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Analysis of heart rate variability in children during high flow nasal cannula therapy

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Abstract

Objective: Heart rate variability (HRV) is a non-invasive measure of the interaction between the autonomic nervous system (ANS) and the cardiovascular system and an indicator of physiologic stress. HRV is proposed as an alternative biomarker to the effect of high flow nasal cannula (HFNC) therapy, a non-invasive ventilation mode, in children with severe respiratory disease. *Approach*: Seven children with severe acute respiratory disease were included in this pilot study. All of them received HFNC treatment. Standard physiological variables, such as heart rate (HR), breathing rate (BR) and blood oxygen saturation (SpO2) were analyzed during HFNC therapy. HRV, which includes the time domain parameters defined by the mean of RR intervals (avRR), the standard deviation of RR intervals (stdRR), the root mean square of differences between adjacent RR intervals (rmsSD), and the frequency domain parameters defined by spectral powers of low frequency (LF, 0.04 Hz–0.15 Hz) and high frequency (HF, 0.15 Hz–0.4 Hz) bands was also analysed during therapy. *Main results*: Only the time domain parameter rmsSD showed a significant increase (from 0.03 to 0.08 s, $p < 0.05$) between the middle and the end of the therapy. No significant changes were observed in HR, BR and SpO2 throughout the therapy. Of these three variables, only HR and BR showed a high and statistically significant positive correlation. *Significance*: HRV analysis seems to be a promising alternative biomarker to monitor the effect of HFNC therapy on children with severe respiratory disease.

1. Introduction

Heart rate variability analysis measures the variation in the sequence of heartbeat-to-heartbeat (RR) intervals.. It is a relatively simple and non-invasive way to monitor the autonomic nervous system (ANS) activity and to display the balance between its two main components; the sympathetic (SNS) and the parasympathetic nervous system (PSNS).

When sympathetic activity increases, there is a decrease in HRV, whereas when parasympathetic activity predominates, there is an increase in HRV. Therefore, HRV reflects how the ANS partly controls the cardiovascular system. A high HRV indicates a correct functioning of the ANS, with a predominance of the parasympathetic nervous system. However, a low HRV indicates an unbalanced or abnormal functioning, insufficient adaptability of the ANS, predominance of the sympathetic nervous system, which corresponds to a poor state of health (Shaffer, Ginsberg (2017))

Traditionally, HRV is calculated from ECG (Electrocardiogram) analysis, detecting the times of the R peak of each beat resulting in an RR interval series that is used to extract features in the time and frequency domain. The time domain HRV parameters evaluate the time variability between successive heartbeats, and the most commonly used are: mean of RR intervals, standard deviation of RR intervals, and root-mean-square of differences of successive RR intervals. On the other hand, power spectral analysis of HRV revealed the oscillations of the heart rate time series in the two main frequencies that resemble ANS activity; the low frequency component (LF) between 0.04 Hz–0.15 Hz, and the high frequency (HF) between 0.15 Hz–0.4 Hz. A power increase in LF is associated with an increase in

sympathetic cardiac modulation, whereas a power increase in HF is associated with an increase in parasympathetic cardiac modulation. The ratio between these two power increments, LF/HF, has been used as an indicator of the autonomic balance (Altuve 2017).

Respiratory diseases are associated to abnormal ANS activity, reflected by an imbalance between its two principal components, which makes HRV an ideal candidate to analyze respiratory diseases (Lewis *et al* 2006, Handa *et al* 2012). Furthermore, HRV has been shown to be an excellent way to follow and predict the prognosis of both adults (Skyba *et al* 2007, Borghi-Silva *et al* 2008) and children (Latremouille *et al* 2018) undergoing non-invasive respiratory therapies for the treatment of different types of respiratory problems.

High-Flow Nasal Cannula (HFNC) therapy has increasingly been used in children with severe respiratory disease in the last decade. HFNC deliveries heated (37 °C) and humidified (44 mg l^{-1}) oxygen enriched air with a high flow rate, and is a safe and well-tolerated alternative to more invasive ventilator supports, such as continuous positive airway pressure (CPAP) and mechanical ventilation. These other forms of non-invasive delivery are often poorly tolerated by children, but HFNC therapy has the potential to reduce the need for intubation and is well tolerated by most children (McKiernan *et al* 2010, Schibler *et al* 2011, Wing *et al* 2012, Kepreotes 2017, Franklin *et al* 2018).

