

Total cavopulmonary and atriopulmonary connections are associated with reduced heart rate variability

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Abstract

Aim—To determine whether cavopulmonary connections are associated with abnormalities of heart rate variability.

Methods—Heart rate variability was studied by 24 hour Holter monitoring in 39 patients (mean (SD) age 12.2 (4.1) years) who underwent cavopulmonary connection operations (partial in 12, total in 13, and atriopulmonary in 14). Two control groups were used: 18 healthy children (11.1 (2.5) years) and 16 patients (11.7 (4.3) years) undergoing cardiovascular surgery for biventricular repair of congenital heart disease. All patients were in sinus rhythm and had normal left ventricular function. Four time domain indices were calculated: mean duration of RR intervals (RR), standard deviation of all RR intervals (SD), square root of the mean squared differences of successive RR intervals (r-MSSD), and percentage differences of successive RR intervals of > 50 ms duration (pNN50). Four frequency domain indices were calculated: total power (TP), low frequency (LF), high frequency (HF), and the LF:HF ratio.

Results—Heart rate variability indices were identical in the two control groups. Significantly reduced heart rate variability was found in patients with total cavopulmonary connections and atriopulmonary connections compared with the two control groups. In patients with partial cavopulmonary connections, heart rate variability was reduced compared with healthy controls. No differences in heart rate variability could be related to clinical status (New York Heart Association functional class), number of surgical interventions, or presence of right atrial enlargement.

Conclusions—Patients with cavopulmonary connections have significantly reduced heart rate variability and a particularly low vagal drive.

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Keywords: heart rate variability; cavopulmonary connections; autonomic nervous system; paediatric cardiology

The Fontan operation and its variants provide palliative surgical treatment for children with cardiac malformations not suitable for biventricular repair.¹ Late atrial arrhythmias are a major complication of these operations.²⁻¹¹ Risk

factors for atrial arrhythmias identified in clinical series are age at surgery, atrial size, haemodynamic variables, type of Fontan circulation, and duration of follow up.²⁻¹¹ In various cardiovascular diseases, arrhythmias have been shown to be related to alterations of the autonomic nervous system.¹²⁻¹³ The rich network of autonomic ganglia located in the root of the caval veins and in the myocardium of the right atrium¹⁴⁻¹⁶ might be damaged during the construction of a cavopulmonary connection. Therefore abnormalities of the balance of the autonomic nervous system may be another important factor in the initiation of arrhythmias in patients with cavopulmonary connections. We therefore studied 39 patients with a cavopulmonary or atriopulmonary connection to determine whether Fontan interventions are associated with abnormalities of heart rate variability.

Methods

Thirty nine patients with a cavopulmonary connection were recruited to the study over a period of one year. Mean (SD) follow up after surgery was 5.8 (3.4) years. Twelve patients had a partial cavopulmonary connection, 13 a total cavopulmonary connection, and 14 an atriopulmonary connection. All patients were in sinus rhythm with normal atrioventricular (AV) conduction. None had experienced arrhythmias. Systolic function of the univentricular heart evaluated by echocardiography was considered normal. Patients received no anti-arrhythmic drugs or drugs known to modify measures of heart rate variability.¹²

A first control group included 18 healthy children referred to our institution to evaluate a history of palpitations. No arrhythmia was found in these subjects. A second control group included 16 patients who underwent biventricular repair for congenital heart disease. All these individuals had a normal 12 lead ECG (except for right bundle branch block in patients with closure of ventricular septal defect) and normal echocardiography. Their data are summarised in tables 1 and 2.

