testing, a previously described tilt table protocol was used. The subjects were tilted to 70° for a maximum period of 10 min or until symptoms occurred. In a subset of patients referred for testing because of history of syncope, if there were no symptoms after initial 10 min, a painful stimulus with the insertion of 0.7 mm needle into the dorsum of hand subcutaneously for 30 s was performed with the patient in the tilted position for further 5 min (10). For patients referred for testing of cardiovascular reflexes

together with a tilt table test, the following protocol was used: heart rate and blood pressure responses to Valsalva maneuver, heart rate response to deep breathing followed by the tilt table test as described above (Task Force Monitor (TFM), CNSystems Medizintechnik AG, Austria) (11). The results were interpreted in the form of adrenergic and cardiovagal indices, which are part of the Composite Autonomic Scoring Scale (CASS) (12). Abnormal results of the tilt table test were interpreted as vasovagal syncope (VVS), POTS, orthostatic hypotension (OH), orthostatic intolerance (OI) or pseudosyncope according to the consensus statement on the definition of these disorders (13).
The following data was systematically collected for all patients: age, sex, diagnoses, and medications. Special emphasis was given to the medications with a known influence on the ANS: antidepressants, beta blockers, ACE inhibitors, calcium channel blockers, alpha-1 blockers, antihistamines, cholinesterase inhibitors, and central antihypertensives.
The objective of the study was to evaluate the COMPASS-31 scale in a cohort of patients referred to ANS testing in a real-life setting. This objective was assessed by comparing COMPASS-31 results depending on: 1) medications patients were taking, 2) results of the tilt table test, and 3) results of cardiovascular reflex tests.
All patients signed an informed consent and the study was approved by the Ethics Committee of the University Hospital Center Zagreb.

Statistical analysis

Statistical analysis was performed using the IBM SPSS software, version 20. Differences in the distribution of qualitative variables were determined with the χ^2 test, while the differences in quantitative variables were determined with the use of nonparametric Mann–Whitney test (CASS, COMPASS-31). To determine the correlation between the variables, the Spearman correlation method was used. P values less than 0.05 were considered as significant.

Results

Altogether 171 patients were enrolled, 125 females, with the mean age of 41.5±19.3 years. Forty-eight patients were referred for the tilt table test only, and 123 patients were referred for testing of cardiovascular reflexes combined with a tilt table test. Referral diagnoses are presented in Table 1.
The tilt table test was normal in 109 (63.7%) patients, 29 (17.0%) had VVS, 7 (4.1%) patients had POTS, 17 (10%) had OH, 8 (4.7%) had OI, and 1 (0.6%) had pseudosyncope. The adrenergic index was ≥1 in 38 (31%) patients and the cardiovagal index was ≥1 in 20 (16.9%) patients. Normal ANS results were defined as normal tilt table test and adrenergic and cardiovagal scores, and this was valid for 78 patients.
Number of patients taking medications with a known influence on the ANS was 52 (30.4%): 16 (9.4%) were taking antidepressants (selective serotonin reuptake inhibitors or selective serotonin–norepinephrine reuptake inhibitors), 24 (14.0%) beta blockers, 24 (14.0%) ACE inhibitors, 11 (6.4%) calcium channel blockers, 4 (2.3%) alpha-1 blockers, 3 (1.8%) antihistamines, 1 (0.6%) cholinesterase inhibitors and 3 (1.8%) central antihypertensives (some patients were taking several medications). Patients taking medications with a known influence on the ANS were significantly older compared to patients not taking medications

(55.90±17.27 vs. 35.16±16.64, respectively, p<0.001), while there was no difference in sex (p=0.997).

There was no statistically significant association between the use of medications and normal ANS results (p=0.406), indicating that both participants with normal ANS results and participants with some type of pathological results are taking medications in a similar percentage.

We found a statistically significant difference in the cardiovagal index between a group of patients taking medications with a known influence on the ANS and a group of patients not taking these medications (p<0.001), while no difference was observed for the adrenergic index (p=0.339).

Similarly, results of the COMPASS-31 were significantly worse in patients taking medications with a known influence on the ANS (Table 2).

Values of COMPASS-31 according to the results of ANS testing are presented in Table 3.

There was no difference in COMPASS-31 between patients with syncope, OH, OI and patients with normal results of ANS tests (all p>0.05). Patients with POTS had significantly higher orthostatic intolerance and vasomotor domains of COMPASS-31 (p=0.048 and p=0.022, respectively).