The use of HFNC therapy in children has shown a reduction in several biomarkers of respiratory distress similar to those observed in other noninvasive respiratory therapies (ten Brink *et al* 2013, Metge *et al* 2014). However, the effect of the HFNC therapy through HRV analysis, both in the time and frequency domain, to the best of our knowledge has not been studied before.

Therefore, the aim of this work was to study HRV in children during HFNC therapy as a possible new biomarker of the clinical condition in children. To address this, we have monitored the evolution of both the time domain and frequency domain parameters of HRV during HFNC therapy in children together with other relevant physiological parameters as heart rate, respiratory rate (breathing rate), and SpO2.

2. Materials and methods

Seven children between 6 weeks and 10 years with different respiratory diseases (table 1) participated in a pilot study at the department of Women and Child of the Medisch Spectrum Twente (MST) hospital in Enschede, The Netherlands. The study was approved by the Ethics Committee of the hospital and written informed consent was obtained from both parents of each participant before operation.

HFNC therapy was used as non-invasive respiratory support in the seven children infants to improve the respiratory function. The therapy duration was different for each child, with an average value for the whole population of 65.28 ± 16.05 h (mean ± std).

Table 1. Demographic characteristic, working diagnosis and duration of the HFNC therapy in the study group of patients (n = 7).

id	Age(months)	Gender	Working diagnosis	Duration therapy (hours)
1	21	Male	RTI	96
2	1.5	Female	Bronchiolitis	60
3	10	Female	Bronchiolitis	76
4	128	Female	Pneumonia	63
5	3	Female	Bronchiolitis	58
6	3	Male	Bronchiolitis	47
7	3.5	Male	Bronchiolitis	57

RTI = Respiratory tract infection.

During the therapy, ECG (sample rate: 500 Hz) and photoplethysmography (PPG (sample rate: 62 Hz)) signals were continuously monitored through three electrodes placed on the chest skin and a pulse oximeter on fingertip, earlobe or foot. Both raw signals together the estimated values of HR, BR (calculated from the respiratory waveform obtained by measuring the thoracic impedance between two ECG electrodes on the patient's chest) and SpO2 every second were extracted from the Philips IntelliVue MX450 using ixTrend Express software (ixellence GmbH, Wildau Germany) and export to a PC. The first hours of therapy were not recorded in some cases due to logistic restrictions.

All data were analysed using Matlab R2018b (MathWorks Inc., Natick, MA). The statistical analyses were performed with IBM SPSS statistics 22 (IBM Corp., Armonk, NY).

2.1. HFNC device

The HFNC set-up was composed of an air/oxygen blender, an actively heated humidifier, a single heated circuit, and a nasal cannula (Optiflow Junior system from Fisher and Paykel Healthcare). At the air/oxygen blender, the inspiratory fraction of oxygen (FiO2) was set between 0.21 to 1.0 with a mixture flow rate up to 25 l min^{-1}. The gas was heated and humidified with the active humidifier and delivered through the heated circuit. The FiO2 was adjusted according to the targeted SaO2-level and the flow was adjusted as guided by the observed clinical effect. The patient inhales the adequately heated and humidified medical gas through a nasal cannula. There are four different cannula sizes for children: premature (red), neonate (yellow), infant (purple) and paediatric (green). The cannulas vary in diameter of the prongs, distance between the two prongs and the maximum flow rate. According to the guidelines of Fisher and Paykel healthcare, the nasal prongs should occupy 50 percent of the area of the nostrils, so a clear gap has to be visible between the prong and the nostril.

2.2. RR intervals detection

The RR interval, is the interval between successive R peaks, where R is a point corresponding to the peak of the QRS complex (ECG heart beat waveform) of the ECG wave (Rawshani). The RR interval time series were obtained from continuous electrocardiographic (ECG) recordings by detecting each QRS complex. We used the Pan and Tompkins (PT) algorithm (Pan & Tompkins 1985) to extract the QRS complex. In this algorithm, QRS detection is based on the analysis of amplitude, slope and width of QRS complexes.

2.3. Linear measures of HRV

We performed the HRV analysis using a timeframe of 5 min. For each segment, we detected the R peaks using the PT algorithm. After detection, we calculated the durations between successive peak locations to obtain RR intervals.

The linear measures of HRV include the time and frequency domain parameters.

