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Heart rate variability in children with cyanotic and acyanotic congenital heart disease: analysis by spectral and non linear indices

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Abstract— **Congenital heart defects affect the efficiency and functionality of the heart, and autonomic control of heart rate and of circulation can display a pathologic behavior in order to compensate for the hemodynamic alterations due to disease. While previous works have investigated heart rate variability (HRV) in specific pathologies, e.g. tetralogy of Fallot, the goal of this study was to assess HRV in children with a congenital heart malformation taking into account the effects of cyanotic and acyanotic defects, and comparing pathologic children with age matched controls. HRV, approximate entropy (ApEn) and sample entropy (SampEn) were calculated to discuss the dynamics and complexity of heart rhythms, and to evaluate the potential impairment of control mechanisms.**

Analyses showed that low frequency (LF) power and total power of HRV were significantly higher in children with a condition than in healthy controls, independently of cyanosis. Non linear indices were also significantly higher in pathologic subjects. Significant differences in LF, total power, ApEn and SampEn were found among cyanotic, acyanotic and healthy children. These results suggested that children with a congenital heart condition display more complex HRV and sympathetic overactivity, which may be aimed at compensating for hemodynamic alterations. Further studies should investigate whether corrective surgery and rehabilitation can improve HRV and restore its physiological features.

I. Introduction

Congenital heart defects represent a large proportion of congenital disease and malformations. Although the advancements in surgical techniques have enabled to greatly improve the life expectancy and quality of patients suffering from congenital defects, such as tetralogy of Fallot (TOF), transposition of the great arteries (TGA), pulmonary atresia (PA) among others, the effect of corrective surgery and post-operative rehabilitation on the restoration of a physiological control of heart rhythms is not fully understood yet.

Congenital heart diseases significantly differ for the type of defects and dysfunctions they cause. However, a possible criterion to classify them independently of the specific etiology is based on the presence of cyanosis.

Acyanotic heart defects are characterized by the presence of a left-to-right shunt, which can induce pulmonary hypertension. Typical acyanotic congenital heart defects include interatrial communications (IAC), interventricular communications (IVC), patent ductus arteriosus (PAD), pulmonary valve stenosis, and aortic valve stenosis.

Cyanotic heart defects are typically caused by defects characterized by the presence of a right-to-left shunt. Cyanosis is observed because the mixture between venous and arterial blood in the arterial side of circulation increases the rate of deoxyhemoglobin above 3 g/dl blood. Typical cyanotic congenital heart defects are TOF, TGA, PA, and tricuspid atresia.

Heart rate variability (HRV) has been widely used to assess autonomic control of heart rhythm [1]. Alterations from spontaneous variability have been reported in several pathologies, not limited to the cardiovascular system. Previous reports have dealt with the analysis of HRV in children with congenital heart disease [2, 3, 4], but they either focused on some specific pathology (e.g., TOF [3, 4]), or measured and analyzed HRV indices several years after surgical repair [3], or observed HRV immediately after surgery [5].

In this paper, we aimed at quantifying HRV in children with congenital heart defects, in order to understand whether the presence of cyanosis can determine a different pattern in HRV with respect to HRV assessed in an age matched population of healthy children. Besides applying standard linear techniques to the analysis of RR interval series, non linear indices such as approximate entropy (ApEn), and sample entropy (SampEn) were applied, in order to derive further information on regularity and complexity of RR in pathologic children.

Given the low number of studies on the topic, and the difficulty to interpret the alterations due to different types of disease, and both the short term and long term impact of corrective surgery, non linear indices may be useful to

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understand the pathologic status of children with a congenital heart condition in terms of complexity of their HRV.

II. Material and Methods

A. Experimental Protocol

Fifteen children with congenital heart defects (CHD) and ten age-matched healthy children (HEA, age 15 ± 10 months, mean ± std) took part in the study. Eight children suffered from a cyanotic (CYA, age 20 ± 7 months) pathology, and the remaining seven had an acyanotic (ACN, age 28 ± 14 months) condition.

