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Heart Rate Variability in Children Submitted to Surgery

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Abstract

Objective: Heart Rate Variability (HRV) is known to reflect the sympathetic/parasympathetic interaction on several physiological and pathological conditions such as the cardiac activity responsiveness to physiological and environmental stimuli. Therefore, it has been widely used to assess nervous autonomic fluctuations and their influence on sinus node. Studies on children have demonstrated the correlation between HRV and different parameters like age, gender, physical activity and autonomic diseases whereas little evidence exists of the effects of surgery and residual anesthesic drugs on HRV. The aim of this study was to define the possible role of minor surgery in HRV in healthy children.

Design: Observational prospective cohort study.

Setting: Pediatric Surgery Department of a tertiary, university-affiliated hospital.

Patients: 47 healthy children who were scheduled for elective minor surgery.

Measurements and main results: HRV measurements of 10 to 15 minutes were obtained before and after surgery, using a Holter recorder and the BioSigBrowser® software. Results showed significant differences in HRV time domain indices before and after surgery in younger patients and in frequency domain in the older ones. They also demonstrated decreased HRV indices until one hour after being submitted to surgery in both time domain and LF parameters, reflecting a parasympathetic withdrawal and sympathetic predominance. Differences were also found when analyzing other variables such as anesthetic drugs.

Conclusion: This study demonstrated that surgery has impact on Autonomic Nervous System function in healthy children but, independently of anesthetic drugs, type of surgery, age and existence of pain 60 minutes after surgery no difference in HRV measures was found and autonomic homeostasis was re-established. However, further investigation in this area is required in order to a better support of the role of HRV monitoring on early prognosis prediction and risk stratification in the surgical context.

Keywords: Heart rate variability; Autonomic nervous system; Children; Surgery; Anesthesia; Healthy

Introduction

Heart Rate Variability (HRV), defined as the variation of the interval between consecutive R peaks of the electrical heart beat signal obtained through the electrocardiogram (ECG) reflects the heart's capacity to respond to physiological and environmental stimuli [1,2]. Heart Rate Variability is widely accepted as a valuable tool to investigate the sympathetic and parasympathetic contribution to regulation of heart rate rhythm. Variations in heart rate may be evaluated by a number of methods (Task Force, 1996). Time and frequency domain measures, determined by either the heart rate or the intervals between successive normal complexes, are a widely used tool in the investigation of autonomic cardiovascular control.

Three main spectral components are distinguished and usually differentiated in the spectral profile (Task Force, 1996): (a) the high frequency (HF) band (0.15 to 0.40 Hz); (b) the low frequency (LF) band (0.04 to 0.15 Hz); and (c) the very low frequency (VLF) band (<0.04 Hz). Evidence suggested that HRV was a tool to understand the interplay between the sympathetic and parasympathetic nervous system on the regulation of cardiac activity and on assessing cardiac

health [3,5], so it was used as a marker of nervous autonomic modulation of sinus node [4], providing an insight into several conditions and enhancing risk stratification [2,5].

Reyes del Paso et al. [6], made a critically review of the state of research challenging the suitability of the LF component of HRV as an index of cardiac sympathetic control and the LF/HF ratio as an index of sympathovagal balance. They concluded that all HRV components predominantly relate to vagal control. However, it does not imply that they provide the same information about autonomic regulation. Each HRV component provides information about different physiological control mechanisms. HF oscillations relate to respiratory influences what reflect effects of respiration on heart rate (HR), also referred to as respiratory sinus arrhythmia (RSA). LF oscillations provide information about blood pressure control mechanisms such as the modulation of vasomotor tone including the so-called 0.1 Hz fluctuation. VLF power is related to kidney functioning and thermoregulation, meaning that HRV also gives information about sympathetic mechanisms (e.g., vasomotor tone fluctuations, rennin-angiotensin system) which manifest resonant phenomena through cholinergic oscillations in the sinus node [6].

Healthy children have higher ranges of normal respiratory rate and heart rate when compared to adults, which can interfere with Autonomic Nervous System (ANS) analysis [7,8]. Some authors suggest different ranges for heart rate and respiratory rate cited in international paediatric guidelines [8]. Since children can breathe at higher rates than 24 cpm we also calculated HFn+ corresponding to frequencies higher than 0.15 Hz (defined later) and can include all high rates of breathing.

Factors known to influence HRV indices includes age, gender, and physical activity [1] or non-physiological conditions, such as smoking, alcohol and drugs [3,5].

The main objective of the ANS is the maintenance of cardiovascular, respiratory, metabolic and thermal homeostasis, representing the primary defense against any internal or external factor jeopardizing systemic homeostasis [5]. The measurement of HRV from the ECG is a bedside, non-invasive and easy to perform method, which, by reflecting the balance of the ANS regulation of heart rate, detects the presence of ANS dysfunction [5].

In children, several studies have shown reduced or delayed cardio-vagal development in different pathologies such as diabetes mellitus [6-8], respiratory distress syndrome of the new-born [9-11], brain death [12] and sudden infant death syndrome [13,14]. There is also evidence of low HRV in functional pain conditions, anxiety and emotional disorders, which may indicate HRV as a potent biomarker of general stress and health [15-18].

