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ACTIVITY-DEPENDENT PHYSIOLOGICAL DYNAMICS ASSESSED BY CONTINUOUS MULTIMODAL DAILY-LIFE MONITORING IN CONGENITAL CENTRAL HYPOVENTILATION SYNDROME: AN EXPLORATORY STUDY

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ABSTRACT

Background: Congenital Central Hypoventilation Syndrome (CCHS) is a rare disorder characterized by impaired autonomic regulation affecting respiratory, cardiovascular and thermoregulatory functions. Previous studies have monitored selected physiological signals in patients with CCHS or investigated physiological responses under experimental conditions. However, no study has continuously monitored multiple physiological signals during daily-life activities to characterize their temporal evolution. This exploratory study aimed to investigate activity-dependent changes in the temporal evolution of multiple physiological signals during prolonged daily-life monitoring in CCHS.

Methods: Eleven patients with CCHS underwent continuous physiological monitoring (22–60 hours) during usual daily activities. Heart rate (HR), respiratory rate (RR), systolic and diastolic blood pressure (SBP and DBP), peripheral oxygen saturation (SpO_2), and skin temperature (T) were acquired using a wearable medical-grade chest sensor. Recordings were segmented into four activity categories based on activity diaries: moderate-intensity activity, low-intensity activity, meals, and nighttime. Linear mixed-effects models were used to assess differences in signal temporal evolution across activities.

Results: HR, RR, SBP, and skin T showed significant activity-dependent temporal patterns, whereas DBP remained stable across all activities. HR and RR exhibited increasing trends during moderate-intensity

activity, consistent with physiological responses to exercise. Interestingly, HR also increased during meals. The decreasing HR trend during low-intensity activities and the SBP decline during moderate activity contrasted with expected physiological responses, suggesting altered autonomic cardiovascular regulation. During nighttime, HR remained relatively stable and SBP showed a slight increase, supporting previous evidence on the impaired autonomic regulation in CCHS. Skin T increased during daytime activities, whereas its stable nighttime pattern may reflect altered thermoregulatory control. SpO2 was not quantitatively analysed due to data loss but remained generally within normal ranges.

Conclusions: This study provides the first characterization of the temporal evolution of multiple physiological signals during daily-life activities in CCHS. Despite its exploratory nature, it expands current knowledge of autonomic dysregulation by identifying physiological patterns and activity-dependent behaviours that may reflect disease-specific autonomic alterations. These findings complement previous evidence obtained from ambulatory monitoring and laboratory-based studies and support the potential of prolonged multimodal monitoring to improve the understanding and future clinical assessment of autonomic dysfunction in CCHS.

Keywords: Congenital Central Hypoventilation Syndrome, Physiological signals, Daily-life activities, Signal dynamics

INTRODUCTION

Congenital Central Hypoventilation Syndrome (CCHS) is a rare genetic disorder of autonomic nervous system development caused mostly by mutations in the PHOX2B gene, a key transcription factor for the development of neuronal structures that control breathing and autonomic function. It is characterized by alveolar hypoventilation with reduced or absent ventilatory response to hypoxia and hypercapnia, more severe during sleep, but sometimes also present when awake(1,2). Autonomic dysfunction also involves the cardiovascular system, specifically causing arrhythmias and bradycardia(3), reduced heart rate

variability(4), neurogenic hypertension(5) , pressure dysautonomia with nocturnal hypertension and daytime hypotension(6). Additional manifestations involve an impaired temperature regulation(7).

In CCHS management the primary objective is to ensure adequate ventilation and oxygenation(2). Continuous monitoring of peripheral oxygen saturation (SpO_2) and respiratory rate (RR) allows for the rapid identification of episodes of hypoxia or hypoventilation, especially during sleep, and for timely adjustment of ventilatory support. However, the monitoring of other physiological signals might be extremely useful to better characterize the autonomic nervous system dysregulation. Tracking heart rate (HR) and systolic/diastolic blood pressure (SBP and DBP) over day and night allow prompt recognition of autonomic deterioration, arrhythmic events, or hypertensive/hypotensive crises and guide treatment decisions. Skin temperature (T) provides a non-invasive indicator of sympathetic/parasympathetic status(8), especially when integrated with SpO_2, HR, blood pressure (BP), and RR in a multimodal framework.

At the current state of the art, there is no evidence in the literature of works that perform a continuous and multi-signal (HR, SBP, DBP, RR, SpO_2, skin T) long time (≥24 hours) monitoring in patients with CCHS during daily life. Indeed, previous studies, that have already monitored these vital signals in CCHS population, have done it mainly separately, or in controlled settings, or for relatively short time periods. Moreover, most of the published studies based their analyses on the comparison between mean values of the signals of interest; rarely the temporal evolution of these physiological signals is investigated.