The time domain measures are based on the beat-to-beat or RR intervals, which are analysed to give the next variables:

- avRR, the average of RR intervals.
- stdRR, the standard deviation of RR intervals.
- rmsSD, the root mean square of differences of successive RR intervals.

The frequency domain measures are obtained from the power spectrum of the RR interval series. To determine the power of the low and high frequencies, respectively, the R-peak data were resampled with a frequency of 4 Hz and detrended before calculating the periodogram with a rectangular window. We calculated:

- Normalized power of LF band [0.04 Hz–0.15 Hz]
- Normalized power of HF band [0.15 Hz–0.4 Hz]
- LF to HF power ratio (LF/HF).

Absolute power of LF and HF bands were normalized by dividing both powers by the summed absolute power of the LF and HF bands.

2.4. Statistical analysis

We compared the different parameters calculated (standard physiological and HRV variables) at two different points; in the middle (t1) and at the end (t2) of the therapy using the Wilcoxon signed rank-test which is a non-parametric statistical procedure.

To study the differences in HR, BR and SpO2 at three different points of the therapy, after the first 12 h (t0), at t1 and at t2, we used the Friedman test which is a nonparametric statistical procedure for three or more related samples

We reported for all parameters studied the median values together with the first (Q1) and third (Q3) quartiles.

3. Results

Seven children were included in this pilot study with different working diagnosis.

During the treatment, HR, BR and SpO2 were recorded each second and we averaged these physiological parameters every two hours for further analysis. Figure 1 illustrates the time series of vital signs for one child included in the study. There is a clear decrease in the HR and BR along the therapy towards values within the limits of what is considered normal for the specific age band (Hartman *et al* 2015). The SpO2 signal varied during the therapy in between a normal healthy range of 0.95–0.98. (Fouzas *et al* 2011).

Four children displayed a decrease in the respiratory rate during the therapy and in three of them, this decrease correlated positively with a decrease in the HR; these results are in agreement with previous studies where significant falls of both physiological parameters are shown throughout the HFNC (McKiernan *et al* 2010, Kallappa *et al* 2014, Milani *et al* 2016). For the whole population, we compared the median values of HR (bpm), BR (breaths/min) and SpO2; in the middle (t1) and end (t2) of the therapy (table 2) and no significance difference between these two moments in HR, BR and SpO2 ($p > 0.05$) were observed.

Furthermore, a high and statistically significant positive correlation was observed between the HR and BR in the majority of patients, with the Pearson correlation equal to 0.9 for the total population. However, no correlation was found between the HR and SpO2 and the BR and SpO2 (Pearson correlation $= 0.18$ and 0.33 respectively).

3.1. Heart rate variability analysis

HRV analysis was performed on 5-min ECG time series and as in the case of HR, BR and SpO2, we averaged each of the parameters obtained every two hours to compare the values of the time domain and frequency domain parameters from the HRV analysis at the middle and at the end of the therapy. Figure 2 shows avRR, stdRR and rmsSD variables from the time domain analysis of HRV (same patient as in figure 1). We appreciate how the three parameters increased during the therapy, which correlates with clinical recovery of the child and normal ANS activity.

The HRV frequency domain analysis for the same child showed similar improvements in the ANS balance; decrease in the low frequency band power (associated with decrease in the sympathetic activity) and increase in the high frequency band power (associated with increase in the parasympathetic activity) (figure 3).