Concerning the post-operative period, it is known, in adults, the correlation between ANS dysfunction and life-threatening complications after surgery [19-21]. The effect of anesthetics per se also affects ANS function. The ANS dysfunction represents a serious source of anesthetic risk affecting the outcome of patients undergoing surgery [5].

The aim of this study was to define the possible role of surgery in HRV in healthy children by HRV assessment both before and after minor surgery (76.7% correction of phimosis and/or inguinal, umbilical or abdominal wall hernia), accounting for several of its dimensions, namely, drugs involved, pain, airway access and surgical stress [5].

Methods

Study design

This observational prospective cohort study included a convenience cohort population of children who were scheduled for elective minor surgery at the Pediatric Surgery Department of a tertiary hospital, Sao Joao Hospital Center in Oporto, between September and November of 2015.

The study was conducted according to the Declaration of Helsinki and the Ethics Committee approved the project protocol. Written informed consent was obtained from the parents.

Sample

Participants included 47 subjects: 35 aged between 4 to 6 years (10 females and 25 males) and 12 aged between 14 to 16 years. Only healthy children, defined as children without any known congenital or chronic disease were enrolled in the study. Subjects under daily medication were also excluded.

Study measurement

HRV was assessed by high resolution 12 lead ECG acquired with a Holter H12+ Mortara recorder, exported using SuperECG propriety software from Mortara Rangoni, Italy and the BioSigBrowser software (BSB) [22,23]. Measurements of 15 minutes (min) were tentatively obtained at two different moments: the first before surgery, with the child seated in 45 degrees chair in the preoperative holding area and the second in the post-anesthesia care unit, with the subject still lying on the bed at 30 degrees. Both environments were dark and quiet. The time elapsed from the end of the anesthesia until the second HRV measurement was also registered.

Other study variables

Other variables were assessed as possible determinants, including physical activity [measured in hours per week (hours/week)] and Body Mass Index (BMI), calculated using the formula weight (Kg)/[height (m)] [2]. The percentiles of BMI were defined according to the growth charts developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion 2000 [21].

Pain after surgery was quantified in younger children according to a pain numeric rating scale (NRS) and in the older ones a visual analog scales (VAS).

Respiratory Rate (RespR) before and after surgery was collected. Heart Rate (HR) in beats per minute (bpm) and Systolic Blood Pressure (SBP) in mmHg before and after surgery were also collected and the difference between the pre and post-surgical values were calculated.

Information regarding the type of anesthesia and drugs used during the procedure was obtained from the anesthetic report.

In order to compare the differences between age and gender, the sample was divided into three groups: group A (n=10) including girls from 4 to 6 years old (yo), group B (n=25) including boys from 4 to 6 yo and group C (n=12) corresponding to male adolescents aged between 14 and 16 yo.

Data analysis

The graphical interface BSB [25] was used to perform the automatic ECG annotation and beat-to-beat series extraction. Namely, a multiscale wavelet-based ECG annotator previously developed and validated [26] was applied to obtain single lead (SL) based annotations and multilead based peak annotations obtained as the median mark of the 8 SL annotators for R peak from leads I, III, V1-V6. The interval RR(n) related to the nth beat is defined as the time from (n-1)th to the nth beat measured between consecutive R multilead based annotated R peaks.

The graphical interface BSB [22] was also used to obtain both "time domain" and "frequency domains" HRV measures following the standards defined by Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [2].

Series were then divided in short segments of a fixed duration of 5 min.

Each segment of analysis was detrended using the approach proposed by Tarvainen [28]. Series were assumed to be equally sampled at the local mean heart rate, as this has been shown acceptable for spectral analysis for frequencies far from Nyquist frequency [29].

HRV "time domain" local measures [2] were obtained over each available 5-min segment and includes "% HRM": mean heart rate (beats/min); "% SDNN": standard deviation of normal-to-normal (NN) intervals (milliseconds-ms); "% RMSSD": square root of the mean squared differences of successive NN intervals (ms) and "pNN50": the NN50 count divided by the total number of all NN intervals (%).

"Frequency domain" techniques, using a fast Fourier transform method applied to 5-min recording allow to estimate a spectrum in which two major bands of frequency assess ANS activity: low frequency (LF) band, from 0.04 to 0.15 Hz, is the expression of baroreceptor-mediated regulation and is mainly due to the contribution of sympathetic discharge; high frequency (HF) band, from 0.15 to 1.4 Hz, reflects the modulation of vagus nerve discharge caused by respiration [2]. We calculate also HFn+ (>0.15 Hz) since small children breathe faster and the window spanning of HF-HRV from 0.15 to 0.4 Hz could not be appropriate. This was calculated by the formula HFn ± (TP-VLF-LF)/TP.

