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Reliability of Composite Autonomic Symptom Score (COMPASS)-31 in Congenital Central Hypoventilation Syndrome

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ABSTRACT

Rationale: Congenital central hypoventilation syndrome (CCHS) is a rare disorder characterized by alveolar hypoventilation and variable autonomic nervous system (ANS) dysfunction (ANSD) due to mutations in *PHOX2B*, a gene crucial for ANS neural crest lineage differentiation.

Objectives and Methods: Our prospective study aims were twofold: to (1) assess the relationships between the subjective Composite Autonomic Symptom Score (COMPASS)-31 and objective indices of ANSD obtained from heart rate variability analyses, ambulatory blood pressure (BP) monitoring, and CO_2 chemosensitivities and (2) describe the organ system ANSD, its relationship to *PHOX2B* genotype, and its consequences on quality of life (PedsQL) in children with CCHS.

Results: Thirty-two *PHOX2B* mutation-confirmed subjects (median [range] age 9.2 years (4.4; 18.0), 15 girls) were enrolled. COMPASS-31 was assessed in 32 matched (sex and age, range: 4.3; 18.9 years) healthy controls. As compared to healthy controls, children with CCHS had increased vasomotor ($p = 0.001$), secretomotor ($p = 0.021$), gastrointestinal ($p = 0.002$) and pupillomotor ($p = 0.028$) scores and decreased orthostatic intolerance scores ($p = 0.050$). There was no difference in overall COMPASS-31 score between CCHS and controls ($p = 0.083$). However, in CCHS, overall COMPASS-31 scores correlated with high frequencies (HF) normalized (cardiac parasympathetic modulation: $R = -0.53$; $p = 0.002$), low frequencies (LF)/HF ratio ($R = 0.56$; $p < 0.001$), and both systolic and diastolic nighttime BP dipping ($R = 0.45$, $p = 0.012$ and $R = 0.40$, $p = 0.028$, respectively). No significant relationships between COMPASS-31 scores and chemosensitivity testing, PedsQL scores, or *PHOX2B* genotype were identified.

Conclusions: COMPASS-31 identified some aspects of CCHS-related ANSD, and scores correlate with objective ANS function measures, supporting the potential utility of COMPASS-31 in CCHS.

1 | Introduction

Congenital central hypoventilation syndrome (CCHS) is a rare, lifelong and life-threatening disorder, characterized by alveolar hypoventilation due to a deficient autonomic central control of breathing and variable autonomic nervous system (ANS) dysfunction/dysregulation (ANSD) [1, 2]. Individuals with CCHS are heterozygous for a mutation in the *paired-like homeobox 2B* (*PHOX2B*) gene, which is a gene crucial for the differentiation of the neural crest lineages of the ANS [3]. *PHOX2B* is required for the formation of all branchial and visceral, but not somatic, motor neurons in the hindbrain [4].

In CCHS, the described *PHOX2B* variants are polyalanine repeat expansion mutations (PARMs) (in ~90% of patients), non-PARMs (NPARMs) (in ~8%–10% of patients) or *PHOX2B* whole or partial gene deletions (in $<1\%$ of patients) [1]. In unaffected individuals, there are 20 alanines on both alleles in the exon 3 polyalanine repeat region of the *PHOX2B* gene. Among CCHS patients with *PHOX2B* PARMs there are 24–33 alanine repeats on the affected allele. An association between genotype (both increasing PARM length and PARM vs. NPARM) and severity of ANSD has been reported [5]. Nevertheless, a wide variability in mutation penetrance and expressivity is emerging for individuals with PARMs and NPARMs [1].

A comprehensive objective and physiologic assessment of ANSD is recommended at diagnosis and with advancing age, including mainly the respiratory, cardiovascular, gastrointestinal and ophthalmologic systems, as well as the metabolic and endocrine status [1, 2]. This monitoring is based on clinical examinations including ECG Holter, awake and asleep physiologic testing in varied activities of daily living, autonomic testing, and neuropsychological assessment. For instance, the dysfunction of the cardiovascular ANS in CCHS has been established by multiple investigators [6–11]. Since these tests are not available in remote settings or even all academic medical centers, screening for ANSD using a standardized questionnaire may be useful. Sletten et al. developed a concise and statistically robust instrument to assess autonomic symptoms, the Composite Autonomic Symptom Score (COMPASS)-31, which provides clinically relevant scores of autonomic symptom severity from 8 to 79 years based on the well-established 169-item Autonomic Symptom Profile and its validated 84-question scoring instrument, the COMPASS [12]. To date, the COMPASS-31 has never been reported in patients with CCHS.