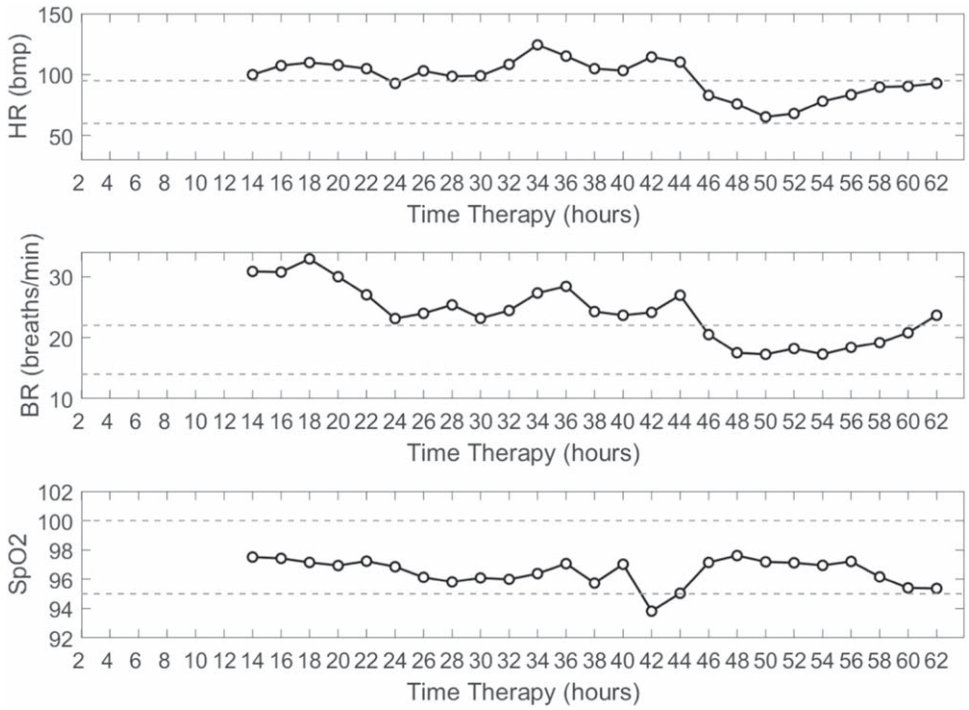

Figure 1. Vital signs from patient 4. From top to bottom; HR, BR and SpO2 (Black trace) averaged every 2 h. The dotted horizontal lines correspond to the upper and lower boundary of HR, BR and SpO2 for healthy children based on Hartman *et al* 2015 and Fouzas *et al* 2011.

Table 2. Median [first quartile—third quartile] values of HR, RR and SpO2 in two different points during the HF therapy (n = 7) and p-values from Wilcoxon signed rank-test.

Parameters	Median t1(Q1–Q3)	Median t2(Q1–Q3)	p-value
HR	120.80 (109.09–143.65)	134.47 (98.47–143.12)	0.735
BR	0.55 (0.51–0.78)	0.66 (0.4–0.72)	0.735
SpO2	96.35 (95.98–98.25)	96.69 (95.7–98.49)	0.612

t1—Middle therapy time point.
t2—End therapy time point.

For the whole population, we compared the median values of the time domain and frequency domain parameters of HRV analysis in the middle and end of the therapy (table 3). Our study group of children showed an increase of stdRR and rmsSD during the treatment, and this increase was statistically significant in the case of rmsSD ($p < 0.05$) (table 3). Only one patient displayed a different tendency both in the temporal and frequency parameters. In the frequency domain, the average values of LF power decreased and the HF power increased (table 3) and the ratio between both decreased which confirms with the time domain results an improvement of the cardiac autonomic balance.

As we have observed, the HRV analysis demonstrated both in the time domain and frequency domain a positive correlation with an improvement of the ANS activity. Except in the case of avRR, all the parameters showed a similar positive trend, although this was only significant for the rmsSD (table 3). However, the current small sample size suggests that a larger size could increase the significance of our results.

4. Discussion

The time domain measure rmsSD from the HRV analysis showed, in contrast to HR, BR and SpO2, a significant increase during therapy that related with an improvement in the functionality of the ANS and thus clinical recovery.

This pilot study investigates, to our best knowledge, for the first time both the time domain and frequency domain parameters of the HRV analysis quantified during the treatment of children with HFNC, together with the physiological variables that are normally monitored during this type of treatment.

The HRV is one of the most commonly used biomarkers in monitoring cardiovascular diseases (Thayer *et al* 2010, Karimi Moridani *et al* (2016)) and non-cardiovascular diseases (Lees *et al* 2018, Zaffalon Júnior *et al* (2018)). However, using HRV in respiratory diseases is not yet widespread, except in the evaluation and tracking of adult patients with severe chronic obstructive pulmonary disease (Roque *et al* 2014, Zamarrón *et al* 2014) and newborn infants with respiratory distress syndrome (RDS) (Cabal *et al* 1980, Ramanathan *et al* 2012, Javorka *et al* 2017). In case of children with respiratory conditions such as bronchiolitis or pneumonia undergoing non-invasive ventilation therapies,