Welch method in 64 points windows, with 50% overlap and 512 points for fast Fourier transform estimation was used over each segment. Non parametric (np) measures were taken as the power in each standard band (LF_np, HF_np), measured as the area under the spectra. LFn_np and HFn_np are power measures respectively at LF and HF bands, normalized by power in the band above 0.04 Hz, which is TP_np-VLF_np. Autonomic balance (B_np) was obtained as LF_np/HF_np and reflects the sympathovagal balance [5]. These measures were taken in normalized units.

Statistical analysis

Descriptive statistics are reported as frequencies for categorical variables and median (iIQR) or (minimum-maximum) for continuous variables. Patient and clinical characteristics were compared using Chi-square test or Fisher's exact test, as appropriate, for the categorical variables and Wilcoxon rank sum test or Kruskall Wallis test for continuous variables. All data were analyzed using SPSS ver. 22 (SPSS, Chicago, IL, USA). A P-value less than 0.05 were considered statistically significant.

Results

Characterization of each group relative to the parameters evaluated, including age, weight, BMI, physical activity, surgery duration and pre and post-surgical HR, respiratory rate (RespR) and systolic blood pressure (SBP) is shown at Table 1.

Group (n)	Age (yo)	Weight (kg)	BMI (kg/m^2)	Physical Activity (hours/week)	SBP (mmHg)		Surgery Duration (min)	Respiratory Rate (cpm)		Heart Rate (bpm)	
					Before Surgery	After Surgery	Before Surgery	After Surgery	Before Surgery	After Surgery	
A (10)	5 (4-6)	20 (18-28)	15 (13.6-16.8)	2 (0-3)	99 (86-112)	102.5 (90-111)	36.5 (23-56)	19.5 (17-28)	18 (15-25)	94 (76-109)	100.5 (83-127)
B (25)	5 (4-6)	20 (11-34)	15 (11-29.9)	1 (0-3)	98.5 (86-120)	104 (84-123)	29 (18-103)	20 (16-26)	19.5 (13-23)	88.5 (61-110)	91 (72-113)
C (12)	15 (14-16)	64.5 (44-104)	20.9 (16.3-32.1)	4.5 (2-10)	124 (100-142)	126 (105-137)	29 (12-130)	18.5 (14-23)	17 (13-24)	75 (61-108)	71.5 (51-101)
Total (47)	6 (4-16)	21 (11-104)	15.8 (11-32.1)	2 (0-10)	104 (86-142)	106 (84-137)	29 (12-130)	19 (14-28)	18 (13-25)	88 (61-110)	88.5 (51-127)
Values are expressed as median (minimum-maximum)											

Table 1: Description of the sample and assessed variables.

When analyzing the nature of the surgeries, 76.7% of patients had phimosis and/or hernia correction (inguinal, umbilical and abdominal wall), three patients (11.6%) had winged ear correction, three (7.0%) cutaneous lesion extraction and two (4.7%) excision of sacroccygeal cyst.

Participants BMI was categorized according to CDC Growth Charts into percentile<5 (n=5; 10.6%), percentile 5 to percentile 85 (n=34; 72.3%) and percentile>85 (n=8; 17%).

Physical activity was divided in three groups: less than 2 hours/week (n=32; 68.1%), 2 to 5 hours/week (n=10; 21.3%) and more than 5 hours/week (n=5; 10.6%).

When studying the influence of physical activity, three groups were formed: children who practiced less than 2 hours/week (n=32; 68.1%), children who practiced from 2 to 5 hours/week (n=10; 21.3%) and children who practiced more than 5 hours/week (n=5; 10.6%).

They were also divided according to surgery duration into three groups: those whose surgery lasted less than 30 min (n=26; 55.3%), those surgeries lasted from 30 to 60 min (n=17; 36.2%) and those whose surgery lasted more than 60 min (n=4; 8.5%). The median time of surgery duration in minutes was 29 ranging from 12 to 130 minutes and with IQR of 26 and 40 minutes.

Concerning the effect of time between surgery and the second measurement of HRV and in order to simplify the analysis, participants were divided in three groups: those whose measurement was performed in less than 30 min (n=15; 31.9%) after surgery, those in which it was performed from 30 to 60 min after surgery (n=23; 48.9%) and those whose measurement was taken more than 60 min after surgery (n=9; 19.1%). The median time between registration and surgery in minutes was 43 (22-57) minutes ranging from 7 to 115 minutes.

Pain after surgery was reported only in 17 (36.2%) cases with a similar distribution between groups A, B and C.

With regard to the anesthesia, all of the participants from A and B group were submitted to induction with sevoflurane, ten of them were also submitted to fentanyl (eight from A group and two from B group) and none of them were submitted to propofol. In C group, sevoflurane was used to induce anesthesia in nine cases, associated to fentanyl in eight of them and to propofol in six. Three cases were submitted to intravenous induction with propofol and, in one of them, in association to fentanyl. In summary, sevoflurane was used in 44 subjects, propofol in nine and fentanyl in seventeen.