Trang et al.(6) conducted a 24-hour ambulatory monitoring in 11 patients with CCHS, simultaneously measuring SBP, DBP, SpO_2, and end-tidal CO_2. However, this study did not include HR, RR or skin T measurements and not all the signals were continuously acquired throughout the entire monitoring period. Dudoignon et al.(9) performed a 24-hour ambulatory monitoring of BP together with continuous ECG recording in 33 patients with CCHS, with BP sampled every 15-20 min in daytime and every 30 min during nighttime. Although addressing different clinical questions, both studies primarily compared physiological measurements between wakefulness and sleep using averaged values, rather than investigating the temporal evolution of multiple physiological signals.

Saiyed et al.(7) collected peripheral skin T and estimated core body temperature in 25 patients with CCHS over 96 hour period, sampled every 3 minutes. Their work aimed at identifying differences in circadian temporal profile of temperature between the CCHS population and healthy controls, as well as at investigating alterations between estimated core body temperature and peripheral skin T in the CCHS population. Thus, their analysis was limited to temperature-related variables and did not include the simultaneous assessment of multiple physiological signals or the evaluation of activity-dependent physiological dynamics during daily life.

More recently, Ismail et al.(10) used a wearable device (Hexoskin) to acquire up to 34 hours of continuous physiological recordings in 33 patients with CCHS. However, their analysis was limited to heart rate variability.

Within this framework our study aims at filling the literature gap by monitoring the previously listed physiological signals (HR, SBP, DBP, RR, SpO_2, skin T) simultaneously and continuously in daily life environment, and investigating how they vary across the type of activities performed. Specifically, our aim was to determine the effect of the activity on physiological signals by studying the biosignal dynamic during different activities in patients with CCHS. As no previous studies have investigated activity-dependent physiological signal dynamics during daily life in patients with CCHS, no a priori hypotheses were formulated, and the study was therefore designed as an exploratory investigation.

MATERIALS AND METHODS

Participants and study design

The study population consisted of 11 subjects affected by CCHS (5 females and 6 males, mean age 17.36±2.06 years). Demographic and clinical subjects' characteristics are reported in Table 1.

All subjects were recruited by the Italian CCHS patients' association (AISICC, Associazione italiana per la Sindrome da Ipoventilazione Centrale Congenita Sindrome di Ondine), that was responsible for data acquisition. Acquired data were retrospectively analysed by the researcher of the scientific Institute IRCCS E. MEDEA. Participants and their parents, where minor subjects were involved, received a complete

description of the study procedures and provided written informed consent for the participation in the study. All procedures were conducted in accordance with the ethical standards laid down in the Declaration of Helsinki and the study protocol was approved by the Ethics Committee CET Lombardia 2 (Protocol number: L2-282, date of approval: March, 24th 2025).

Physiological data acquisition

Physiological signals were acquired continuously in a range of 22-60 hours (mean 42.5±15.5 hours), while carrying out usual daily activities. In Table 1 are reported the total hours of acquisition for each subject. For all subjects but one the recordings were longer than 24 hours. One participant badly tolerated the acquisition device, resulting in the collection of only 22 hours.

Sex	Age (years)	Type of respiratory assistance	Cardiac pacemaker (yes or no)	Genotype	Hours of data collected
M	15.41	Invasive ventilation (tracheostomy)	N	PARM 20/27	60
M	19.67	Invasive ventilation (tracheostomy)	Y	PARM 20/27	51
F	20.46	Invasive ventilation (tracheostomy)	N	NPARM (Frame shift)	59
M	19.53	Noninvasive ventilation	Y	PARM 20/27	60
F	18.73	Noninvasive ventilation	N	PARM 20/27	28
M	17.04	Noninvasive ventilation	N	Not available	60
F	14.00	Noninvasive ventilation	N	PARM 20/26	32
M	16.00	Noninvasive ventilation	Y	PARM 20/26	26
F	19.55	Invasive ventilation (tracheostomy)	N	PARM 20/29	35
F	19.00	Noninvasive ventilation	Y	NPARM (Frame shift)	22
M	15.00	Noninvasive ventilation	Y	PARM 20/26	34

Table 1: Demographic and clinical subjects' characteristics and hours of data collected for each subject.

The device used was a non-invasive medical grade photoplethysmography chest patch (Biobeat Technologies Ltd., Israel) which allows to acquire the following physiological signals: heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), respiratory rate (RR), skin temperature (skin T) and oxygen saturation (SpO_2).

Data were collected every 5 seconds during day and 5 minutes during night; they were transmitted wirelessly in real-time through Bluetooth Low Energy to a gateway device, and from there through Wi-Fi to a cloud-based management application for their visualisation. The extraction of the raw data from the Biobeat cloud was possible by means of an ad hoc developed Application Programming Interface (API). Data

acquired every 5 seconds were automatically available for the extraction aggregated into 1-minute values by averaging all samples collected during each minute of acquisition.