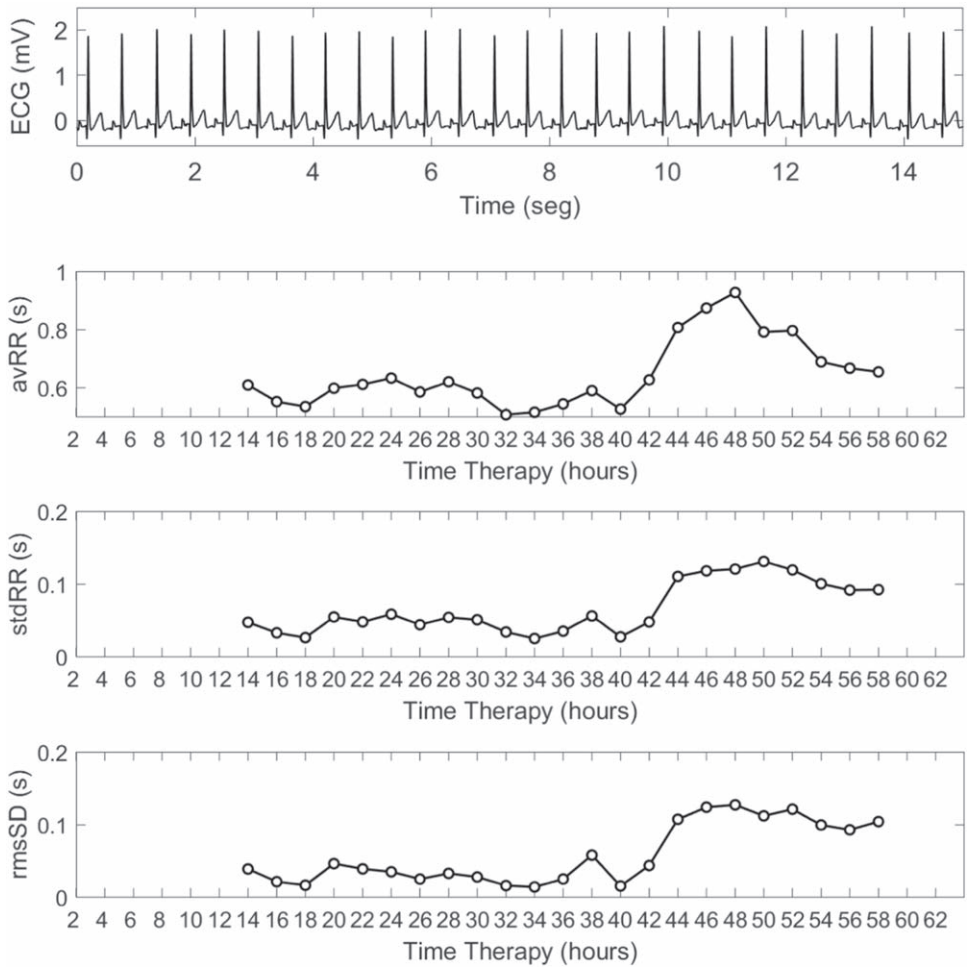

Figure 2. ECG and time domain analysis of HRV from patient 4. From top to bottom: ECG signal example (15 s) and avRR, stdRR and rmsSD (Black trace) averaged every 2 h.

including CPAP and HFNC, HRV analysis is not applied.

During HFNC therapy, the most commonly monitored and studied physiological parameters are HR, BR and SpO2 (Mikalsen *et al* 2016). Beggs and collaborators (Beggs *et al* 2014*)* showed in a comparative study between HF therapy and oxygen delivery via a head box in infants with bronchiolitis younger than 24 months of age, a significant increase in SpO2 in the first 8 and 12 h of the high flow therapy, but no significant change at 24 h of therapy. This seems to be consistent with our results (table 1), where no significant changes in these parameters were observed during the mid-phase and end-phase of the therapy, leaving as incognito if only changes occur at the beginning of the therapy. We also investigated in four patients (id $=$ 2, 3, 5 and 7), the SpO2 changes during the first 12 h of treatment, the mid-phase and the end-phase of the treatment, but no changes were noticed (table 4).

Similar studies showed a fall in HR and BR within the first 12 h of treatment (Bressan *et al* 2013, Kallappa *et al* 2014, Mayfield *et al* 2014) which continues to corroborate that the lack of changes in our data is due to the significant change in these variables are produces within the first 12 h of therapy, despite the fact that Milani and collaborators showed a decrease of the BR beyond the first 24 h of therapy (Milani *et al* 2016). However, it is important to note that not only the number of subjects in all these studies was much higher than in our case, but in all of them the effect of HFNC in children under 15 months with bronchiolitis was investigated.

