

Impaired cardiac autonomic nervous control after cardiac bypass surgery for congenital heart disease^{☆,☆☆}

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Abstract

We undertook a study to describe changes in heart rate variability (HRV) postoperatively in children undergoing cardiac bypass surgery for congenital heart disease (CHD). HRV was recorded for a 1-h period preoperatively and a 24-h period postoperatively in 20 children with CHD. We found a highly significant reduction in HRV in both time and frequency domain indices compared to preoperative values, which was sustained throughout the 24-h study period. There was a negative correlation between both time and frequency domain HRV measurements and length of cardiac bypass. HRV is reduced postoperatively and correlates with cardiac bypass time. Length of cardiac bypass time may be one mechanism whereby HRV is reduced following surgery.

Keywords: Cardiopulmonary bypass; Congenital; Autonomic nervous system; Heart rate

1. Introduction

Heart rate variability (HRV) is a measure of cardiac autonomic nervous control. In adult patients, reductions in HRV are independent predictors of mortality in congestive heart failure and after myocardial infarction [1–3].

In children with congenital heart disease (CHD), HRV is reduced compared to normal controls and is predictive of sudden cardiac death [1]. Following cardiac surgery for congenital heart disease, HRV is further reduced and may remain reduced years after operation [2, 3].

The purpose of this study was to investigate cardiac autonomic function following cardiac bypass surgery for CHD, by recording HRV in the immediate 24 h period postoperatively, and to compare this to preoperative HRV values. We also wished to assess whether postoperative HVR was affected by length of cardiac bypass.

2. Methods

This descriptive cohort study was conducted in the paediatric intensive care unit (PICU) and paediatric cardiology ward of The Royal Hospital for Sick Children, Glasgow. Children were included if they were <16 years of age and were to undergo cardiac bypass surgery for CHD. Children were excluded if they had a history of arrhythmias, had a

pacemaker, or if they required cardiac pacing postoperatively. Approval was obtained from the Local Ethics Committee prior to study commencement and informed parental consent was obtained for all participants.

2.1. HRV recording

HRV was recorded for 1 h preoperatively (24–48 h prior to surgery) and for a 24-h period immediately postoperatively on return to PICU.

A 3-channel Holter monitor was used for recording (Pathfinder 700 series, Reynolds Medical Ltd, UK). After skin preparation, electrodes were placed in lead positions 11, V₁ and V₅. A built-in clock was started after electrode attachment.

2.2. HRV analysis

A digital commercial Holter scanner was used to analyse HRV in the time and frequency domain (Pathfinder and HRV Tools™ software, Reynolds Medical Ltd, UK, on a PC running Windows 2000™). Noisy data and artefacts were excluded from analysis. The following time domain parameters were measured from the Holter recording: 1) the sum of all pairs of adjacent NN intervals differing by >50 ms (sNN50), 2) the standard deviation of all valid NN intervals in the recording (SDNN), 3) standard deviation of the average of valid NN intervals in 5-min segments in the recording (SDANN), 4) the average of the hourly means of S.D.s of all NN intervals in 5-min segments in the recording (SDNNi) and 5) the average of the hourly square root of the mean

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Table 1
Subject demographics

Subject	Age (years)	Diagnosis	Operation
1	5	ASD	ASD repair
2	6	TGA, post switch, MR	MV replacement
3	0.1	Truncus	Truncus repair
4	5	ASD	ASD repair
5	0.5	Anomalous LCA	LIMA graft
6	0.5	VSD, PFO	VSD, PFO repair
7	0.4	AVSD	AVSD repair
8	16	Branch PA stenosis	Patch enlargement PAs
9	4	DILV, TGA, VSD	TCPC/damrus
10	14	Sub aortic membrane	Membrane resection
11	0.5	AVSD	AVSD repair
12	1	VSD/RVOTO	VSD repair/resection RVOTO
13	5	Partial AVSD	AVSD repair
14	0.5	VSD	VSD repair
15	0.8	AP window	AP window repair
16	5	TA/VSD/PS	TCPC
17	5	PA/AVSD	TCPC/PA reconstruction
18	5	TA/VSD	TCPC
19	15	TGA/VSD/MR	MV repair
20	0.5	VSD	VSD repair

ASD, atrial septal defect; TGA, transposition of great arteries; MR, mitral regurgitation; MV, mitral valve; LCA, left coronary artery; LIMA, left internal mammary artery; VSD, ventricular septal defect; PFO, patent foramen ovale; AVSD, atrio-ventricular septal defect; PA, pulmonary artery; DILV, double inlet left ventricle; RVOTO, right ventricular outflow tract obstruction; AP window, aorto-pulmonary window; TA, tricuspid atresia; PS, pulmonary stenosis; TCPC; total cavo-pulmonary connection.

of the sum of the squares of differences between adjacent NN intervals (RMSSD).