The first aim of our prospective study was to assess the relationships in CCHS between subjective, patient-reported experiences of ANSD using the COMPASS-31 and objective indices of ANSD obtained from heart rate variability (HRV) analyses, ambulatory blood pressure monitoring (ABPM), and CO_2 chemosensitivities. The secondary aim was twofold: to (1) describe the dysfunction of organ systems served by the ANS as reported in the COMPASS-31 and assess their consequences on quality of life (QoL), and (2) describe the relationship between COMPASS-31 score and *PHOX2B* genotype in children with CCHS.

2 | Methods

2.1 | Design

This was a prospective study based on both subjective, patient-reported and objective, physiologic measures of ANSD in the French pediatric CCHS cohort. Data were collected over 24 months between January 2022 and December 2023 in the national referral center at Robert Debré Universitary Hospital in Paris.

2.1.1 | Inclusion Criteria

Children/adolescents (4–18 years) with CCHS confirmed by *PHOX2B* PARMs or NPARMs with standard of care (French national guidelines) physiologic recordings and tests (https://www.has-sante.fr/jcms/c_2829809/fr/syndrome-d-ondine) including ambulatory blood pressure monitoring (ABPM) and objective measure of CO_2 sensitivity. Participants provided consent to complete COMPASS-31 and a 48-h Holter electrocardiogram recording during the same hospitalization (each child participated once in the study).

2.1.2 | Institutional Review Board Approval

Ethical approval was obtained from the Robert Debré Ethical Committee for the assessment of this cohort (PHENONDINE; N° 2022-629). The parents were informed of the collection of prospective clinical data for research purposes, and they could request that their child be exempted from this study in accordance with French law (non-interventional observational research). For children over the age of 12 years, assent was obtained.

2.2 | Questionnaires

2.2.1 | COMPASS-31 Questionnaire

The COMPASS-31 questionnaire was administered by one of the authors (BD) to the child in the presence of and with the help of the parents (duration of completion ~15 min). Administration and evaluation of COMPASS-31 were done independently, blinded to the results of the objective tests. The scale has 31 questions in six domains (orthostatic intolerance, four items; vasomotor, three items; secretomotor, four items; gastrointestinal, 12 items; bladder, three items; pupillomotor, five items) developed in subjects from 8 to 79 years [12]. The maximum weighted domain scores are as follows: orthostatic intolerance 40; vasomotor 5; secretomotor 15; gastrointestinal 25; bladder 10; pupillomotor 5, yielding a total score range of 0–100. Higher scores indicated greater autonomic dysfunction. It has been externally validated in patients with and without objective diagnosis of small fiber polyneuropathy [13].

Since normative COMPASS-31 data are not available for children, the questionnaire was also administered to a group of children, age- (± 1 year) and sex-matched to the CCHS cohort,

who were referred for suspicion of obstructive sleep apnea but who had a normal polysomnography.

2.2.2 | PedsQL Questionnaire

French versions adapted to age: 2–25 years [14]. The self and proxy PedsQL4.0 generic health related quality of life questionnaires each have four multidimensional scales: physical (eight items), emotional (five items), social (five items), and school (five items) functioning. The three summary scores are the total score (23 items), the physical health summary score (eight items), and the psychosocial health summary score (15 items). Each item uses a 5-point Likert scale from 0 (never) to 4 (almost always). Items are reverse scored and linearly transformed to a 0–100 scale, higher scores indicating a better health-related quality of life.

2.3 | Physiologic Testing

2.3.1 | Ambulatory Holter Electrocardiogram Recording

Holter recording 48 h was performed during the admission hospitalization, with the Holter recorder SpiderView (ELA Medical, SORIN Group, Clamart, France), as previously described [11]. The Holter frequency-domain measurements included very low frequencies (VLF: 0–0.04 Hz), low frequencies (LF: 0.04–0.15 Hz), and high frequencies (HF: 0.15–0.40 Hz) calculated for both daytime (8 a.m. to 9 p.m.) and nighttime (11 p.m. to 6 a.m.). LF and HF were also expressed as normalized values (LFnu, HFnu), and the LF/HF ratio was calculated. These measurements (means of the 2 daytime assessments for this study) were available from the SineScope software (ELA Medical, SORIN Group, Clamart, France).