During all days of data acquisition, participants were asked to keep a diary detailing the activities carried out during the day and the corresponding starting and ending times.

Data processing

First of all, the quality of the data was assessed, in particular data loss was evaluated separately for each signal type across two time windows: day and night. Night-time periods were defined based on the diary completed by participants, with all remaining periods classified as day. The percentage of data loss was calculated by comparing the number of samples with zero or empty values versus the number of theoretical samples from the start to the end of the specific acquisition window.

Data of each subject were then segmented according to the activities recorded in the diary and each segment was classified in low or moderate intensity activity, meals and night. Specifically, all activities mostly performed while sitting (e.g. studying/school, playing instruments) were considered low intensity, and motor activities (e.g. walking, dancing, canoeing) were considered moderate intensity. Meals were considered separately since clinical experience suggests that they might represent a critical event in CCHS population and also due to the critical link between respiration and swallow. A single segment corresponding to a specific activity was included in the analysis only if the data loss was lower than 40%.

Statistical analysis

To compare data loss between daytime and night-time periods, statistical analysis was performed in MATLAB (Release R2024b, The MathWorks, Inc., Natick, Massachusetts, United States). First, data loss distribution for each type of signal during day and night was assessed for normality using the Lilliefors test. For signals displaying a normal distribution in both groups, a two-sample independent Student's t-test was applied to evaluate differences. Conversely, when the assumption of normality was violated, the non-parametric Wilcoxon-Mann-Whitney (Rank-Sum) test was employed. Statistical significance was set at $p < 0.05$.

Successively, each physiological signal was analysed through Linear Mixed-Effects Models (LMMs) to investigate group-level differences among the 4 types of activities (meals, night, moderate intensity, low intensity). Based on the real-life nature of our dataset, LMMs were chosen because they do not require the same number of observations for every subject and can naturally accommodate repeated-measures datasets with unequal sequence lengths and missing observations(11). Signals were modelled including the main effects of activity and time as well as their full factorial interaction (i.e., main effects and their interaction term). Furthermore, given the multi-level nature of the experimental design, random intercepts were included for subjects to account for inter-individual baseline differences and for time windows nested within subjects to account for the hierarchical structure of repeated measurements. The objective of this model was to assess the interaction between activity and time, thereby determining whether the temporal evolution of the physiological signals differed across activities while accounting for within-subject dependencies. Main effects and their interactions were then evaluated using the Analysis of Variance (ANOVA) performed on the fitted LMMs. When significant effects were detected, to explore specific differences between activities, post-hoc pairwise comparisons were performed; p-values were adjusted using the Benjamini-Hochberg False Discovery Rate (FDR) procedure (12), and the statistical significance threshold was set at $\alpha = 0.05$. All the analyses were performed in MATLAB (Release R2024b, The MathWorks, Inc., Natick, Massachusetts, United States).

RESULTS

Data description

Table 2 shows the percentages of data loss, divided in day and night segments. The SpO_2 signal shows the higher percentage of data loss, higher than 50%, thus it was only qualitatively analysed. All the other signals show percentages of data loss lower than 23% both during day and night. RR, HR and skin T signals are the ones which have been better recorded with a data loss lower than 19% both during day and night. No differences emerged in data loss between daytime and night-time periods. Thus, the data loss does not

appear to be influenced by the difference in light levels between day and night, nor by the greater number of movements that occur during the day.

	Day [%]	Night [%]	Test performed	p-value
HR	16.92	15.54	Wilcoxon-RankSum	0.479
RR	18.95	16.15	T-Test	0.816
SBP	20.84	22.48	Wilcoxon-RankSum	0.847
DBP	21.08	20.95	T-Test	0.971
Skin T	17.05	15.91	Wilcoxon-RankSum	0.479
SpO2	55.05	57.13	T-Test	0.659

Table 2 Percentages of data loss for each type of signal during day and night plus description of statistical test performed to identify differences between day and night data loss and resulting p-value.

Table 3 reports details regarding epochs included in the analysis. The duration of epochs varies in a range between 13 and 676 minutes, strongly depending on the type of activity considered: meals and moderate activity windows are the shortest (respectively mean duration of 54 and 85 minutes), followed by low intensity activity (mean duration: 161 minutes) and night (mean duration: 476 minutes); however, this variability in duration is well managed by the LMMs.