HOLTER RECORDINGS AND ANALYSIS

All subjects underwent 24 hour Holter monitoring. Two channel recordings (CM1 and CM5) were made. Tacker recorders (Reynolds Medical, St Germain en Laye, France; and Rozinn Electronics, Technimed, Saint Leu la Foret, France) were used. All recordings were analysed by using a Holter analysis system (ELA Medical, Montrouge, France). The data

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Table 1 General characteristics of subjects studied

	TCPC	APC	PCPC	Biventricular repair	Healthy controls
Number	13	14	12	16	18
Age (years)	11.4 (2)	13.8 (3.2)	11.2 (6.2)	11.9 (4.5)	11.1 (2.5)
Age at surgery (years)	6.6 (3.2)	5.6 (3.4)	6.7 (4.6)	1.6 (1.3)*	–
Follow up (years)	4.9 (3.4)	7.0 (2.8)	4.4 (3.3)	10 (3.7)*	–
NYHA I	9	7	5	16	18
NYHA II	4	6	7	0	0
NYHA III	0	1	0	0	0
NYHA IV	0	0	0	0	0
No RAE	12	1	11	15	18
Moderate RAE	1	2	1	1	0
Severe RAE	0	11	0	0	0
NI < 2	5	12	8	15	0
NI > 2	8	2	4	1	0

Values are n or mean (SD).

* $p < 0.0001$ v TCPC, APC, and PCPC.

APC, atrial cavopulmonary connection; NI, number of interventions; NYHA, New York Heart Association functional class; PCPC, partial cavopulmonary connection; RAE, right atrial enlargement; TCPC, total cavopulmonary connection.

Table 2 Congenital heart disease in the subjects studied

	TCPC	APC	PCPC
Univentricular heart	6	2	1
Tricuspid atresia	4	7	10
Pulmonary atresia and intact ventricular septum	1	1	2
Hypoplastic right ventricle	1	0	1
Complete atrioventricular canal with hypoplastic left ventricle	0	3	0

APC, atrial cavopulmonary connection; PCPC, partial cavopulmonary connection; TCPC, total cavopulmonary connection.

were reviewed and edited manually by a physician. After classification of QRS configuration, the frequency histogram of RR intervals was displayed and ECG strips of the intervals in both tails of the RR distribution were manually confirmed until no QRS complex was mislabelled as either an artefact or an ectopic beat. Only normal to normal intervals were included. Tapes were eligible only if they had more than 18 hours of analysable data.¹²

HEART RATE VARIABILITY ANALYSIS

The heart rate variability analysis was made using the version 2.00 Elatec (ELA Medical).

Time domain and spectral domain indexes were calculated for the length of the recordings.

Time domain analysis included the following indices: mean duration of RR intervals (RR; ms); standard deviation of all RR intervals (SD, ms); square root of the mean squared differences of successive RR intervals (r-MSSD, ms); and percentage differences between adjacent RR intervals of > 50 ms duration (pNN50; %). SD quantifies the variation in heart rate on time intervals ranging from minutes to hours, and is influenced by both short term (respiratory) and long term (physical activity, circadian pattern) changes in heart rate.¹² pNN50 and r-MSSD estimate short term variations in heart rate variability and predominantly reflect vagal activity.¹²

Spectral measures (*frequency domain analysis*) were computed using the fast Fourier transform algorithm. To obtain variance reduction, sequential averaging of the spectrum was used. A spectral plot for one hour was the average of the spectra over two minute periods (256 points). A Hanning windowing function was applied to minimise spectral leakage between segments. Power spectra from sequential windowed segments were averaged over each hour

and over the entire 24 hours. Spectral plots allowed the identification of two major peaks: a low frequency component (LF, 0.04–0.15 Hz) and a high frequency peak centred around the respiratory frequency (HF, 0.15–0.4 Hz). Total power spectrum (TP, 0.01–0.4 Hz) and the LF:HF ratio were computed. The power within each band was expressed in ms^2 . TP is an expression of the overall variability.¹² HF is a marker of vagal activity.¹² There is disagreement over the LF component. Some investigators regard it as a marker of sympathetic activity while others consider it an index influenced by both sympathetic and vagal systems.¹² LF:HF is considered to reflect sympathovagal balance.¹²

STATISTICAL ANALYSIS

Data are expressed as frequency for the nominal variables, as medians for the ordinal variables, and as mean (SD) for continuous variables. For each variable, the independence of the observations was controlled by the runs test and the normality of the distribution by using the Wilk-Shapiro test. Nominal variables (sex) were compared using the χ^2 test or the Fisher exact test as appropriate. Differences between groups were tested by one way analysis of variance (ANOVA). If the distribution of the variable was not normal or the test for the homogeneity of the variance gave a significant result, we used the Kruskal–Wallis test. If a significant p value was obtained, post-hoc comparisons were made using the Tukey's HSD multiple range test or the non-parametric test for multiple comparisons. All tests were two sided. A p value < 0.05 was considered significant.