2.3.2 | Ambulatory Blood Pressure Monitoring (ABPM)

Each child underwent 24-h ABPM using an oscillometric device (SpaceLabs 90207; SpaceLabs Medical; Redmond, WA) during the admission hospitalization, as previously described [11]. The arm cuff BP monitor was programmed to measure and store BP every 20 min during daytime (8 a.m. to 10 p.m.) and every 30 min during nighttime (10 p.m. to 8 a.m.). Bedtime and wake-up times were further recorded by the parent. BP measurements were compared to normative values of children ABPM (5–17 years) [15], and hypertension ($\geq$ 95th percentile) was defined according to current pediatric recommendations [16]. Decrease in systolic and diastolic BP at night versus daytime (dipping) was also determined. A validated percentage of BP measures < 70% or BP measures < 40 were exclusion criteria for ABPM. Percentiles for each BP measurement were extrapolated from natural logarithmic relationships that were established between BP norms and 50th, 75th, 90th, and 95th percentiles, available from literature [15, 16]. For children under 5 years of age, BP norms were obtained from auscultatory measurements [16]. Since normal BP varies during childhood with sex, age and height, all BP measurements were expressed as percentiles relative to the published norms.

2.4 | CO_2 Chemosensitivity

2.4.1 | Baseline Tidal Breathing Preceding CO Chemosensitivity Testing

This protocol was previously described [17]. Briefly, the participant was seated and breathed through a cushion-sealed face mask (Intersurgical, Wokingham, UK) fitted with elastic bands around the head and connected to a Validyne transducer (Northridge, CA). Flow rate (pneumotachography), end-tidal PO_2 ($PETO_2$) and end-tidal PCO_2 ($PETCO_2$) were continuously monitored, and signals were digitized using the MP-100 system (Biopac System Inc., Santa Barbara, CA) at a rate of 50 Hz; these were stored for further analysis. A constrained bivariate (minute ventilation V'E and $PETCO_2$ of tidal ventilation recording) analytical model was used, allowing for calculation of the components of controller and plant gains [17], as previously described in detail [18]. The controller gain was assumed to assess peripheral CO_2 chemosensitivity.

2.4.2 | CO_2 Chemosensitivity Testing

After tidal breathing measurement, ventilatory response to hypercapnia was measured using a modification of the Read hyperoxic hypercapnic rebreathing technique, as previously described [17]. The participants rebreathed from a 4-L bag filled with a gas mixture with the initial composition of 95% O_2 and 5% CO_2. Ventilatory responses to hypercapnia were expressed as V'E versus end-tidal CO_2. Hypercapnic ventilatory response slope under hyperoxia assesses the central ventilatory chemosensitivity since hyperoxia silences the peripheral chemoreceptors' response to CO_2 [17].

2.5 | Statistics

Results were expressed as medians [25th–75th percentiles] (Table 1). Comparisons of continuous variables between > 2 subgroups utilized Kruskall-Wallis test and subsequent or separate two-group comparisons utilized the Mann–Whitney test. Categorical variables were compared using the chi-square test. Correlations were evaluated using Pearson's correlation coefficient. A p value < 0.05 was considered significant. No correction for multiple testing was done due to the pathophysiological design of the study [19]. All statistical analyses were performed with Statview software (SAS Institute, Cary, North Carolina, USA).

3 | Results

Thirty-two CCHS subjects (median (range) age 9.2 years (range: 4.4–18.0), 15 girls) diagnosed in the newborn period ($n = 27$) or after 1 month of age ($n = 5$) were enrolled. All were *PHOX2B* mutation-confirmed including both PARM ($n = 27$) and NPARM ($n = 5$: nonsense-mediated decay variants, 2; missense variants, 2; and non-nonsense-mediated decay variant, 1) variants. All of the patients but one (NPARM variant) relied on mask ventilation during sleep for life-support. None of the

TABLE 1 | Clinical characteristics of the Congenital Central Hypoventilation Syndrome (CCHS) cohort and control subjects.