	Activity	Total number of epochs	Minimum/maximum duration (min)	Duration mean ±SD (min)
HR	Moderate intensity	27	27/191	84±45
	Meals	35	13/91	53±19
	Low intensity	30	31/389	161±83
	Night	13	416/676	477±65
RR	Moderate intensity	26	27/191	84±46
	Meals	34	13/91	54±19
	Low intensity	29	31/329	153±73
	Night	13	416/676	477±65

SBP	Moderate intensity	23	31/191	88±46
	Meals	34	29/91	55±18
	Low intensity	26	59/389	167±82
	Night	12	416/676	474±67
DBP	Moderate intensity	25	27/191	86±46
	Meals	34	29/91	55±18
	Low intensity	27	31/389	162±86
	Night	12	416/676	474±67
T	Moderate intensity	27	27/191	84±45
	Meals	35	13/91	53±19
	Low intensity	30	31/389	161±83
	Night	13	416/676	477±65

Table 3: Characterization of the epochs retained in the analysis in terms of number, minimum and maximum duration, average and SD in hours, divided by type of activity.

Boxplots representing each physiological signal distribution in each different type of activity are reported in the following Figure 1 .

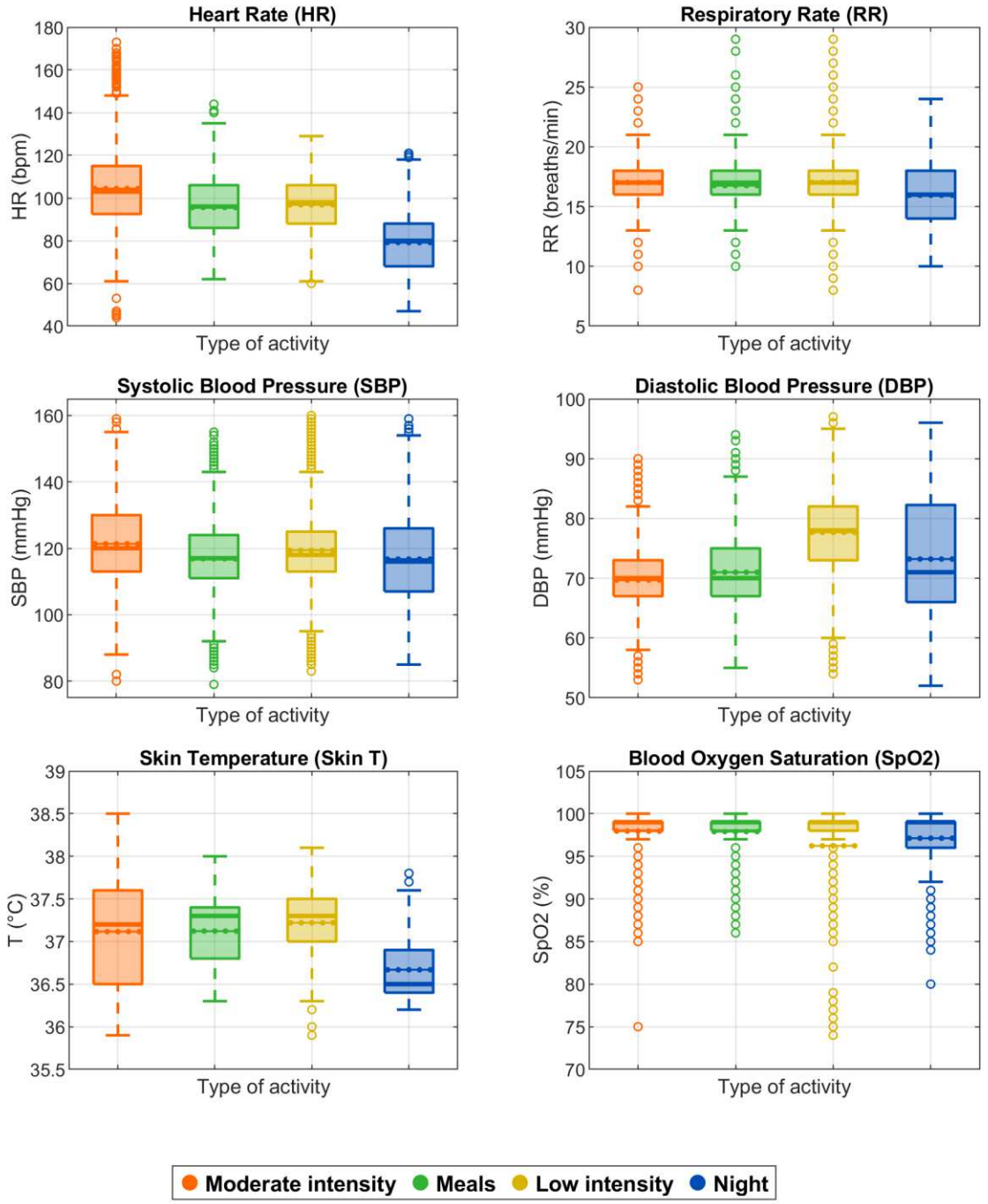


Figure 1: Boxplots representing the real data distribution, obtained from all the samples available for each type of activity across subjects for each acquired signal: HR, RR, SBP, DBP, T andSpO_2. Median value = solid line, mean value = dashed-dotted line, dots = outliers.