There was no difference in COMPASS-31 between patients with an adrenergic index ≥1 and patients with normal results of ANS tests (all p>0.05). Patients with a cardiovagal score ≥1 had a significantly higher vasomotor domain of COMPASS-31 compared to the patients with normal results of ANS tests (p=0.030).

In patients with abnormal results of ANS testing, there was a significant correlation between the adrenergic index and GI and pupillomotor domains of COMPASS-31 (r_s=0.366, p=0.02 and r_s=0.324, p=0.041, respectively).

Discussion

The main finding of this study was that patients taking medications with a known influence on the ANS have significantly worse results on the COMPASS-31 questionnaire in comparison with other patients. Significant difference was found for all domains of the questionnaire, except for the domains of bladder and pupillomotor function. There is an evidence that medications affecting ANS could have an influence on the ANS battery of tests. In the study of De Wandele et al., a larger drop of blood pressure during the Valsalva maneuver and a larger decrease of heart rate at the end of the tilt table test were associated with an increasing number of vasoactive medications used (14). Although similar effect of medications on ANS questionnaires could be assumed, evidence of a link between medication intake and COMPASS-31 questionnaire, both original and refined, is lacking. However, one previous study of autonomic dysfunction in patients with multiple sclerosis showed that results of COMPASS-31 questionnaire were abnormal only when confounders such as vasoactive medications (anticholinergics, antidepressants, antihypertensives, beta blockers, diuretics, antiarrhythmics, sympathomimetics, parasympathomimetics) or other comorbidities were present, thus indicating a possible connection between medications and results of the questionnaire (8). On the other hand, another study of autonomic dysfunction in patients with multiple sclerosis showed no significant correlation between COMPASS-31 results and fatigue-causing drugs, amongst which were beta blockers and anticholinergics

(9). Results of the present study, however, provide evidence for the association between COMPASS-31 results and intake of medications with a known influence on the ANS.

An additional finding is that some domains of COMPASS-31 were significantly different in the group of patients with specific results of ANS testing. Vasomotor domain was higher in patients with POTS and patients with a cardiovagal index ≥1. Furthermore, orthostatic intolerance domain was also higher in patients with POTS and, finally, pupillomotor and GI domains were significantly correlated with the adrenergic index in patients with abnormal results of ANS testing. Few other previous studies found correlations between COMPASS-31 and the results of ANS tests (3, 5, 6, 15). Results are varying, with the most common findings of significant correlations between secretomotor, GI and orthostatic intolerance domains of the questionnaire and the results of ANS tests. Our study is therefore consistent with findings of stronger association between GI and OI domains of COMPASS-31 with the results of ANS tests, but inconsistent for a stronger association for secretomotor domain. This inconsistency could be easily explained by the fact that in this study we did not perform the quantitative sudomotor axon reflex test which belongs to the standard battery of ANS tests and which was done in the above mentioned studies. However, scientific evidence of the association between COMPASS-31 and ANS tests is still vague and lacking. One of the reasons for that is a relatively low research activity in this field. It is also important to keep in mind that COMPASS-31 represents a subjective evaluation of symptoms reported by patients, which are not always compatible with objective findings on ANS tests. For example, it is possible that patients with an objective finding of profound OH on the tilt table test do not experience any symptoms at all (16). Keeping that in mind, we suggest that the contrary is also possible, i.e. subjects enrolled in this study already had various symptoms associated with ANS before the evaluation was performed and possibly, therefore, had higher results on the questionnaire as a subjective evaluation without objective evidence of dysautonomia. With the inclusion of healthy individuals this sampling bias could possibly be avoided and a stronger association between COMPASS-31 and ANS tests could be found, which represents the main limitation of this study. Further limitations include referral bias, as all patients were enrolled in the tertiary medical center and relatively small group of patients which does not allow stratification of patients according to clinical and demographic parameters. In order to better clarify the role of medications on COMPASS-31 score a further prospective study is ongoing, on a larger sample, with homogeneous subgroups and healthy individuals.

Despite these limitations, the results of this study suggest the COMPASS-31 might be a valuable screening tool for autonomic dysfunctions, as it is associated with impaired ANS tests. Furthermore, one should always consider relevance of the pharmacological history with respect to the onset of ANS symptoms and the importance of stopping medications acting on heart rate and blood pressure before testing of the cardiovascular reflexes.

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Tables

Table 1. Referral diagnoses of the study cohort.