Median [25th – 75th percentile] or *n*	Healthy children *n* = 32	Whole cohort *n* = 32	*p* value	20/25 PARM, *n* = 12 Group 1	20/26 PARM, *n* = 7 Group 2	≥ 20/27 PARM, *n* = 8 Group 3	NPARM, *n* = 5 Group 4	Between group, *p* value	Intergroup comparisons
Clinical characteristics									
Sex, female/male, n	15/17	15/17	0.413	5/7	2/5	6/2	2/3	0.295	
Age, years	10.8 [7.9; 13.6]	9.2 [7.6; 12.8]		9.6 [6.2; 13.3]	9.1 [8.9; 14.7]	7.8 [7.0; 9.6]	10.6 [9.5; 13.5]	0.326	
Height, cm		135 [125; 158]		136 [119; 161]	148 [121; 158]	127 [115; 136]	137 [136; 164]	0.256	
Weight, kg		34.0 [25.5; 48.1]		34.0 [22.8; 45.2]	45.1 [29.5; 49.6]	27.2 [21.4; 31.8]	34.2 [32.3; 54.6]	0.309	
Neonatal onset/later-onset, n		27/5		8/4	7/0	8/0	4/1	NA	
Hirschsprung disease, n		5		0	0	3	2	NA	
Ophthalmologic characteristics[a]									
Intrinsic ocular anomalies, n		4		0	0	3	1	NA	
Extrinsic oculomotor anomalies, n		12		3	4	4	1	NA	
Questionnaires									
COMPASS 31 (/% of total score)									
Orthostatic intolerance/40	0.0 [0.0; 14.0]	0.0 [0.0; 0.0]	0.050	0.0 [0.0; 4.0]	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.366	
Vasomotor/5	0.0 [0.0; 0.0]	0.0 [0.0; 1.7]	0.001	0.0 [0.0; 0.0]	0.8 [0.0; 1.7]	0.8 [0.0; 2.1]	0.0 [0.0; 0.8]	0.468	
Secretomotor/15	0.0 [0.0; 2.1]	4.3 [0.0; 4.3]	0.021	4.3 [0.0; 4.3]	4.3 [1.1; 4.3]	2.1 [0.0; 5.4]	0.0 [0.0; 6.4]	0.942	
Gastrointestinal/25	0.9 [0.0; 5.4]	4.5 [2.7; 7.1]	0.002	4.9 [2.7; 8.5]	2.7 [1.3; 6.9]	5.4 [2.7; 6.7]	5.4 [4.5; 8.7]	0.450	
Bladder/10	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.077	0.0 [0.0; 1.1]	0.0 [0.0; 0.8]	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.475	
Pupillomotor/5	0.0 [0.0; 1.0]	0.8 [0.0; 1.7]	0.028	1.0 [0.0; 1.3]	0.3 [0.1; 1.5]	1.2 [0.3; 1.7]	0.7 [0.2; 1.7]	0.813	
Total score/100	2.1 [0.8; 20.1]	10.7 [6.5; 16.0]	0.083	11.4 [6.5; 20.4]	10.2 [4.8; 15.8]	11.4 [9.2; 13.1]	8.8 [7.5; 15.1]	0.926	
PedsQL									
Physical score		83 [73; 92]		84 [78; 98]	84 [67; 89]	83 [77; 91]	80 [46; 91]	0.811	
Psychosocial score		71 [60; 76]		71 [63; 78]	72 [53; 75]	67 [60; 78]	70 [50; 77]	0.913	
Total score		74 [66; 82]		76 [70; 85]	71 [59; 80]	74 [67; 83]	75 [49; 84]	0.740	
ECG Holters (*n*=32)									
Daytime measurements									
Mean heart rate		97 [92; 107]		94 [89; 97]	96 [87; 99]	112 [106; 114]	95 [92; 102]	0.002	1, 2, 4 < 3
VLF, ms^2		978 [600; 1352]		984 [711; 1881]	1220 [1060; 1894]	600 [381; 1065]	859 [352; 1065]	0.054	1, 2 > 3, 4
LF, ms^2		457 [212; 647]		543 [410; 833]	533 [466; 589]	212 [152; 452]	285 [87; 466]	0.079	
LFnu, %		69 [61; 72]		67 [61; 73]	71 [69; 72]	65 [57; 70]	68 [57; 75]	0.744	
HF, ms^2		103 [50; 173]		123 [96; 277]	142 [110; 155]	49 [33; 73]	49 [32; 88]	0.008	
HFnu, %		17 [15; 22]		19 [14; 30]	19 [16; 23]	17 [16; 19]	13 [12; 19]	0.255	
LF/HF ratio		3.87 [2.98; 4.66]		3.56 [2.25; 5.23]	3.89 [2.79; 4.44]	3.85 [3.20; 4.16]	4.76 [3.82; 5.95]	0.550	
ABPM (*n* = 30)									
Mean systolic BP, mmHg		114 [104; 117]		113 [104; 119]	116 [114; 117]	108 [101; 123]	112 [104; 116]	0.686	
Mean systolic BP percentile		62 [51; 73]		64 [60; 74]	59 [52; 63]	74 [32; 97]	38 [28; 64]	0.219	

(Continues)

TABLE 1 | (Continued)