The values of HRV parameters comparing the different groups (A, B or C) before and after surgery are expressed in Table 2. Group A (girls from 4 to 6 yo) and group B (boys from 4 to 6 yo) presented significant lower values of HRV in the time domain measures after the surgery while no difference was found in spectral components except for Group B that showed a significant decrease of HFn+. On the other hand, group C (boys from 14 to16 yo) showed a decrease in HF component, non-significant in HFn but significant in HFn+, and an increase in LFn values after surgery and, consequently, in balance (B). Furthermore, no significant differences were found in the time domain measures. Globally, significant differences were found for HRV decrease in the time domain measures and HFn+ component and an increase in LF component.

Group (n)	Measure	Before surgery	After surgery	Difference (before-after)	P (Wilcoxon test)
A (10)	SDNN	57.6 (48.6-70.8)	42.3 (24.3-54.5)	25.2 (-0.1-30.2)	0.037*
	RMSSD	40.0 (19.6-60.8)	20.1 (11.6-32.2)	22.5 (2.6-39.0)	0.013*
	pNN50	11.4 (2.5-19.4)	2.4 (0.2-10.2)	10.8 (-0.3-15.3)	0.028*
	LFn	1.7 (1.4-3.5)	1.9 (1.5-3.1)	0.2 (-0.3-1.4)	0.553
	HFn	38.6 (24.8-50.5)	37.9 (24.7-64.7)	-0.1 (-5.9-7.9)	0.959
	B(LF/HF)	0.07 (0-0.1)	0.1 (0.0-0.1)	0.0 (-0.07-0.06)	0.914
	HF+	0.98 (0.97-0.99)	0.98 (0.97-0.99)	-0.001 (-0.01-0.01)	0.646
B (25)	SDNN	66.6 (58.6-85.2)	52.9 (40.4-84.6)	14.9 (-2.3-27.4)	0.028*
	RMSSD	56.2 (41.3-71.3)	29.3 (16.9-71.8)	18.2 (7.6-42.8)	0.011*
	pNN50	22.2 (16.1-34.3)	5.6 (0.9-27.5)	13.1 (1.2-23.7)	0.004*
	LFn	1.7 (1.4-2.3)	1.9 (1.3-3.9)	-0.2 (-1.3-0.3)	0.072
	HFn	30.9 (24.4-40.9)	37.9 (28.5-48.1)	-1.8 (-18.7-5.3)	0.166
	B(LF/HF)	0.1 (0.04-0.10)	0.1 (0.0-0.1)	0.0 (0.0-0.0)	0.221
	HF+	0.98 (0.97-0.99)	0.97 (0.96-0.99)	0.005 (-0.002-0.15)	0.026*
C (12)	SDNN	76.4 (52.3-93.2)	65.7 (44.5-98.3)	-4.6 (-22.5-21.6)	0.638
	RMSSD	43.7 (18.5-69.7)	22.1 (16.4-78.9)	2.9 (-42.8-24.6)	0.875
	pNN50	17.6 (2.4-42.3)	3.3 (0.9-36.7)	3.1 (-7.6-13.8)	0.583
	LFn	6.2 (3.9-9.8)	8.9 (5.6-26.2)	-4.1 (-14.7-0.2)	0.023*
	HFn	61.8 (42.2-70.7)	59.8 (52.4-63.9)	1.9 (-14.2-14.2)	1

	B(LF/HF)	0.1 (0.1-0.19)	0.2 (0.1-0.4)	-0.07 (-0.3-0.0)	0.017*
	HF+	0.93 (0.89-0-96)	0.90 (0.78-0.96)	0.03 (0.004-0.15)	0.028*
All	SDNN	66.6 (55.4-80.8)	53.6 (39.6-78.1)	9.4(-5.5-28.5)	0.021*
	RMSSD	48.6 (35.7-70.7)	23.4 (15.9-50.6)	17.7 (-3.6-36.7)	0.003*
	pNN50	18.9 (10.1-32.8)	3.9 (0.9-25.3)	42.2 (-1.1-18.7)	0.00*
	LFn	2.1 (1.6-5.0)	2.8 (1.6-5.0)	6.3 (-2.4-0.3)	0.024*
	HFn	39.1 (26.2-50.5)	43.2 (31.2-62.2)	61.5 (-16.8-7.8)	0.288
	B(LF/HF)	0.1 (0.05-0.1)	0.10 (0.0-0.1)	0.1 (-0.05-0.0)	0.272
	HF+	0.98 (0.95-0.99)	0.97 (0.94-0.98)	0.06 (-0.002-0.02)	0.005*

Values are expressed as median (IQR-interquartile range); *Significant difference between measures before and after surgery (p<0.05)

Table 2: HRV parameters by age and gender.

No significant difference was found on HRV measures when comparing them by BMI percentile.

With respect to physical activity influence on HRV parameters before and after surgery, statistically significant decreases were found in the time domain measures in children who practiced less than 2 hours/week (SDNN: 63.3 (53.4-76.8) versus 51.2 (40.6-73.9), p=0.02; RMSSD: 48.6 (36.6-65.8) versus 23.4 (15.2-48.9), p=0.003; pNN50: 19.4 (10.2-32.5) versus 3.7 (0.8-21.4), p=0.002). No other significant findings related to physical activity were observed.