All parents of the enrolled children gave informed consent to the protocol, which was approved by the ethical committees of the Universidade Nove de Julho, Sao Paulo – SP, Brazil, and of the Hospital Sìrio-Libanês, Sao Paulo – SP, Brazil. The study was carried out at the Hospital Sìrio-Libanês, where the children with a condition were planned to have corrective surgery. Heart rate (HR) measurements were collected with the Polar S810i monitor, for 10 minutes, with the children lying comfortably in bed.

B. Heart rate variability analysis

HRV series were built from RR intervals identified from measurements. Three minute long, artifact free segments were selected from recordings for each child.

For each subject, mean value of RR interval duration was computed. Autoregressive (AR) spectral analysis was applied to estimate power spectra. Power density (in s^2) was determined in the very low frequency (VLF, 0.003 - 0.04 Hz), low frequency (LF, 0.04 - 0.15 Hz) and high frequency (HF, 0.15 - 1 Hz) bands. LF/HF ratio, normalized LF power, normalized HF power, LF+HF power and total power were computed, too.

Besides calculating standard, linear indices of HRV power spectra, the regularity and complexity of the HRV series was examined by computing non linear indices, i.e. Approximate Entropy (ApEn) [6] and Sample entropy (SampEn) [7]. Choice of parameters for these two indices was: ApEn (2, 0.15), SampEn (2, 0.15).

C. Statistical comparisons

As regards the statistical analysis of results, both t-test and Wilcoxon rank-sum test were performed to compare each population all pathologic subjects (CYA+ACN, i.e. CHD) vs. HEA.

One-way repeated measures ANOVA test was applied to compare healthy subjects, acyanotic (ACN) and cyanotic children (CYA). Post-hoc comparisons were performed by Fisher's least significant difference (LSD), to verify if any significance found by the ANOVA test was due to the difference between two specific populations.

III. Results

Table I shows time domain, spectral and non linear indices for each population included in the study, i.e. cyanotic and acyanotic children with a congenital heart condition, and healthy controls. In figure 1, results are reported after lumping all children with congenital heart defects (CHD, i.e. CYA + CAN) together.

No significant difference was found in heart rate of patients (0.70 ± 0.03 s, mean ± s.e.) vs. healthy controls (0.71 ± 0.03 s).

LF power in CHD (0.31 ± 0.07 s^2) was higher than in HEA (0.15 ± 0.04 s^2) (p-value = 0.06, rank-sum < 0.05), as well as LF+HF (0.44 ± 0.12 s^2 in CHD vs. 0.18 ± 0.04 s^2 in HEA, p-value = 0.07, rank-sum < 0.05) and total power (0.62 ± 0.17 s^2 in CHD vs. 0.24 ± 0.05 s^2 in HEA, p-value < 0.05, rank-sum < 0.05). Also ApEn (0.84 ± 0.02 in CHD vs. 0.66 ± 0.08 in HEA, p-value < 0.05) and SampEn (1.36 ± 0.13 in CHD vs. 0.90 ± 0.10 in HEA, p-value < 0.05) were significantly different, as they displayed higher values in pathological subjects.

ANOVA test showed a significant difference by comparison of CYA, ACN and HEA for the same indices. However, following application of post-hoc comparison tests, the significance of the ANOVA test was shown to be due to the ACN population.

IV. Discussion

The increased LF power, LF + HF, and subsequently total power found in the HRV spectral power of the children with a congenital heart condition may indicate the effects of a sympathetic overactivity in the control of heart rhythm. However, this was interestingly not consistent with the absence of significant differences in the heart rate of pathological vs. healthy children. This may in part be due to the relatively low variability of heart rate in children, especially neonates, as their heart rate is rather high in physiological conditions. However, the wide range of age in the children included in the study may affect the interpretation of heart rate and HRV.