Median [25th – 75th percentile] or *n*	Healthy children *n* = 32	Whole cohort *n* = 32	*p* value	20/25 PARM, *n* = 12 Group 1	20/26 PARM, *n* = 7 Group 2	≥ 20/27 PARM, *n* = 8 Group 3	NPARM, *n* = 5 Group 4	Between group, *p* value	Intergroup comparisons
Mean diastolic BP, mmHg		69 [65; 73]		65 [63; 69]	72 [68; 74]	69 [64; 76]	69 [66; 75]	0.161	
Mean diastolic BP percentile		42 [36; 80]		40 [34; 75]	53 [39; 63]	67 [21; 95]	41 [33; 65]	0.867	
Systolic BP dipping, %		7 [5; 11]		7 [5; 7]	8 [3; 17]	6 [5; 13]	9 [6; 10]	0.576	
Diastolic BP dipping, %		9 [5; 14]		10 [5; 13]	9 [7; 17]	9 [4; 12]	12 [8; 18]	0.925	
CO_2 chemosensitivity									
Peripheral, L/min/mmHg, n		0.86 [0.42; 1.59], 23		1.26 [0.53; 1.82], 9	0.94 [0.35; 1.14], 5	0.28 [0.08; 4.58], 6	0.62 [0.33; 0.81], 3	0.388	
Central, L/min/mmHg, n		0.29 [0.14; 0.41], 21		0.29 [0.13; 0.65], 8	0.12 [0.10; 0.31], 5	0.29 [0.24; 0.38], 5	0.45 [0.31; 0.60], 3	0.412	

Abbreviations: ABPM, ambulatory blood pressure measurement; BP, blood pressure; HF, high frequencies; LF, low frequencies; LFnu and HFnu are normalized frequencies; NA: not available because conditions of validity of the test are not met; PedsQL: quality of life questionnaire; VLF is very low frequencies.
[a]Ophthalmologic characteristics were classified as recommended by the more recent guidelines, ocular globe disorders were not recorded since they may be related to CCHS or be incidental associations [1].

patients had a tracheostomy at the time of testing but some had a previous tracheostomy before transitioning to mask ventilation. Thirty-two age- and sex-matched controls were enrolled.

4 | Characteristics of the Cohort

The CCHS cohort was divided into four groups based on *PHOX2B* genotype, as in previous studies. Table 1 describes the characteristics of the cohort, by *PHOX2B* genotype grouping and the control group (COMPASS-31 values). Compared to the control group, children with CCHS had increased vasomotor, secretomotor, gastrointestinal and pupillomotor scores while their score of orthostatic intolerance tended to be lower. There was not a significant difference in COMPASS-31 total score between CCHS and the control group. This finding was driven by the absence of score difference in orthostatic intolerance, which is highly weighted in the COMPASS-31 total score calculation.

The only phenotype difference between the genotypes was a higher impairment of parasympathetic modulation (HF power) in the children with PARM ≥ 20/26 as compared to those with PARM 20/25 and NPARM.

Two patients had no ABPM results due to an insufficient number of validated BP measurements ($n = 1$) or unavailability of the device ($n = 1$).

Ophthalmologic disorders were found in 14/32 children (44%, 95% confidence interval: 26–62) as described in Table 1 (two children had both intrinsic and extrinsic abnormalities). The pupillomotor score of the COMPASS-31 of the children with abnormalities was higher than that of children without abnormalities (1.5 [0.7; 1.7] vs. 0.3 [0.0; 1.0], $p = 0.018$) while their total scores were not significantly different (11.3 [8.5; 13.5] vs. 9.5 [5.4; 17.7], $p = 0.621$).

4.1 | ANSD of Organ Systems Served by ANS and Their Consequences on Quality of Life

Table 1 shows the organ dysfunctions based on subjective results from the six different domains of the COMPASS-31. Overall, children with CCHS reported negligible symptoms of orthostatic intolerance, and no vasomotor or bladder symptoms. A mild impairment of digestive, secretomotor and visual functions were subjectively reported. We did not observe any significant relationship between total COMPASS-31 score and quality of life (total score: R = 0.13, $p = 0.461$ and subscale scores, physical: R = 0.05, $p = 0.778$; psychosocial: R = 0.16, $p = 0.378$).