From a qualitative observation of Figure 1, it can be observed that HR reaches higher values during moderate intensity activity compared with meals and low intensity activity; in addition, it generally maintains lower values during night. RR shows similar distributions in all the day-life activities with a lower

mean/median value during night. Accordingly with HR activity, SBP boxplots shows slightly higher values during moderate intensity activity. DBP has a similar signal distributions during moderate activity and meals, but it assumes higher values during low intensity activity and it shows a higher variability during night. Skin T is more variable and reaches its higher values during moderate intensity activity, it shows similar values during meals and low intensity activity, while it assumes lower values during the night. SpO_2 distributions remain over 95% for all the considered activities, showing lower values within the 25^{th} percentile during night (note that during sleep subjects were all ventilated). Potentially dangerous SpO_2 values, lower than 90%, were recorded in 5.1% of samples during night, in 3.2% during low intensity activity, in 1.4% during meals and 1.2% during moderate activity. Low intensity activity shows the lower mean value and more outlier points with SpO_2 values lower 90%.

LMM results

Results of the LMM analysis indicate that the temporal evolution of all the analysed signals, except for the DBP, was different across the identified activities (i.e. moderate intensity activity, low intensity activity, meals and night). Table 4 reports the results of the ANOVA performed on the fitted LMMs, as well as the results of the post-hoc comparisons.

	LMM (interaction)				
	ANOVA p-value	**FStat**	**Post-hoc p-values (FDR corrected):**		**tStat**
HR	**< 0.001**	31.429	Moderate-meal	0.207	-1.262
			Moderate-low	**< 0.001**	8.319
			Moderate-night	**< 0.001**	6.640
			Meals-low	**< 0.001**	5.347
			Meals-night	**< 0.001**	4.474
			Low- night	**< 0.001**	-4.260
RR	**< 0.001**	22.979	Moderate-meals	**0.046**	2.162
			Moderate-low	**0.046**	2.260
			Moderate-night	**< 0.001**	5.615

			Meals-low	0.272	-1.208
			Meals-night	0.718	0.361
			Low- night	**< 0.001**	6.829
SBP	**< 0.001**	5.649	Moderate-meals	0.112	-1.782
			Moderate-low	**< 0.001**	-3.864
			Moderate-night	**0.013**	-2.855
			Meals-low	0.962	0.047
			Meals-night	0.671	0.585
			Low- night	**0.032**	2.408
DBP	0.382	1.022	Moderate-meals	/	/
			Moderate-low	/	/
			Moderate-night	/	/
			Meals-low	/	/
			Meals-night	/	/
			Low- night	/	/
Skin T	**< 0.001**	24.926	Moderate-meals	0.257	1.242
			Moderate-low	0.257	-1.307
			Moderate-night	**0.031**	2.560
			Meals-low	0.098	-1.969
			Meals-night	0.875	-0.158
			Low- night	**< 0.001**	8.519

Table 4: Results of statistical analysis on LMM modelled considering interaction between type of activity and time. Significant results are reported in bold.