The discussion of differences in LF and total power may be integrated by the inclusion of non linear indices of HRV, which represented the novelty of our study with respect to other data reported in the literature.

Both ApEn and SampEn were found to be significantly higher in pathologic children. This result showed a larger complexity of HRV series in children with heart condition, independently of the presence of cyanosis.

Combining the observations inherent to both spectral and non linear indices of HRV, it appears that the increased variability is obviously not an indicator of a physiological, healthy variability. Rather, although mean values of RR duration were not different in pathologic children and healthy children, the increased variability could reflect a less effective control of heart beat.

TABLE I : TIME DOMAIN, FREQUENCY DOMAIN, AND ENTROPY INDICES FOR EACH GROUP (DATA ARE EXPRESSED AS MEDIAN (25°, 75°))
*: P-VALUE < 0.05 °: RANKSUM < 0.05

	CIA	ACN	CHD	HEA
Mean RR (s)	0.68(0.63,0.719)	0.68(0.66,0.86)	0.69(0.60,0.70)	0.71(0.68,0.73)
ApEn(2,0.15)	0.85(0.82,0.86)	0.79(0.76,0.91)	0.86(0.78,0.92) *	0.73(0.56,0.85)
SampEn(2,0.15)	1.01(0.93,1.61)	1.71(0.94,2.00)	1.25(1.04,1.35) *°	0.98(0.84,1.13)
VLF (s2)	0.17(0.13,0.37)	0.31(0.20,0.52)	0.16(0.07,0.17)	0.05(0.03,0.06)
LF (s2)	0.20(0.16,0.31)	0.31(0.26,0.36)	0.19(0.14,0.20) °	0.12(0.07,0.21)
HF (s2)	0.03(0.02,0.04)	0.04(0.03,0.26)	0.02(0.01,0.07)	0.02(0.01,0.05)
LF%	79.41(73.22,83.13)	72.41(58.07,81.33)	81.73(63.64,88.80)	79.40(69.87,85.02)
HF%	9.72(7.81,16.38)	13.37(8.31,36.23)	12.04(6.31,24.69)	16.08(13.27,29.14)
LF/HF	8.42(4.85,10.70)	5.53(1.64,10.65)	7.14(2.91,14.11)	4.95(2.40,6.41)
LF+HF (s2)	0.24(0.18,0.35)	0.41(0.29,0.57)	0.22(0.21,0.25) °	0.14(0.09,0.29)
total power (s2)	0.42(0.37,0.84)	0.80(0.61,0.94)	0.38 0.30,0.39) *°	0.20(0.12,0.36)