Frequency domain analysis was performed using a fast Fourier transform algorithm. An analysis period of 5 min and a resample rate of 4 Hz were used. A Hamming windowing function was applied to minimise spectral leakage between segments. Power spectral analysis was reported as high frequency power (HF, range 0.15–0.4 Hz), low frequency power (LF, range 0.04–0.15 Hz), and total power. The HF:LF ratio was also calculated. All values were calculated preoperatively and at 1 h, 6 h, 12 h, 18 h and 24 h postoperatively.

Other data recorded included patient age, diagnosis and operation, cardiac bypass time, cross-clamp time, incidence of cardiac arrest, and mortality.

2.3. Statistical analysis

As this was a descriptive study no data were available to inform a power calculation. We recruited the maximum

number of patients possible within the 1-year time constraint of the study. Correlations were used to investigate relationships between quantitative variables. Response variables were modelled over time using a general linear model and comparisons were done with pre-op levels using the Bonferroni method for multiple comparisons. All analyses were done using Minitab, version 14, with a significance level of 5%.

3. Results

Twenty-seven patients were recruited for the study and results were obtained for 20 (11 males and 9 females). Five patients were excluded because they received external cardiac pacing postoperatively, three for complete heart block and two for sinus bradycardia. Two patients had accidental disconnection of the Holter monitor and insufficient data for analysis. No patients had a tachyarrhythmia postoperatively. The age range was from 1 month to 15 years. Diagnosis and operation undertaken are listed in Table 1.

All cases involved a period of cardiac bypass and 16 cases involved a period of cross-clamping. Length of PICU stay ranged from 1 to 23 days (4.6 ± 6.6 , mean \pm S.D.) and hospital stay from 5 to 38 days (11.5 ± 8.9). All patients had standard intensive care monitoring postoperatively. All patients received analgesia with morphine 20 μ g/kg/h and dopamine 5–10 μ g/kg/min in the immediate postoperative period. There were no episodes of cardiac arrest in the study population and all patients survived to discharge.

3.1. Time domain HRV

There were significant reductions in all time domain measures of HRV at all time points postoperatively compared to the pre-op values (Table 2 and Fig. 1), except for the reduction of sNNS50 which did not reach statistical significance at 6 h ($P=0.07$) and 12 h ($P=0.059$). There were negative correlations between all time domain measures of HRV postoperatively and both cardiac bypass time and cross-clamp time (Table 3). The negative correlation between SDNNi and cardiac bypass time was statistically significant ($P=0.035$).

3.2. Frequency domain HRV

HRV total power, high frequency power and low frequency power was significantly reduced at all time points post-op,

Table 2
Time domain analysis of HRV

Time post-op	Time domain index				
	sNNS50	SDNN (ms)	SDANN (ms)	RMSSD (ms)	SDNNi (ms)
Pre-op	80 (6–183)	33 (25–65)	19 (15–44)	15 (8–25)	27 (13–45)
1 h	11* (2–26)	14* (10–18)	11* (7–15)	5* (3–9)	7* (3–12)
6 h	27 (7–113)	19* (12–27)	16* (9–20)	8* (5–14)	9* (6–18)
12 h	14 (8–32)	15* (8–20)	12* (6–15)	6* (4–17)	8* (5–16)
18 h	10* (2–25)	14* (12–25)	10* (7–18)	6* (3–11)	10* (6–13)
24 h	7* (3–21)	22* (12–28)	17* (7–26)	6* (4–11)	10* (6–18)

Values are median (IQR, Q1–Q3). *Post-op vs. pre-op, $P<0.05$. HRV, heart rate variability.

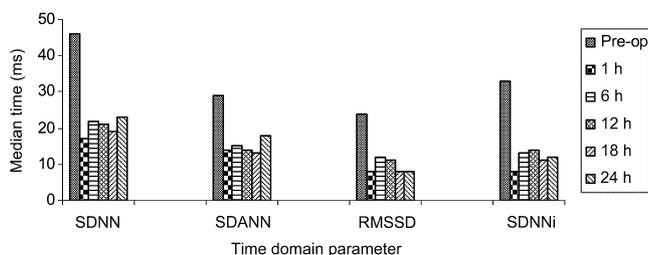


Fig. 1. Time domain measures of HRV pre- and post-op. Significant reduction in SDNN, SDANN, RMSSD and SDNNi at all time points post-op vs. pre-op. ($P < 0.05$).