In this study, we have introduced a non-invasive evaluation of the effect of HFNC, through HRV, in pediatric patients with respiratory diseases. A previous study investigated HRV in children (with an average age of 6 $\pm$ 2 months) with bronchiolitis while they were undergoing the conventional physical therapy (CPT) (Jacinto *et al.* 2013). Jacinto and collaborators showed that this therapy intervention restored the autonomic modulation patterns of HRV by improving the cardiac autonomic balance, which was confirmed by the significant reduction in the LF/HF ratio, which agrees with our result trends. Moreover, as in our study, no significant changes were observed in the respiratory rate and SpO2. We only found a study which displayed the results of comparing the variables

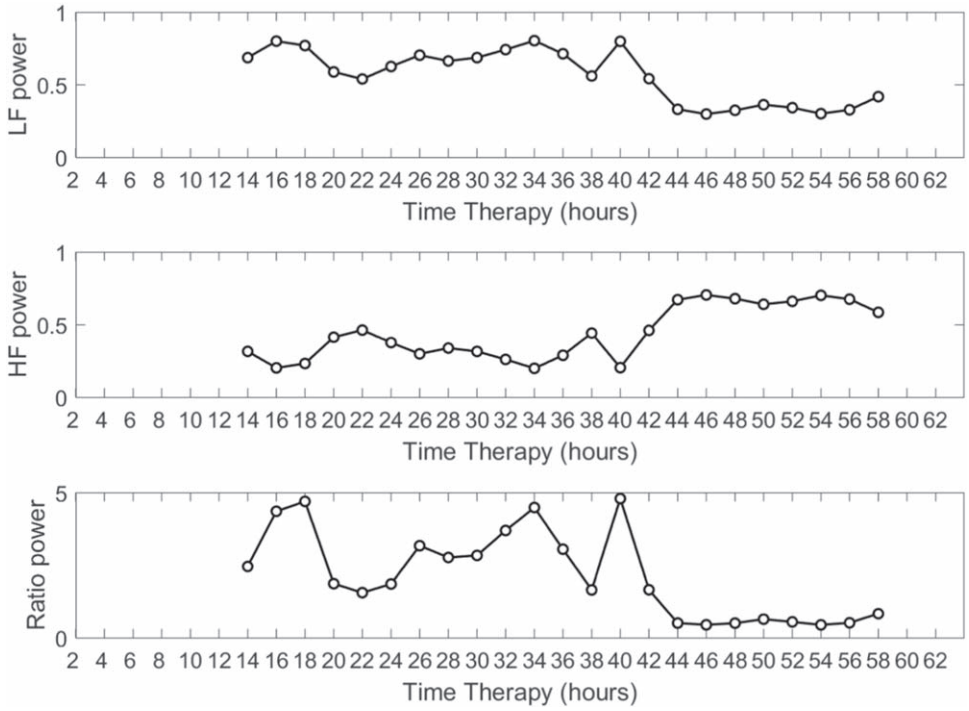

Figure 3. HRV frequency domain analysis from patient 4. From top to bottom: normalized LF power, normalized HF power and LF/HF ratio power (Black trace) averaged every 2 h.

Table 3. Median [first quartile—third quartile] values of the time domain and frequency domain parameters of HRV analysis in two different points during the HF therapy (n = 7) and p-values from Wilcoxon signed rank-test.

Parameters	Median t1(Q1–Q3)	Median t2(Q1–Q3)	p-value
avRR	0.49 (0.42–0.55)	0.44 (0.39–0.62)	0.49
rmsSD	0.03 (0.01–0.04)	0.08 (0.04–0.18)	0.043
stdRR	0.03 (0.02–0.04)	0.05 (0.03–0.12)	0.075
LF	0.69 (0.65–0.73)	0.42 (0.41–0.65)	0.091
HF	0.30 (0.26–0.34)	0.57 (0.34–0.58)	0.091
LF/HF ratio	2.79 (2.68–3.71)	0.98 (0.82–3.04)	0.063

t1—Middle therapy time point.
t2—End therapy time point.

from the HRV analysis during two different non-invasive respiratory supports after extubation in extremely preterm infants; in no case it compared the effect of NHFT (Latremouille *et al* 2018, Latremouille *et al* 2019).