Diagnosis	**Number of patients with the diagnosis**	**Percentage**
Syncope	100	58.48%
Cardiovascular diseases	31	18.13%
Orthostatic hypotension	26	15.20%
Epilepsy	16	9.36%
Hypothyreosis	14	8.19%
Diabetes	13	7.60%
Mixed anxiety-depressive disorder	9	5.26%
Ataxia	6	3.51%
Tumor disease	6	3.51%
POTS	5	2.92%
Migraine	3	1.75%
Parkinson's disease	3	1.75%
Multiple sclerosis	2	1.17%
Rheumatoid arthritis	2	1.17%
Anemia	2	1.17%
Asthma	2	1.17%
Juvenile idiopathic arthritis	2	1.17%
Other (one of each diagnoses: Hepatitis, Pain, Longitudinal extensive transverse myelitis, Fever of unknown origin, Post-traumatic stress disorder, Schizophrenia, Obstructive sleep apnea, Narcolepsy, Systemic lupus erythematosus)	9	5.26%

POTS = postural orthostatic tachycardia syndrome

Table 2. Difference in the COMPASS-31 score depending on the usage of medications with the known influence on autonomic nervous system.

	N	Orthostatic intolerance	Vasomotor	Secretomotor	Gastrointestinal	Bladder	Pupillomotor	Total
No medications	119	16.00 (0.00, 48.00)	0.00 (0.00,4.17)	0.00 (0.00, 6.43)	3.57 (0.00, 12.500)	0.00 (0.00, 6.67)	1.00 (0.00, 3.67)	20.91 (0.00, 50.27)
Medications	52	20.00 (0.00, 64.00)	0.00 (0.00, 6.70)	2.14 (0.00, 6.43)	5.36 (0.000, 13.39)	1.11 (0.00, 10.000)	1.00 (0.00, 3.00)	30.99 (0.33, 55.93)
P value*		<0.0001	0.012	0.008	0.028	0.293	0.888	<0.001

*Mann-Whitney test

Table 3. Values of the COMPASS-31 score depending on the results of the ANS testing.

	N	Orthostatic intolerance	Vasomotor	Secretomotor	Gastrointestinal	Bladder	Pupillomotor	Total
VVS	29	16.00 (0.00, 28.00)	0.00 (0.00, 2.50)	0.00 (0.00, 4.29)	2.68 (0.00, 11.61)	0.00 (0.00, 6.67)	1.00 (0.00, 3.00)	20.89 (0.33, 45.11)
POTS	7	24.00 (0.00, 28.00)	0.00 (0.00, 4.17)	2.14 (0.00, 4.29)	5.36 (1.79, 9.83)	0.00 (0.00, 3.33)	1.33 (0.00, 2.67)	35.15 (12.17, 50.27)
OH	17	16.00 (0.00, 48.00)	0.00 (0.00, 4.17)	0.00 (0.00, 6.43)	2.70 (0.00, 11.61)	1.11 (0.00, 3.33)	1.33 (0.00, 2.33)	22.67 (0.33, 49.25)
OI	8	20.00 (8.00, 28.00)	0.00 (0.00, 2.50)	0.00 (0.00, 2.14)	2.68 (0.00, 7.14)	0. 56 (0.00, 1.11)	1.17 (0.00, 3.67)	27.57 (16.68, 33.43)
AI=0	85	16.00 (0.00, 64.00)	0.00 (0.00, 6.70)	0.00 (0.00, 6.43)	3.57 (0.00, 13.39)	1.11 (0.00, 10.00)	1.00 (0.00, 3.67)	25.30 (0.33, 55.93)
AI≥1	38	16.00 (0.00, 32.00)	0.00 (0.00, 4.17)	1.07 (0.00, 6.43)	4.02 (0.00, 13.39)	0.56 (0.00, 5.56)	1.33 (0.00, 2.67)	26.38 (0.89, 49.98)
CI=0	98	16.00 (0.00, 32.00)	0.00 (0.00, 3.33)	0.00 (0.00, 6.43)	3.57 (0.00, 13.39)	1.11 (0.00, 10.00)	1.33 (0.00, 3.67)	24.11 (0.33, 55.93)
CI≥1	20	20.00 (0.00, 64.00)	0.00 (0.00, 6.70)	1.07 (0.00, 4.29)	3.13 (0.00, 11.61)	0.00 (0.00, 3.33)	0.67 (0.00, 2.00)	28.57 (0.89, 47.08)
Normal	78	16.00 (0.00, 32.00)	0.00 (0.00, 3.33)	0.00 (0.00, 6.43)	4.91 (0.00, 13.39)	0.00 (0.00, 10.00)	1.17 (0.00, 3.67)	24.14 (0.00, 55.93)

VVS vasovagal syncope, POTS postural orthostatic tachycardia syndrome, OH orthostatic hypotension, OI orthostatic intolerance, AI adrenergic index, CI cardiovagal index.