Table 3
Correlations with time domain HRV

	Age	Bypass time	Cross-clamp time
sNN50	0.12 (0.56)	-0.28 (0.25)	-0.21 (0.40)
SDNN	0.36 (0.13)	-0.36 (0.13)	-0.35 (0.15)
SDANN	0.29 (0.23)	-0.28 (0.24)	-0.33 (0.18)
RMSSD	0.29 (0.23)	-0.40 (0.09)	-0.28 (0.25)
SDNNi	0.43 (0.07)	-0.49 (0.04)	-0.39 (0.10)

Values are given as correlation, r (P -value).
HRV, heart rate variability.

compared to pre-op (Table 4 and Fig. 2). There was no significant difference between the HF:LF ratio post-op and pre-op. There were negative correlations between all frequency domain measures of HRV postoperatively and both cardiac bypass time and cross-clamp time. The negative correlation between total power and cardiac bypass time was statistically significant ($P = 0.048$) (Table 5).

4. Discussion

Markers of autonomic control, including HRV, are a useful predictor of mortality in adult patients with cardiovascular disease and HRV is reduced in children with CHD [1–6].

HRV can be reported by time domain and frequency domain analyses. Time domain indices are derived from simple statistical calculations based on inter-beat intervals. Frequency domain analysis assesses heart rate variance as a function of frequency. The total power spectrum is an expression of overall variability reflecting the combined effects of sympathetic and parasympathetic control of HRV. The power spectra can be subdivided into high and low frequency ranges. HF power represents vagal activity. Controversy exists as to whether LF power represents sympa-

thetic control alone or a combination of both sympathetic and parasympathetic control [7–9].

To our knowledge, this is the first study to monitor HRV in the immediate 24 h post-op and we demonstrate a significant fall in HRV in both time domain and frequency domain parameters. This reduction in HRV was present from 1 h post-op and sustained for the first 24 h.

These findings of reduced HRV post-op in children with CHD are in accordance with prior studies; Gordon et al. demonstrated reduced frequency domain measures, although no preoperative data were obtained for comparison [5]. Heragu et al. have shown a reduction in time and frequency domain measures of HRV compared to pre-op, but post-op measurements were made on average 5.8 days following surgery, and not in the immediate 24 h after surgery [9]. Kaltman et al. have also demonstrated a reduction in LF power early after cardiac surgery in newborn infants with single ventricle physiology [10].

The mechanism of this reduction in HRV is unclear. That both LF and HF were reduced post-op, without significant change in the HF:LF ratio suggests that both parasympathetic and sympathetic activity were reduced. This may be due to reduced sensitivity of the sinus node to autonomic nervous input, or alternatively to a central suppression of autonomic stimulation, or a combination of both. Factors which may potentially alter autonomic regulation at this time include the direct effects of surgery [11], the length of cardiac bypass and cross-clamping, and the many pharmaceutical agents used in the peri-operative period. HRV may also be influenced by many additional factors including circulating catecholamines, stress, acid-base status, myocardial ischaemia and reperfusion. Unravelling the confounding effects of these different factors was beyond the scope of this study due to the small numbers studied.

We demonstrated a significant negative correlation between SDNNi and cardiac bypass time, and total power and cardiac bypass time. Length of cardiac bypass time may be one mechanism whereby HRV is reduced in the immediate postoperative period. This is in accordance with Heragu's group who saw greater reductions in time domain parameters in the group of post-op patients with longer bypass times [6]. A criticism of our study is the heterogeneous nature of the population studied, both in terms of age and surgery performed. Future studies should investigate changes in HRV in a more homogenous group and involve comparisons with a control group of children undergoing surgery which does not involve cardiopulmonary

Table 4
Frequency domain indices of heart rate variability

	Total power (beats/min ² /Hz)	LF power (beats/min ² /Hz)	HF power (beats/min ² /Hz)	HF:LF
Pre-op	345 (162–2199)	125 (46–592)	21 (7–189)	0.21 (0.14–0.4)
1 h	20* (5–70)	1* (0–3)	1* (0–2)	0.52* (0.13–2.3)
6 h	64* (30–257)	7* (2–52)	3* (1–44)	0.78* (0.09–3.3)
12 h	73* (20–282)	10* (2–69)	3* (0–22)	0.31* (0.12–2.2)
18 h	109* (36–176)	18* (3–42)	2* (1–21)	0.26* (0.1–2.8)
24 h	59* (21–136)	8* (2–25)	3* (0–19)	0.47* (0.13–1.9)

Values are median (IQR, Q1–Q3). *Post-op vs. pre-op, $P < 0.05$.
HF, high frequency; LF, low frequency.