Comparing the groups by the surgery duration significant differences were observed between pre and post-surgical HRV values only in the group in which it lasted from 30 to 60 min and in time domain parameters, with decreased values in SDNN [62.9 (54.3-70.2) versus 36.1 (26.9-53.6), p=0.002], RMSSD [46.3 (27.3-62.0) versus 17.1 (12.5-20.1), p=0.001] and pNN50 [14.8 (6.3-20.6) versus 0.58 (0.3-2.4), p=0.001]. No differences were found in the frequency domain parameters in any of the groups.

When analyzing the effect of the time occurred since the end of the surgery until the measurement of HRV (Figure 1), a statistically significant reduction in RMSSD [43.3 (19.7-52.1) versus 19.2 (12.7-32.1), p=0.003] and pNN50 [12.6 (2.5-26.4) versus 7.2 (1.9-12.2), p=0,005] was observed in those patients whose HRV measurement was taken in less than 30 min after surgery. Those whose measurement was taken between 30 to 60 min after surgery presented a statistically significant decrease in pNN50 [28.7 (14.7-38.8) versus 8.4 (1.3-28.8), p=0.036] and LF [29.9 (23.8-39.4) versus 3.2 (1.6-5.3), p=0.013]. Beyond these, no other significant differences were found in the other HRV measures related to time after surgery.

The patients who have reported pain after surgery (Figure 2) showed a significant decrease in all time domain indices [SDNN: 63.3 (51.1-83.1) versus 48.7 (38.3-60.1), p=0.031; RMSSD: 44.1 (29.6-74.4) versus 19.2 (15.2-33.6), p=0.011; pNN50: 20.7 (6.3-36.4) versus 2.1 (0.5-11.9), p=0.002] while in those with no reported pain only pNN50 was significantly reduced [18.5 (12.9-32.5) versus 6.6 (0.9-28.5), p=0.043].

Analysis of propofol and fentanyl influence on HRV is presented in Table 3. Most of the patients (93.6%) were submitted to sevoflurane (only 3 were not) so the results of HRV parameters on sevoflurano are very similar to the general population posted on Table 2. In the group in which propofol was used there was only significant differences in LFn component, in balance (B) and in HFn+. Nevertheless, time domain parameters revealed to be significantly different among those cases in which propofol were not used during anesthesia. All patients that were submitted to propofol were from C group, they presented lower values of HR before and after surgery than the others were not submitted to propofol and HR lowered after surgery. SBP was lower in the patients who did propofol also.

		Measure	Before surgery	After surgery	p (Wilcoxon test)
Propofol (n)	Yes (9)	HR	76 (68-106)	71 (60-88)	0.032*
		SBP	127 (119-133)	129 (122-135)	0.889
		RespR	19 (15-21)	17 (16-20)	0.669
		SDNN	67.9 (49.7-102.9)	59.8 (38.7-109.1)	0.767
		RMSSD	44.1 (12.9-66.8)	18.1 (15.6-73.8)	0.953
		pNN50	17.3 (0.5-41.6)	1.5 (0.6-31.2)	0.953
		LFn	7.4 (4.5-10.7)	12.2 (8.0-29.5)	0.038*

		HFn	66.4 (43.3-70.1)	60.6 (47.3-64.2)	0.953
		B (LF/HF)	0.1 (0.1-0.2)	0.2 (0.2-0.6)	0.027*
		HFn+	0.92 (0.89-0.95)	0.87 (0.74-0.92)	0.038*
	No (38)	HR	96 (91-102)	99 (89-109)	0.049*
		SBP	100 (93-108)	104 (97-107)	0.081
		RespR	20 (18-22)	19 (17-22)	0.050*
		SDNN	65.3 (56.1-79.9)	51.2 (39.4-78.8)	0,007*
		RMSSD	50.9 (36.9-71.0)	25.2 (16.3-52.1)	0.001*
		pNN50	19.4 (12.0-32.8)	4.4 (0.9-25.6)	0.001*
		LFn	1.8 (1.5-3.6)	2.01 (1.6-3.9)	0.177
		HFn	33.7 (24.8-47.8)	39.6 (28.4-59.4)	0.252
		B (LF/HF)	0.1 (0.04-0.1)	0.1 (0.0-0.1)	0.573
		HFn+	0.98 (0.91-0.99)	0.97 (0.96-0.98)	0.064
Fentanyl	Yes (17)	HR	87 (77-105)	87 (72-100)	0.489
		SBP	112 (99-124)	109 (104-121)	0.571
		RespR	19 (18-21)	19 (17-22)	0.073
		SDNN	63.2 (50.9-79.1)	53.3 (32.1-75.9)	0.218
		RMSSD	41.9 (22.7-53.4)	20.5 (15.4-33.9)	0.033*
		pNN50	13.9 (3.9-30.2)	2.9 (0.5-12.5)	0.011*
		LFn	3.5 (1.7-6.2)	4.5 (2.1-10.2)	0.025*
		HFn	46.4 (30.6-64.1)	57.3 (36.0-63.9)	0.433
		B (LF/HF)	0.1 (0.04-0.1)	0.1 (0.1-0.2)	0.014*
		HFn+	0.96 (0.93-0.98)	0.96 (0.89-0.98)	0.021*
	No (30)	HR	87 (76.75-105.25)	87 (72-100.25)	0.097
		SBP	112 (99-124)	104 (96-107.5)	0.083
		RespR	19 (18-21)	18.5 (17-21.5)	0.228
		SDNN	70.1 (57.9-90.1)	53.6 (41.2-91.1)	0.039*
		RMSSD	58.3 (40.3-72.0)	29.3 (16.7-87.1)	0.027*
		pNN50	22.2 (15.8-37.0)	5.6 (0.9-28.3)	0.012*
		LFn	1.7 (1.5-3.6)	1.9 (1.4-4.1)	0.275
		HFn	43.1 (24.6-45.3)	38.2 (30.0-52.0)	0.509
		B (LF/HF)	0.1 (0.05-0.1)	0.1 (0.0-0.1)	0.446
		HFn+	0.98 (0.97-0.99)	0.97 (0.96-0.98)	0.136