4.2 | Relationships Between the COMPASS-31 Composite Score and Both HRV and ABPM Indices

Figure 1 shows that the COMPASS-31 composite score correlated with HFnu and LF/HF ratio (upper panels), and with both systolic and diastolic BP nocturnal dipping (lower panels). Since HFnu is closely related to parasympathetic modulation, it emphasizes that higher COMPASS-31 scores were associated with

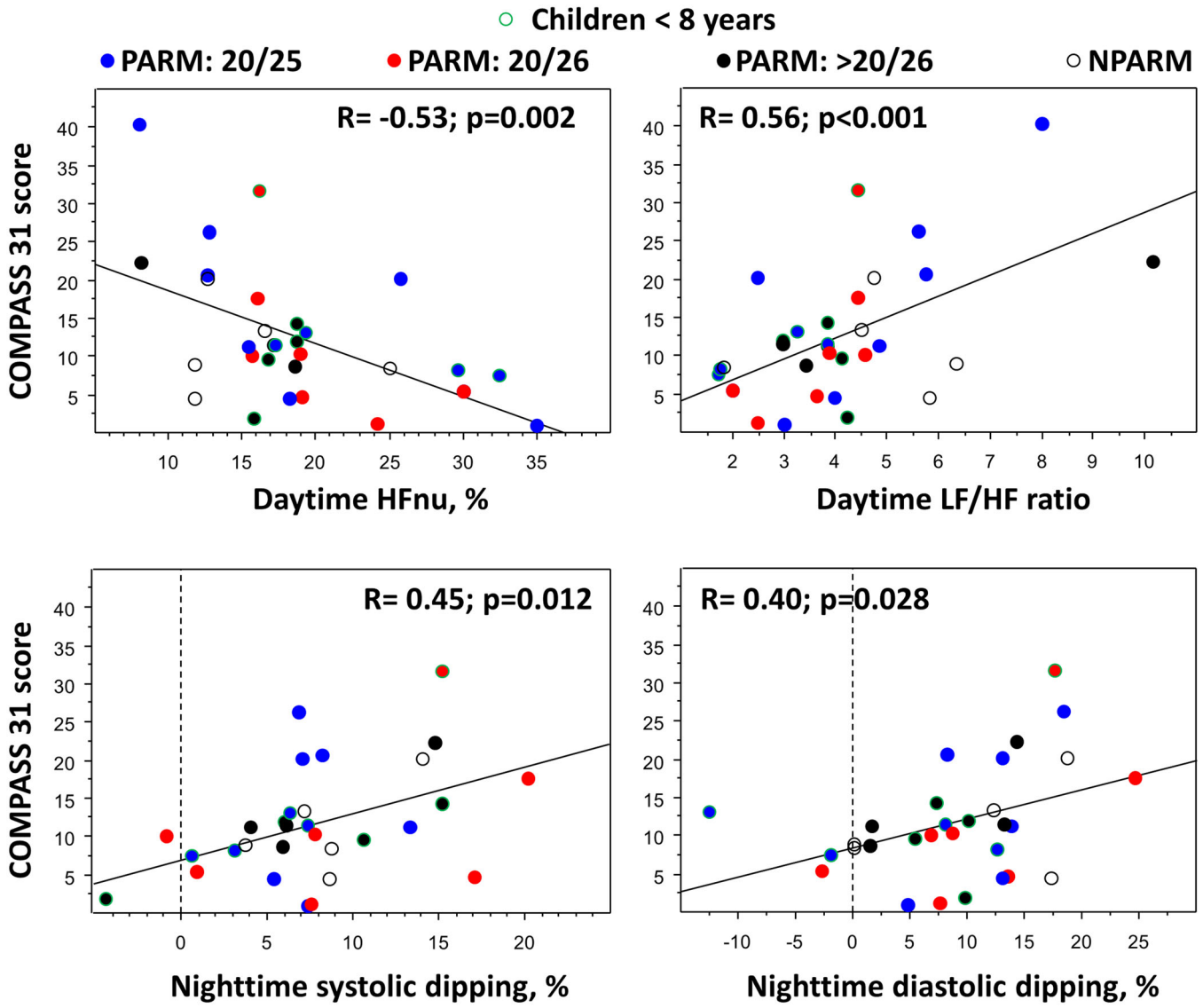

FIGURE 1 | Relationships between subjective COMPASS-31 and both heart rate variability indices and blood pressure objective indices. The upper panels describe the relationship between COMPASS-31 (total score/100, higher scores indicative of more ANS dysfunction) and daytime HFnu (index of parasympathetic modulation) obtained from ECG Holter (left panel) and LF/HF ratio (right panel). The lower panels describe the relationships between COMPASS-31 and systolic blood pressure dipping at night (left panel) and diastolic blood pressure dipping at night (right panel); ABPM results were available in 30/32 participants. The four *PHOX2B* genotypes are represented with different colors and children younger than 8 years of age ($n = 9$) are green circled. The correlations of COMPASS-31 with HFnu ($R = -0.61$, $p = 0.002$), LF/HF ratio ($R = 0.62$, $p = 0.002$) and diastolic blood pressure dipping ($R = 0.48$, $p = 0.028$) remained significant in children of at least 8 years of age (no formal validation of the PedsQL COMPASS-31 in [12]) while significance was lost for systolic blood pressure dipping ($R = 0.28$, $p = 0.212$). [Color figure can be viewed at wileyonlinelibrary.com]

a lesser degree of cardiac parasympathetic modulation and a relatively higher sympathetic modulation (increased LF/HF ratio). These correlations are further confirmed with nocturnal BP dipping (Figure 1, lower panels), another marker of ANS modulation. Figure 1 also shows that the degree of ANSD by COMPASS-31 is not related to the *PHOX2B* mutation.