Contrary to what we noticed in the HR, BR and SPO2 during the therapy, the different parameters obtained from the HRV analysis showed much more robust and sensitive for the child's clinical recovery during therapy. Except in the case of avRR, the time domain parameters displayed an increase between the middle and the end of the therapy. This increase in the temporal variability between successive heartbeats indicates a recovery of the autonomous nervous system that correlates with an improvement in the symptomatology of the children; remaining to know if this trend is also observed in the first hours of the treatment how it has been noticed in the physiological parameters routinely monitored (Bressan *et al* 2013, Kallappa *et al* 2014, Mayfield *et al* 2014, Mikalsen *et al* 2016).

Similar results were observed with the HRV frequency parameters which have the ability to discriminate between sympathetic and para-sympathetic contributions of HRV. The decrease of the power in low frequencies and the increase of power in high frequencies, between the middle and the end of the therapy correlate with an increase in the balance between the two components of the ANS, reflected also by a decrease of the power ratio of the two frequency ranges. These changes observed in the mid-phase and end-phase of the therapy would help to understand that despite the improvement in HR, BR and SpO2 during the first hours of therapy presented by other authors, this is sufficiently indicative to terminate the HFNC therapy.

One might question whether our results have a bias due to the circadian cycle, since previous studies have shown a circadian rhythm of heart rate and HRV in both infants and children (Massin *et al* 2000). However, it is not until after weeks or months that children acquire the circadian rhythm, in fact, Massin and collaborators indicated that the circadian variation of HR is observed in infants from 4 months onwards, and in the case of HRV from one year onwards. In our study, where more than half of the population is less than 4 months old, we observed HR changes due to the circadian rhythm only in patient 1. However, both t1 and t2

Table 4. Median [first quartile—third quartile]) values of HR, RR and SpO2 in three different points during the HF therapy (n = 4) and p-values from Friedman test.

Parameters	Median t0(Q1–Q3)	Median t1(Q1–Q3)	Median t2(Q1–Q3)	p-value
HR	138.30 (109.43–142.33)	125.65 (119.50–150.77)	135.20 (134.08–141.32)	0.77
BR	0.60 (0.52–0.64)	0.53 (0.51–0.72)	0.67 (0.65–0.71)	0.17
SpO2	96.61 (95.51–98.61)	96.32 (96.06–97.20)	96.77 (95.81–98.21)	1

t0—First 12 h therapy point.
t1—Middle therapy time point.
t2—End therapy time point.

occurred at the same moment of the circadian cycle but at different days, when the child was sleeping.

Previous studies have not investigated how HFNC therapy affects the ANS activity, despite the known relationship between respiratory diseases and the ANS imbalance. Our results indicate that monitoring HRV introduces a new perspective to assess the effect of HFNC therapy. This new non-invasive analysis can help clinicians to assess patient's condition and more efficiently apply this non-invasive respiratory therapy.

4.1. Study limitations

Two important limitations of the present study have to be mentioned. In the first place, the small sample size (n = 7) means that although the HRV analysis results showed the same positive trend only for one parameter, the changes were not statistically significant. Secondly, there is a lack of data during the first hours of therapy, despite the fact that throughout the therapy the different signals and physiological variables were monitored. These were extracted from the monitor at least 12 h after the beginning of HFNC therapy. Only four monitors had the output port needed to connect the monitor to the computer. During busier periods, these were sometimes already in use for other patients. The monitors could be swapped but then they had to be sanitized first, leading to missing data at the beginning of the therapy.

5. Conclusions

The result of the HRV analysis showed a positive recovery of the patients during the HFNC not observed in the traditional parameters monitored. Although only the rmsRR results were significant, the positive correlation of the trend of the variables with the clinical recovery of the patient suggests that HRV is an excellent clinical indicator candidate to objectively monitor the progression of the child's respiratory condition during high-flow treatment.

No changes were observed in the physiological variables normally studied, HR, BR and SpO2; although according to previous studies the physiological significant changes take place in the first hours of therapy, which we could not verify for logistical reasons. HR and BR displayed a high correlation, indicating the existing relationship between the degree of activity of the respiratory and the heart rate. However, there was correlation between HR and BR with SpO2.

Future work with larger samples will be required to further explore HRV as an indicator of disease progression. Finally, it would be interesting to compare the different parameters not only during therapy but before and after it.

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