Results

PATIENT CHARACTERISTICS

The groups studied did not differ in age and sex distribution. Age at surgery was lower in the patients who underwent biventricular repair (table 1).

HEART RATE VARIABILITY IN GROUPS STUDIED

These results are shown in table 3. In patients with a total cavopulmonary connection, all heart rate variability indices except RR and LF:HF were significantly reduced compared with healthy controls or with children who had a biventricular repair, showing a strong reduction in the autonomic nervous system tone with low vagal drive (reduction of r-MSSD, pNN50, and HF).

Patients with an atriopulmonary connection had a significant reduction in heart rate variability compared with control subjects (reduction of SD, r-MSSD, pNN50, TP, LF, and HF) and a reduced vagal drive compared with surgical patients (reduction of r-MSSD, pNN50, and HF).

Patients with partial cavopulmonary connection showed reduced variability compared with healthy subjects (reduction of r-MSSD, pNN50, TP, LF, and HF).

Surgical patients did not differ from healthy children.

Table 3 Indices of heart rate variability in the groups studied

	TCPC	APC	PCPC	Biventricular repair	Healthy controls
RR (ms)	698 (99)	752 (64)	700 (100)	790 (155)	845 (134)
SD (ms)	94 (31)*	121 (31)†	121 (44)†	153 (60)	170 (43)
r-MSSD (ms)	22.6 (9.7)*	29 (22)*	34.5 (15)†	69 (45)	75 (36)
pNN50 (%)	3.6 (4.8)*	6 (9)*	8.8 (5.7)†	25 (13)	32 (13)
TP (ms ²)	760 (980)*	972 (718)†	1925 (1590)†	3062 (2400)	6550 (5000)
LF (ms ²)	159 (210)*	176 (156)*	531 (550)†	775 (548)	1862 (1418)
HF (ms ²)	65 (117)*	98 (120)*	244 (240)†	659 (637)	1443 (2039)
LF/HF	3.1 (2.25)	3.0 (2.0)	2.8 (2.6)	1.75 (0.9)	2.0 (0.8)

Values are mean (SD).

* $p < 0.0001$ v biventricular repair and healthy controls; † $p < 0.0001$ v healthy controls.

APC, atrial cavopulmonary connection; HF, high frequency (ms²); LF, low frequency (ms²); LF/HF, LF to HF ratio; PCPC, partial cavopulmonary connection; pNN50, per cent of differences of successive RR intervals > 50 ms; r-MSSD, square root of the mean squared differences of successive RR intervals (ms); RR, mean duration of RR intervals (ms); SD, standard deviation of all RR intervals (ms); TCPC, total cavopulmonary connection; TP, total power (ms²).

No differences in heart rate variability indices were observed between the three subgroups of cavopulmonary connection with respect to the number of surgical interventions before the Fontan operation, right atrial enlargement, or New York Heart Association functional class (data not shown).