Values are expressed as median (IQR-interquartile range); *Significant difference between measures before and after surgery ($p<0.05$).

Table 3: HRV parameters according to Propofol, Sevoflurane and Fentanyl.

Fentanyl effect on HRV parameters was related to significant changes in RMSSD, SDNN, LFn and in balance (B).

In those cases in which this drug was not used, significant decreases were observed in all time domain components. 88.8% of the patients who were not submitted to fentanyl did lumbar epidural anesthesia.

Discussion

Over the last years, literature has highlighted the relevance of HRV on assessing ANS status as a mean of predicting post-operative complications, considering surgery and all its implications (pain, anesthetic drugs, emotional distress) as a cause of autonomic disruption with effects on systemic homeostasis [5,16-18]. The analysis of HRV can complement the reasoning for invasive monitoring and may hopefully guide preventive strategies for risk reduction [24-26]. Thus, the post-operative period is a period of increased cardiovascular and respiratory risk and a decreased HRV is recognized to be a more powerful predictor for mortality [5].

On children, little information exists regarding surgery effects on HRV, which means that research in this area is required. With this study, we sought to determine HRV changes among healthy children submitted to minor surgery and presents descriptive information about each HRV parameter.

It is known that HRV reflects the fluctuation in autonomic inputs to the heart. Diminished HRV occurs when there's both autonomic inactivity and excessive sympathetic inputs [2], showing an ANS imbalance that may be induced by increased stress or autonomic neuropathy [30]. Time domain parameters (SDNN, RMSSD and pNN50) strongly reflect parasympathetic modulation of sinus node [4] and, although there´s not a consensus among the scientific community about frequency domain parameters, most authors consider HF component as an expression of vagal activity influenced by respiration and LF component as a reflection of both cardiac sympathetic and parasympathetic activity with predominance of the sympathetic discharge [5]. Thus, LF/HF ratio represents a sympathovagal balance [5].

Regarding the results, with an overall analysis, it is possible to conclude that surgery influenced HRV values of the entire sample independently of other variables, as showed in Table 2. These findings suggest an increase in sympathetic control of the heart or a decrease in parasympathetic control of the heart. Probably, in younger children, surgery influences parasympathetic activity the most whereas, in the older children, it influences mostly the sympathetic activity as found in previous studies that suggest a decrease in the influence of parasympathetic activity that occurs with increasing age [8].

Normal ranges of respiratory rate in children are still under discussion. Fleming et al. [7] created new centiles of respiratory rate in children demonstrating a decline in respiratory rate from birth to early adolescence decreasing from a median of 44 breaths/minutes at birth to 26 breaths/minute at age of two. In our study only four children presented a respiratory rate over 24 breaths/minute (maximum RR of 28 breaths/minute). Since HF-HRV is defined in a spaning 0.15 to 0.4 Hz we calculated HFn+ to include the patients with RR >24 breaths/minute, but no significant differences were found from the HF-HRV.

Although sometimes conflicting, information in literature demonstrated age related changes in HRV due to ANS maturation [31,32]. Some authors describe a gradual decrease of the sympathetic activity in the first decade of life [3,31], while others describe an increase of parasympathetic activity in the same period of time, reflected by increased values of all the time domain indices, followed by a gradual decrease [4, 32,33].

When comparing pre and post-surgical values between boys and girls, no significant differences were found in the same HRV parameters, which is consistent with previous studies that stated no differences in children HRV values according to gender [1,30].

Even though studies show a correlation between HRV and physical activity [1,34], in the present study, differences seen on HRV indices related to physical activity are probably biased by age because the group that practiced less than 2 h/week consists of younger children and the group that practiced more than 5 h/week is composed of the older participants.

Only the group in which surgery lasted from 30 to 60 min (Figure 1) revealed significant differences in time domain values, thus in parasympathetic modulation of ANS. One possible explanation could be the use of a lighter anesthesia used in short and less aggressive surgery with very low influence on ANS. There were only four cases in which surgery duration lasted more than 60 min (two adolescents), not enough cases to find any statistically difference.