4.3 | Description of the Relationship Between COMPASS-31 Score and CO_2 Chemosensitivities and the Length of Polyalanine Expansion

There were no significant relationships between COMPASS-31 score and either peripheral or central CO_2 chemosensitivity (central, $R = 0.008$, $p = 0.973$; peripheral, $R = 0.14$, $p = 0.532$). Table 1 shows that the COMPASS-31 scores were not significantly different in the four *PHOX2B* genotypes/variant groupings.

5 | Discussion

The primary results of our prospective descriptive study indicate that (1) the subjective COMPASS-31 responses correlate with objective indices of cardiac parasympathetic dysfunction but not with CO_2 chemosensitivities, (2) the degree of ANSD captured by COMPASS-31 is not related to quality of life, and (3) the ANSD of the different organ systems served by the ANS,

as captured by COMPASS-31, did not differ by specific *PHOX2B* genotypes/variants.

Our study highlights the necessity to distinguish the report of subjective symptoms (COMPASS-31) from objective measures of ANSD and physiologic compromise in any clinical condition, but especially among children with known dysregulation of the ANS. The COMPASS-31 values were not clearly increased (median in the normal range of previous studies in young adult patients [20] and overall score not different from our control group) in our CCHS patients, which is at variance with other diseases associated with less severe and diffuse genetic ANSD [20]. Nevertheless, children with CCHS had increased vasomotor, secretomotor, gastrointestinal and pupillomotor scores as compared to matched healthy children, but not proportionate to the physiologic manifestations of ANSD.

By contrast, their score of orthostatic intolerance tended to be lower explaining the absence of total score difference given the weight of the latter score in the total score. The orthostatic intolerance perception (symptoms) seems reduced in patients with CCHS accordingly with the results of two studies showing early or classic orthostatic hypotension [21] in patients with CCHS [9, 22]. In the recent study of Vu et al. during head-up tilt testing, none of the patients with CCHS ($n = 50$) were syncopal despite dramatic drops in blood pressure in some subjects and only two adolescent girls described pre-syncopal vision changes [22]. In contrast, patients without CCHS with syncope due to orthostatic hypotension had significantly higher COMPASS 31 scores than healthy subjects [23]. Thus, the low prevalence of subjective syncopal symptoms in CCHS [22, 24] may explain the low COMPASS-31 despite decrease in BP, and may explain the trend toward lower score than in a healthy pediatric population, in which disorders of orthostatic intolerance are prevalent [25]. Sletten and colleagues justified the exclusion of syncope in the COMPASS-31 as [12]: "Another domain eliminated for scoring was the syncope domain. There was considerable overlap with the orthostatic intolerance domain, and questions related to reflex syncope were not considered to be a meaningful measure of autonomic dysfunction." Sleep domain was also excluded in COMPASS 31, which was justified by the very low internal consistency of the domain that was not an independent domain in their factor analysis [12]. This could be a limitation since children with CCHS seem to be at risk for subjective sleep disturbances [26].

Moreover, despite the major role of *PHOX2B* in ANS development [3], symptoms of ANSD may be modest due to the relative preservation of some ANS functions. Interestingly, CCHS children with ophthalmologic disorders had a higher pupillomotor score of the COMPASS-31 compared to CCHS children without ocular disorders, suggesting the sensitivity of the COMPASS-31 in CCHS, at least for some symptoms. Table 1 shows that CCHS patients in our cohort did not report altered bladder function. The recent demonstration that the pelvic organs receive no parasympathetic innervation [27] suggests the potential that the sympathetic system is relatively preserved in CCHS, although sometimes reminders of the need to empty the bladder seem necessary [28]. Thus, the relative preservation of the sympathetic system [9] could explain the preservation of 2/6 domains of the COMPASS-31, and the major relative weight of orthostatic intolerance in COMPASS-31 may explain the low scores observed in spite of physiologic ANSD.