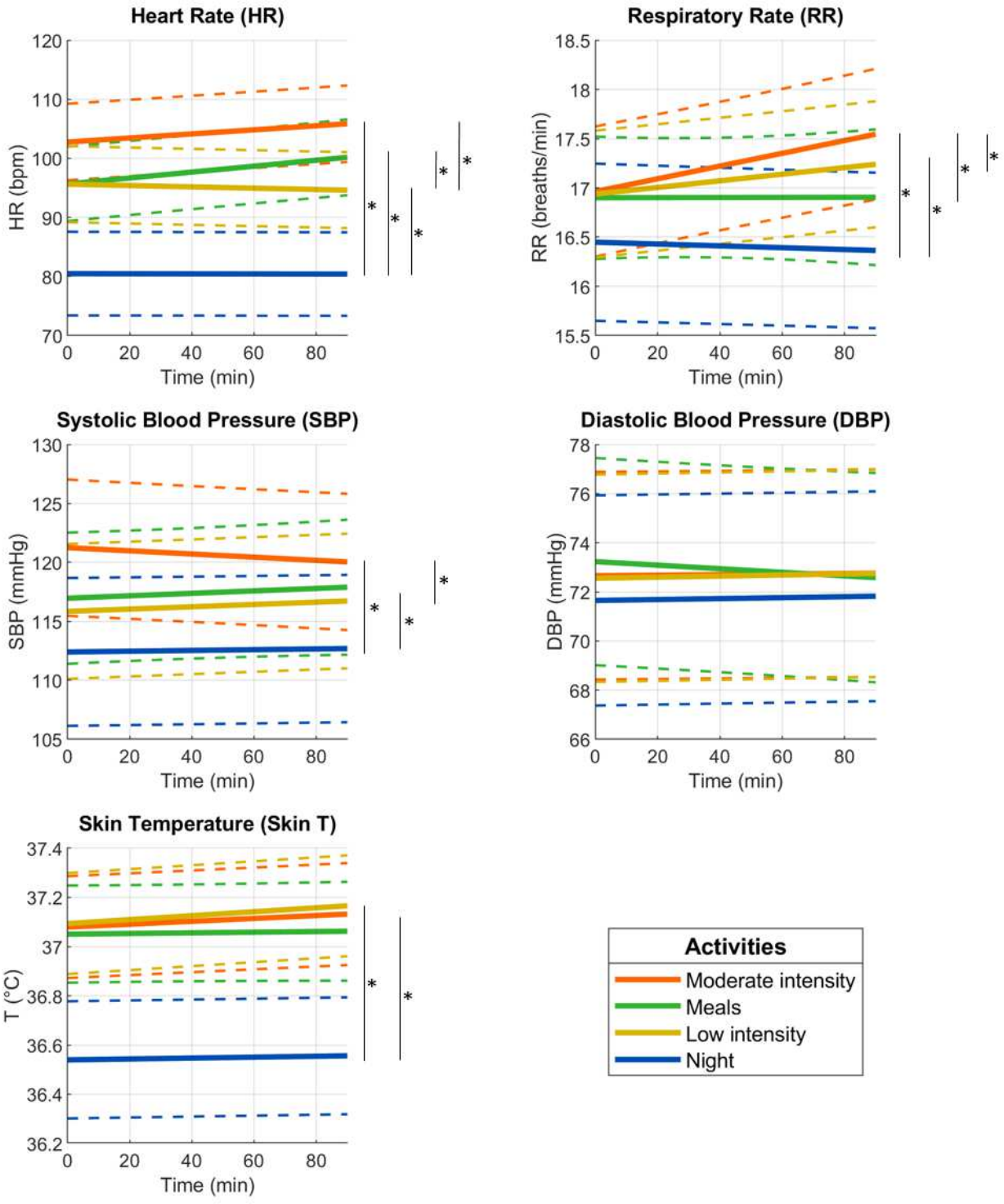
Figure 2 shows, for each signal, the prediction lines generated by the LMMs. A 90-minute time window was arbitrarily selected for visualization purposes. The solid line represents the model prediction, whereas the dashed lines indicate the 95% confidence intervals.

The temporal evolution of HR differed significantly across activities. Specifically, it showed an increasing trend during moderate activity and meals versus a slightly decreasing trend during low intensity activity and a stable trend during night.

Taking into account RR signal, we found an increasing temporal evolution associated with moderate intensity and low intensity activities both statistically different from the slightly decreasing trend observed during night. Moreover, the RR value increase associated with moderate intensity activity resulted to be steeper than the one associated with low intensity activity and also statistically different from the more stable trend recorded during meals.

The temporal evolution of SBP showed an increasing trend for low intensity activity, meals and night versus a decreasing trend for moderate intensity activity. Specifically, the SBP temporal evolution of moderate intensity activity significantly differed from both the ones of low intensity activity and night. Moreover, SBP associated with low intensity activity differed significantly from SBP trend during night. The temporal evolution of DBP remained stable across activities and did not show any statistical difference.

Finally**,** the temporal evolution of skin T showed slightly increasing trends during both moderate and low intensity activities significantly different from the more stable trend associated with the night period.



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232 *Figure 2: Model prediction for each signal (solid lines) and respective 95% confidence intervals (dashed lines). * next to each graph*
233 *identify statistical significant differences in post-hoc test.*

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DISCUSSION

To our knowledge, this is the first study that monitored continuously a set of physiological signals in patients with CCHS over an extended period (22-60 hours) during daily-life, with the aim of investigating how their temporal evolution differs across different types of activities. As highlighted in the Introduction, previous studies involving prolonged physiological monitoring in CCHS have either monitored a single or a limited set of physiological signals, have been conducted in controlled environments, or relied on relatively short recording periods. In addition, none has examined activity-dependent changes in the temporal evolution of these physiological signals.

Besides studies based on prolonged physiological monitoring, some investigations have assessed the physiological responses of patients with CCHS to physical activity, using standardized exercises(13–15) or passive induced movements (16) under controlled laboratory condition. However, their analysis relied on the comparison between baseline and peak values of the signal of interest, or on the comparison between average physiological values across predefined experimental phases; thus, also in these studies, the continuous temporal evolution of the data is not described and discussed. Some descriptions of the temporal evolution of physiological signals during specific type of activities are found only in the literature regarding healthy adolescents and adults (17–21).

Our findings will be discussed in the context of both the limited literature on CCHS and the available evidence in healthy populations, acknowledging that previous CCHS studies addressed different physiological questions and experimental settings from those investigated in the present work.