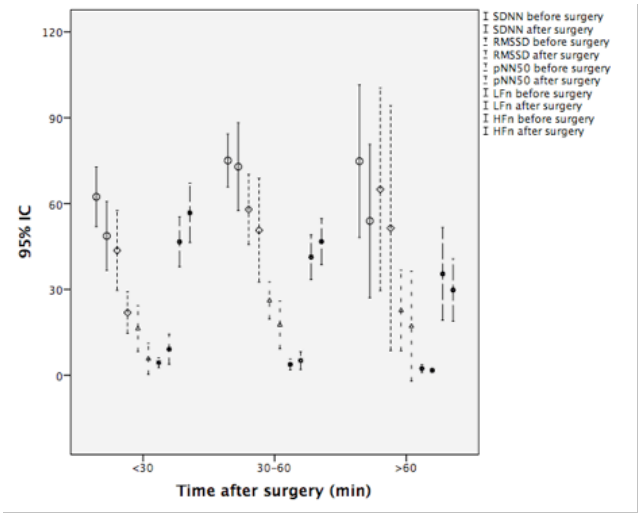

Figure 1: HRV parameters by time after end of surgery.

Results related to analysis of the time occurred from the end of the surgery until the measurement of HRV (Figure 2) showed a decreased parasympathetic activity in those patients whose HRV measurement was made in less than 30 min after surgery. A parasympathetic decrease and a sympathetic activity increase in those whose measurement was taken between 30 to 60 min after surgery was also found.

It is important to notice that, when measurements were taken after more than 60 min after surgery, no differences were found in HRV parameters. This can reflect a decreasing interference of surgery (and, possibly, the drugs used during the procedure) on ANS over time, with reestablishment of autonomic homeostasis. Despite the fact that our patients were only submitted to short duration anesthetic drugs, our study helps to support the time of 60 minutes as the minimum required period of standing in a post anesthesia care unit despite age or type of minor surgery.

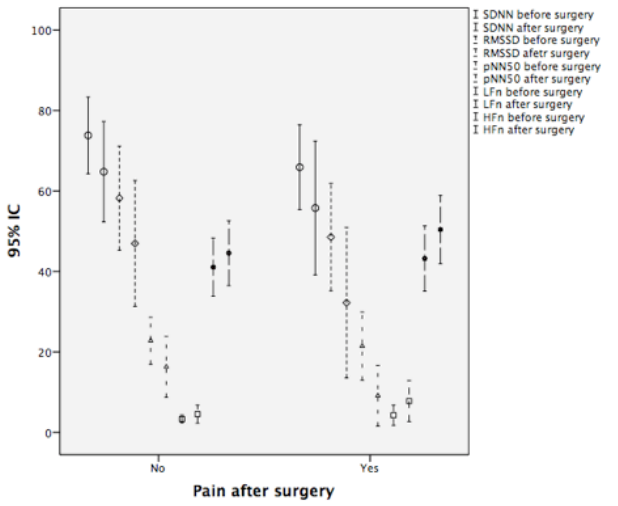

Figure 2: HRV parameters according to pain.

A diminished parasympathetic activity was seen on patients who have reported pain after surgery, as opposed to those who have not reported any pain (Figure 2). This result possibly leads to the establishment of a positive correlation between pain and parasympathetic inhibition and so a sympathetic dominance, also described in literature [35].

Anesthetics per se are known to affect ANS and HRV measurements. Despite this, during general anesthesia, anesthetic drugs may suppress autonomic activity oscillations and, depending on the combination of agents used, care must be taken when studying its influence on HRV [5,33]. Yet, inhalational anesthesia is known to negatively interfere with HRV indices [5].

HR decreases and SBP increases with age, this fact can explain why HR was lower and SBP higher, before and after surgery, in the cases submitted to propofol. Studies on propofol effect on HRV revealed a decrease in BP and HF proportional to the depth of anesthesia without any significant change on HR or LF, meaning that the cardiac parasympathetic nerve was inhibited to a higher degree than sympathetic nerve [5,36,37]. Other studies suggested propofol to induce cardiovascular depression by depressing sympathetic nervous activity [38].

In this study, results also showed an influence of propofol on the ANS activity. Patients who were submitted to propofol presented an increase of LF values and decrease of HF and HFn+ values after surgery. Reyes del Paso et al, suggested HRV power spectrum, including its LF component, is mainly determined by the parasympathetic system. These findings challenge the interpretation of the LF and LF/HF ratio as indices of sympathetic cardiac control and autonomic balance. According to this study findings we assume that our results suggests that propofol is an inhibitor of parasympathetic system that influenciate, in a higher proportion, the HF component. However, these results can have limited significance as propofol was only used in the older participants. In this population, induction of anesthesia with propofol was associated with a significant decrease in HR but not in SBP, as found in literature [36].

Sevoflurane was associated with decrease in BP or LF with little or no effect on the cardiac parasympathetic tone (5). The majority of our patients (93.6%) were submitted to sevoflurane so we cannot calculate the influence of this drug in our population. We found higher values of BP after surgery and no decrease of LF component. This finding could support the studies that suggest a mainly parasympathetic influence on LF component [38,39].