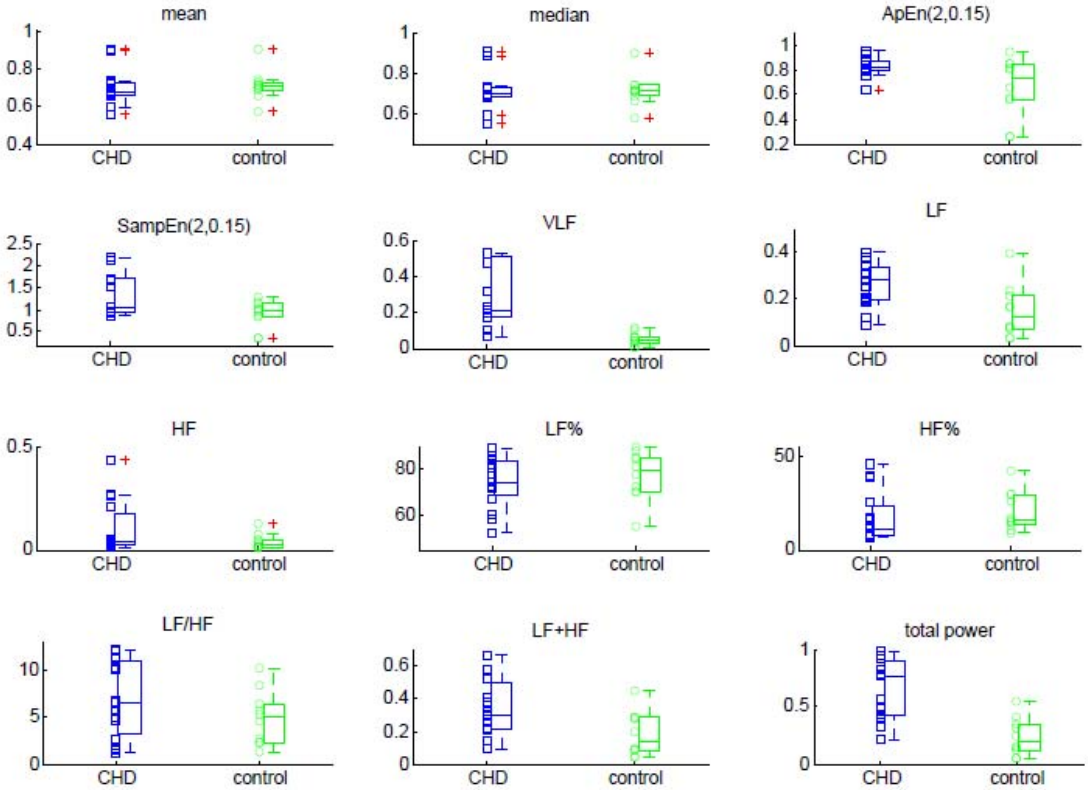

Figure 1: Time domain indices (mean, median of RR interval series, frequency domain indices, and non linear indices (ApEn, SampEn) of HRV: CHD (CYA + CAN children) vs. control children (HEA).

The larger value of LF power in patients could reflect the effort of the sympathetic system to compensate for other effects due to the pathology, although this did not translate directly into an increase of HR.

The higher complexity of HRV in children with a condition could also be consistent with the idea of a less efficient control, which produces larger oscillations on a beat-by-basis.

As regards the possible role of an increased sympathetic activity, it must be taken into account that congenital heart defects in children are extremely delicate for their hemodynamic implications. Moreover, a key problem is hemoglobin saturation, especially in cyanotic children, whose problem is that the right-to-left shunt redirects venous blood into arterial circulation, limiting the oxygenation of venous blood. Still, one of the most surprising results was that the

difference between pathologic groups and healthy controls was shown to be due to the acyanotic group (by means of post-hoc comparison tests). The availability of saturation signals would help to shed further light on this point, but it may be hypothesized that from the point of view of autonomic control saturation may be less important than the potential risk of pulmonary hypertension due to the left-to-right shunt typical of acyanotic pathologies.

V. Conclusion

In this study we proposed the simultaneous use of spectral indices and non linear indices of HRV to understand the differences in autonomic control of heart rhythm between children with congenital heart defects, independently of the presence of cyanosis and of the type of pathology, and healthy children. The use of non linear indices to characterize this population of pathologic children represents a novel approach, to our knowledge. Furthermore, non linear indices have been shown to be helpful to characterize HRV in fetuses and critically ill neonates [8].

We found an apparent augmented sympathetic activity in the children with a condition, but this was not reflected by an accelerated heart beat. Given the larger complexity of HRV series in these children, we hypothesized that both spectral and non linear analysis hinted at a less effective control of heart rate.

Future studies, besides the preliminary results presented in this study on a rather unique population, will take into account children following surgery and post-surgical cardio-respiratory rehabilitation to evaluate the effect of corrective surgery from the point of view of autonomic control of heart rate. The availability of further measurements, such as saturation and blood pressure, may enable to take into account the complex interactions between cardiovascular and respiratory control systems, which may help directing rehabilitation procedures following corrective surgery.

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