HR in healthy adolescents has been reported to increase linearly with workload, i.e. with the intensity of activity (17,18). Our results seem to confirm the increasing trend of HR during moderate activity also in patients with CCHS, and a similar finding was reported also by Silvestri et al. (14) , who showed a significant HR increase at activity peak in CCHS population during a walking protocol on a treadmill with progressive increases in speed and incline. Our results suggest a similar HR increasing trend during meals, which is the only activity that didn't significantly differ from HR temporal evolution in moderate activity. This result is difficult to be interpreted, also in light of no evidence about how the HR varies in healthy subjects in the

same condition. The act of swallowing itself may contribute to transient autonomic activation and HR fluctuations during meals, although its contribution to the progressive HR increase observed in our study remains uncertain. Thus, the HR increase during meals might suggest that meals represent a demanding activity for CCHS population. This is also supported by unpublished clinical observations that proposed the occurrence of psychophysical stress associated with meals in patients with CCHS. Moreover, the increase in HR might be triggered by a concomitant decreased of SpO_2, that is again an unpublished clinical observation. Unfortunately, we were not able to test this hypothesis due to the high data loss we encountered for the SpO_2 signal, but meals definitely represent an activity to be further investigated in CCHS population. During low intensity activity we found a slightly decreasing drift in HR in contrast with the HR trend observed in moderate activity. This is also in contrast with the study of Rabbia et al. (19) that reported, in a group of healthy adolescents, a constant trend of HR measured at 3 time points (5,10 and 15 minutes) in sitting position. Since all the activities we identified as low intensity were performed mostly in sitting position, our results might suggest an anomalous trend of HR in low intensity activity in CCHS population. Finally, during the nighttime our results show a relative stable trend of HR, with a temporal evolution that differed significantly from all the other activity categories. Although Dudoignon et al. (9) investigated heart rate variability rather than HR temporal evolution, their finding of reduced autonomic cardiac modulation in patients with CCHS is consistent with the limited temporal variation in HR observed during the nighttime in our cohort. This finding may reflect the impaired autonomic regulation that characterizes CCHS.

The LMM performed on the RR signal showed that, in our CCHS population, it increased during both moderate and low intensity activity. The increase was greater during moderate intensity activity, whose trend resulted to be statistically different from the one of all the other type of activities. This is in line with what has been observed in healthy population, in which RR usually increases progressively with exercise intensity (20), and also with the RR increase observed at maximal exercise by Paton et al. (15) in patients with CCHS during an incremental treadmill exercise test. During meals, RR signal exhibited a constant temporal evolution. Unlike HR, whose temporal evolution during meals was similar to that observed during

moderate-intensity activity, RR did not show a comparable pattern. Again, providing a physiological interpretation of this finding is difficult because of the scarcity of studies investigating physiological signal activity during meals both in healthy subjects and in patients with CCHS. Finally, the nighttime period showed a stable temporal evolution of RR, with only a slight decrease over time. This observation is consistent with our expectations, as all participants received ventilatory support during the night, likely contributing to the maintenance of a stable respiratory pattern.

Looking at blood pressure, the LMM showed a clear downward trend in SBP during moderate activity, in contrast with the increase reported in literature among healthy children during exercise (18). Both low intensity activity and meals showed an increasing temporal evolution, even if the only statistically significant difference is between moderate and low intensity activities. The trend observed in low intensity activity is in antithesis with the decline identified by Rabbia et al. (19) in healthy subjects. Thus, our results suggest that the control of SBP during both moderate and low intensity activity might be dysregulated compared to healthy subjects. During night, SBP temporal evolution was quite stable, with only a slight increase, and was statistically different from the temporal evolution observed during both moderate and low intensity activity. In patients with CCHS it is often observed an abnormal blood pressure pattern, with blood pressure being lower than in healthy individuals during wakefulness but higher at night, resulting in a nocturnal blood pressure drop of less than 10% (a phenomenon known as “nondipping”)(6). Our findings extend these observations by showing that blood pressure dynamics also differ between night-time and daily-life activities in CCHS.

No statistically significant differences emerged in DBP temporal evolution during the various types of activities; all trends, appear to be fairly stable, including moderate activity whose response in healthy subjects is controversial, with some authors reporting an increase and others reporting no changes or a slight decrease (18). Our results suggest that the mechanisms regulating DBP might be less sensitive to activity-related changes than those influencing systolic pressure.