Few data on the effect of fentanyl on HRV are available [38]. Low dose fentanil led to sympathetic withdrawal and is believed to reduce LF power reflecting an increased parasympathetic tone [5]. We found that children who were on fentanyl showed a significant increase in LF and decrease in RMSSD and HFn+ component supporting the vagomimetic properties of this drug.

There are a number of studies that report a strong positive correlation between mean R-R interval and various time domain indices of HRV (e.g., the standard deviation of normal beats, SDNN) [40-42] such that HRV was greater during longer mean R-R intervals (slower heart rates) than at shorter mean R-R intervals (faster heart rates). Frequency domain analysis of HRV is similarly affected by mean heart rate. Sacha and Pluta [43] found that LF was directly related, while HF was indirectly related, to the average heart rate of the subject. As a consequence, they further report that LF/HF varied depending on heart rate, lower at slower and higher at faster heart rates. Thus, heart rate per se can influence LF/HF independent of changes cardiac autonomic nerve activity [39].

Respiratory parameters can also alter heart rate and R-R interval variability independent of changes in cardiac autonomic regulation (i.e., against a constant background level of automatic regulation) [44-48]. It is now well established that increases in respiratory frequency reduce the amplitude of heart rate oscillations [44,46,47] conversely, reductions in respiratory frequency increase HRV [44,46,47]. Thus, it is important to control breathing (paced or timed breathing) in order to interpret HRV data accurately. Brown and co-workers reported that respiratory parameters not only altered HF power but also strongly influenced the LF components of the R–R interval power spectrum, a component that previously was viewed to vary independently of changes in respiration [39].

Some studies suggest that opioids predominantly reduce LF power (reflecting an increased parasympathetic tone) and that general anesthesia with fentanyl leads to sympathetic withdrawal [49,50]. Our study showed an overall parasympathetic tone reduction on the patients submitted to minor surgery independently of receiving fentanyl or not. This can be explained by the use of epidural lombar anesthesia in 88.8% of patients not submitted to fentanyl. Tanaka et al. found that lumbar epidural anesthesia resulted in a significant increase in the low-frequency/HF ratio of HRV and unchanged spontaneous sequence baroreflex indices, suggesting sympathetic predominance [51].

With respect to sevoflurane impact on HRV parameters, although previous data suggests that it has little or even no effect on parasympathetic tone [52], no reliable conclusion can be made because almost all (but three cases) of the sample was submitted to sevoflurane during induction of anesthesia.

The interpretation of the results of this study naturally is subject to certain limitations. The main limitation is the measurement position. Although not very different concerning the degrees of inclination (45º before surgery and 30º after surgery) subjects were in a chair and sitting position before surgery and in a bed and supine position after

surgery. Nepal et al. [39], found that a significant decreased in HRV parameters reflecting vagal activity and reciprocal increase in sympathetic activity in standing as compared to sitting and supine but there was no significant change in HRV in sitting as compared to supine.

Moreover, the small sample size compared with the diversity of the variables studied and the fact that the observed variables were not normally distributed is a strong impeditive to achieve more conclusions about some of the variables analyzed, particularly regarding multivariate analysis. No significant complications after surgery were found in our sample so any relation between ANS dysfunction and perioperative complications could be established.

Data in literature suggests that the measurement of HRV is a good tool to evaluate perioperative risk in patients with suspected autonomic dysfunction, select individuals who need further cardiac testing and optimize pre-operative status [5]. In this study, only healthy children with no surgical complications were studied and, still, they showed reduced HRV measurements. Further studies in children with suspected autonomic dysfunction or complicated surgery are necessary to better support the role of HRV monitoring on early prognosis prediction and risk stratification.

In addition, several other aspects that are known to influence HRV measurements were not taken into account, such as physical and emotional stress due to anticipation of the surgery, other drugs used during surgery, volemic status and changes in position [5]. Finally, because the studied population was composed of children and measurements were realized in the presence of other people, it was not always possible to have the desired and ideal quiet environment.

Conclusion

The measurement of HRV can be used as a helpful, non-invasive, bedside tool to evaluate the risk in patients who are going to be submitted to surgery. This study showed a decreased HRV in healthy children until one hour after being submitted to minor surgery in both time-domain and low frequency-domain parameters, reflecting a parasympathetic withdrawal and sympathetic predominance. When analyzing all patients no difference was found in HF domain and in balance.

Younger patients presented significant differences in HRV in time domain measures before and after surgery and older patients showed a difference in low frequency spectral component. In healthy children submitted to minor surgery no significant ANS dysfunction was found over 60 minutes after surgery. This data can support the time of 60 minutes as the required period for standing in post anesthesia care unit.

Nevertheless, it is important to notice that further investigation about this subject is required in order to a better comprehension of ANS behavior, particularly in the pediatric age group.

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Statement

Ethics

The study was conducted according to the Declaration of Helsinki and the local Ethics Committee approved the project protocol. Written informed consent was obtained from the parents.

Disclosures

No conflicts of interest declared.

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