The observed correlations of COMPASS-31 with HRV indices and BP dipping highlights that the subjective evaluation is dose-dependently related to objective indices of cardiac ANSD, excepting orthostatic intolerance. This result is consistent with those of previous studies that showed significant correlations between COMPASS-31 and HRV indices in other diseases with ANSD [29, 30].

The severity of the PARM genotype is not associated with the degree of subjective ANSD evaluated by the COMPASS-31, even if patients with more severe genotypes ($\geq 20/26$) had a more reduced parasympathetic modulation, further highlighting the necessity to distinguish subjective and objective ANSD. Patwari et al. showed in 22 *PHOX2B* mutation-confirmed cases with CCHS and 68 healthy controls that pupillometry indices reductions were indicative of both sympathetic and parasympathetic deficits in CCHS, with an inverse linear relationship apparent in pupil diameter and velocity measurements among the CCHS patients with the most common heterozygous *PHOX2B* polyalanine expansion repeat mutations, suggesting a graded phenotype/genotype dose response based on PARM length [31]. Nevertheless, a wide variability in mutation penetrance and expressivity for PARMs has been demonstrated [1, 2]. Finally, retrotrapezoid nucleus (the lynchpin of the central respiratory chemoreflex [32]) development relies on transcription factors, including *PHOX2B*. Thus, one may have hypothesized that a parallel impairment of CO_2 chemosensitivities (both central and peripheral) and ANSD would exist, which was not observed, further arguing for the wide variability of expressivity. Table 1 shows that the only significant difference between the four *PHOX2B* groups was the degree of HF power reduction (vagal withdrawal), with lower powers in severe PARM ($> 20/26$) and NPARM variants as compared to moderate PARM (20/25 and 20/26) variants.

Our study also shows that quality of life in children with CCHS is modestly altered. Verkaeren et al. have previously shown that CCHS is associated with an impairment of health-related quality of life in young adults that remains moderate [33]. We confirm that the physical dimension of quality of life is normal while there is a slight reduction of the psychosocial dimension, consistent with the frequent problems in social interaction that have previously been evidenced [34, 35]. It is remarkable that patient reported quality of life in technology-dependent children with severe and chronic disease is not substantially different from that reported in healthy controls. This may be due to typical presentation with disease in the first days of life, so they have always known ventilator dependence (it becomes their baseline), perhaps limiting the perceived impact. The absence of a relationship between the ANSD captured by COMPASS-31 and quality of life score indicates that neither patient reported outcomes of ANSD nor quality of life may be an ideal therapeutic endpoint.

Our prospective cross-sectional study has some limitations. The COMPASS-31 questionnaire was administered to parents/young patients (from 4 years of age). This may be a limitation since the

COMPASS-31 was validated in patients who are 8 years of age and older [12]. To address this limitation and because normal values of COMPASS-31 in childhood are not available, we obtained COMPASS-31 testing in a control group, though referred for sleep apnea suspicion (most were snorers) without identified physiologic compromise. The validation indices comprised only cardiovascular indices, which were those obtained in our current practice (ECG and BP monitoring) accordingly with French guidelines. The comparison of COMPASS-31 with other tests would be useful; the higher median pupillomotor score of children with objective ocular disorders further argue for the potential usefulness of COMPASS-31 in CCHS. Finally, due to the single center design together with the small sample size these results may not fully capture the CCHS-related symptoms of ANSD. Our proof-of-concept results are too preliminary to modify current clinical practice concerning ANSD evaluation in CCHS. Given the modest sample size, the clinical utility of the COMPASS- 31 in patients with CCHS cannot be demonstrated. A larger multicenter trial is warranted for that objective.

In conclusion, results support the COMPASS-31 as an adequate means to evaluate cardiac ANSD in young subjects with CCHS. The symptoms of ANSD captured by COMPASS-31 do not seem to alter quality of life in these patients and does not seem to be related to *PHOX2B* polyalanine expansion length.

Author Contributions

Benjamin Dudoignon: investigation, validation, writing – review and editing. **Plamen Bokov:** conceptualization, investigation, methodology, validation, writing – review and editing. **Fatima Benterki:** investigation, writing – review and editing, visualization. **Nathalie Couque:** investigation, writing – review and editing, visualization, resources. **Casey M. Rand:** conceptualization, methodology, writing – review and editing. **Debra E. Weese-Mayer:** conceptualization, methodology, writing – review and editing. **Christophe Delclaux:** conceptualization, methodology, validation, formal analysis, project administration, writing – original draft.

Ethics Statement

approval was obtained from the Robert Debré Ethical Committee for the assessment of this cohort (PHENONDINE; N° 2022-629).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data are available upon reasonable request from the corresponding author.

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