As for skin T, the LMM identified fairly constant temporal patterns during meals and night, and a slight increasing temporal evolution during moderate and low intensity activities, which resulted to be

statistically different from the night pattern. Despite the thermoregulatory abnormalities already observed in the CCHS population(7), during daily-life activities the increasing trend is in line with what has been observed in healthy population (21). Indeed, in healthy individuals, skin T during exercise reflects the balance between metabolic heat production and thermoregulatory responses. Depending on exercise intensity, duration, and measurement site, skin temperature may initially decrease because of peripheral vasoconstriction but subsequently increase as cutaneous vasodilation facilitates heat dissipation. During the nighttime, skin T remained relatively stable and was lower than during daytime activities. This finding differs from the physiological circadian pattern generally observed in healthy individuals (22,23), in whom skin T typically increases during sleep owing to enhanced cutaneous vasodilation. This might reflect the altered thermoregulatory control associated with autonomic dysfunction in CCHS. Although Saiyed et al. (7) reported altered circadian thermoregulation in patients with CCHS compared with healthy controls, their study evaluated circadian temperature profiles rather than activity-dependent temporal dynamics, limiting direct comparison with our findings. Consequently, the physiological interpretation of the lower and stable nighttime skin T observed in our cohort remains uncertain and warrants further investigation. Moreover, the interpretation of skin T measurements should be made with caution, as recordings were obtained from a single chest-mounted sensor and may have been influenced by local environmental conditions and clothing. Indeed, skin T is a debated parameter; its value depends on the area where it is measured (24,25), showing even different trends if sampled in different body locations during the same activity.

As previously illustrated, despite using a medical grade device, it was not possible to analyse the temporal evolution of the SpO_2 due to the high data loss. From the acquired data we can qualitatively observe that SpO_2 values remained generally over the 95% threshold during all the activities analysed. Excluding nighttime, known to be the most critical situation for the CCHS population requiring ventilator support in most cases, our results show that low intensity activities had the lowest SpO_2 mean value and more outlier points with SpO_2 values lower than 90%. This suggests that low intensity activities might represent a potentially critical situation for CCHS patients.

LIMITATIONS AND FUTURE DEVELOPMENTS

The main limitation of this study is the small sample size, as only 11 patients with CCHS could be enrolled because of the rarity of the disease. In addition, although the wearable device was non-invasive, some participants perceived it as bulky and uncomfortable, which, in one case, limited the monitoring duration to 22 hours.

The classification of daily-life activities relied on activity diaries completed by the participants, which may have introduced inaccuracies in the assignment of recording windows to specific activity categories and, consequently, may have affected the estimation of activity-related differences. Furthermore, the high percentage of missing data in the SpO_2 signal prevented its quantitative analysis, limiting the multimodal characterization to the remaining physiological signals.

Another limitation is the absence of a concurrently monitored healthy control group. Therefore, comparisons with previous studies should be interpreted with caution, as they involve populations differing in age, experimental conditions, monitoring protocols, and measurement methodologies. In addition, the interpretation of our findings is constrained by the scarcity of previous studies investigating the temporal evolution of physiological signals during daily-life activities in patients with CCHS, making direct comparisons with the existing literature difficult.

Future studies should include larger multicentre cohorts and a healthy control group to strengthen the interpretation of activity-dependent physiological dynamics. Moreover, it would be valuable to investigate the joint temporal behaviour of multiple physiological signals by modelling their concurrent evolution within the same activity windows, thereby exploring the interactions between cardiovascular, respiratory, and thermoregulatory responses during daily-life activities.

CONCLUSIONS

This exploratory study provides the first characterization of the temporal evolution of multiple physiological signals in patients with CCHS during daily-life activities through prolonged continuous

multimodal monitoring, preliminarily investigating the temporal evolution of five physiological signals during different activities classified as low and moderate intensity, meals and night. Although preliminary, our findings expand the current knowledge of autonomic dysregulation in CCHS by showing that the temporal behaviour of physiological signals is activity-dependent (except for the DBP). While some of the observed patterns were consistent with physiological responses described in healthy individuals, others differed from the expected behaviour, suggesting disease-specific alterations in autonomic regulation. Furthermore, our results complement and extend previous evidence obtained from ambulatory monitoring and laboratory-based studies in CCHS by providing a dynamic characterization of cardiovascular, respiratory, and thermoregulatory responses during real-life conditions. Overall, these findings highlight the potential of continuous multimodal monitoring to improve the understanding of autonomic dysfunction in CCHS and provide a foundation for larger prospective studies.

DECLARATIONS

Ethics approval and consent to participate

The study followed the ethical standards of the Declaration of Helsinki, as well as national laws. The study protocol was approved by the Ethics Committee CET Lombardia 2 (Protocol number: L2-282, date of approval: March, 24th 2025). Participants and their parents, where minor subjects were involved, received a complete description of the study procedures and provided written informed consent for the participation in the study.

Availability of data and materials

The dataset analysed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

A.C., F.M., E.B., and C.P. conceptualized and designed the study; C.P., E.B, A.P., and R.R. defined the methodology; A.P. performed the analysis; A.P., C.P. E.B. and F.M. interpreted the results, A.P. and C.P. drafted the first version of the manuscript; all authors reviewed and edited the manuscript; A.C. and E.B. acquired the founds.

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