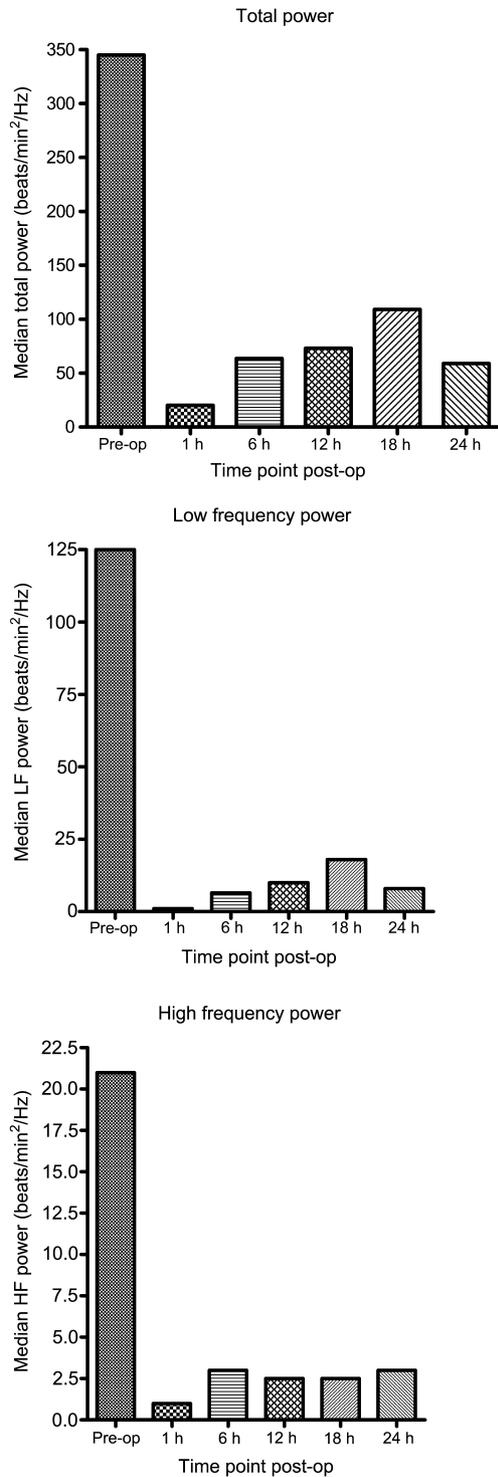


Fig. 2. Frequency domain measures of HRV pre- and post-op. Significant reduction in total, HF and LF power at all time points post-op vs. pre-op ($P < 0.05$).

bypass. It was also beyond the scope of this study to investigate the potential underlying mechanisms whereby cardiac bypass time was correlated with HRV, which may include factors such as duration of hypothermia and amount of cardioplegia. Studies involving a larger number of children would be required to further clarify this.

Table 5
Correlations with frequency domain HRV

Power spectrum	Age	Bypass time	Cross-clamp time
Total	0.35 (0.13)	-0.439 (0.048)	-0.338 (0.15)
LF	0.245 (0.30)	-0.303 (0.19)	-0.267 (0.2)
HF	0.083 (0.73)	-0.293 (0.21)	-0.126 (0.59)
HF:LF	0.283 (0.23)	-0.229 (0.33)	-0.242 (0.30)

Values are given as correlation, r (P -value).

HRV, heart rate variability; HF, high frequency; LF, low frequency.

5. Conclusion

We have demonstrated a highly significant fall in all time and frequency domain measures of HRV in the immediate 24 h post cardiac bypass surgery in children with CHD. Frequency domain analysis suggests that both sympathetic and parasympathetic cardiac control is affected. There was a significant negative correlation between both time and frequency domain HRV measurements and length of cardiac bypass. Further studies are needed to investigate the mechanisms of changes in HRV and its role as a potential predictor of outcome.

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