Discussion

Cavopulmonary connection has largely been done for palliation where there is a univentricular heart.¹ Atrial arrhythmias and sinoatrial disease are frequent complications of cavopulmonary connections.^{2-8 10} Risk factors which have been so far studied include older age at surgery, duration of follow up, right atrial enlargement, increased mean pulmonary artery pressure, and atrioventricular valve regurgitation.^{2-4 6 10} Beside surgical and haemodynamic risk factors, the autonomic nervous system could play an important role in the initiation of arrhythmias.^{12 13} Reduction in vagal activity and an increase in sympathetic tone have been found to be associated with supraventricular tachycardias,¹³ ventricular tachycardias,¹³ and ventricular fibrillation.¹³ In addition, an autonomic imbalance has been shown to be an important risk factor for mortality after myocardial infarction.^{13 17 18}

Analysis of heart rate variability is widely used in adult cardiovascular disease to obtain quantitative markers of autonomic nervous system function.¹² The predictive value of heart rate variability for late mortality in these diseases is similar to the left ventricular ejection fraction, while it is better at predicting life threatening arrhythmias.¹⁸⁻²⁰ Reduced heart rate variability has also been identified as a prognostic factor in cardiomyopathies,¹² heart transplantation,¹² diabetic neuropathy,¹² and congestive heart failure.¹²

Various factors have been reported to be responsible for the reduction of heart rate variability. These include drugs,¹² such as flecainide, encainide, propafenone, and β blockers, all of which may affect heart rate variability indices. None of our patients received any treatment known to influence heart rate variability. Second, reduced heart rate variability has been found in patients with severe myocardial dysfunction.¹² All the patients in our series had normal ventricular function. Third, heart surgery and cardiopulmonary bypass are associated with transient imbalance of the

autonomic nervous system.²¹⁻²³ In adults undergoing coronary artery grafting there is a transient reduction in heart rate variability that improves within a month of the intervention.²¹

There are few data on modifications of the autonomic nervous system after cardiac surgery for congenital heart disease. Finley *et al* showed that heart rate variability in children with atrial septal defects improved after surgery.²² In our series, patients with a total cavopulmonary connection or an atriopulmonary connection had a markedly reduced heart rate variability and low vagal drive. In patients with a partial cavopulmonary connection, reduced variability was found only in comparison with healthy controls. These alterations in heart rate variability in patients with cavopulmonary connections could not have been caused by heart surgery or by cardiopulmonary bypass as the average delay between surgery and the heart rate variability study was as long as 5.8 (3.4) years. These patients should therefore have recovered from any transient autonomic nervous system damage. In addition, the control group of patients who underwent cardiovascular surgery for biventricular repair of congenital heart disease had normal heart rate variability.

As no known factors influencing heart rate variability could be identified in our patients, we hypothesise that surgery to the caval veins and right atrium, as in cavopulmonary connection operations, may alter the intracardiac nervous system. Recent studies¹⁴ have shown that the largest populations of cardiac ganglia are located close to the sinoatrial and atrioventricular nodes. Other important collections of ganglia are present in the interatrial septum, at the atrial appendage-atrial junctions, at the junction of the superior vena cava with the right atrium, and in the superior and anterior wall of the right atrium.¹⁴⁻¹⁶ Postganglionic fibres from these ganglia innervate the atrioventricular node and the sinoatrial node. These fibres extend dorsally around the superior vena cava to the sinus node, into the free wall of the right atrium, and through the mid- and anterior portions of the low interatrial septum.^{15 16} The integrity of this network, along with the extracardiac autonomic nervous system, plays an important role in the maintenance of the electrical stability of the heart.^{14 15 24-26} In adult heart transplants, increased sinus rhythm recovery, decreased atrial

arrhythmia frequency, and reduced mortality were reported when a bicaval anastomosis technique was used compared with the standard procedure of atrial anastomosis.^{27 28} This could be related to the preservation of the intracardiac autonomic network, leading to better electrical stability and faster reinnervation.^{14 27 28} In our patients, cavopulmonary connections may have altered the intracardiac ganglia and the postganglionic fibres, leading to diminished electrical stability, compromising the substrate for neural processing, and reducing the beneficial effects on sinus node function. This alteration is particularly evident in atriopulmonary and total cavopulmonary connections, in which there is major involvement of areas containing the intracardiac autonomic nervous system. Conversely, in patients with a partial cavopulmonary connection, the alteration in heart rate variability is less important because only ganglia at the root of the superior vena cava are likely to be damaged.

The main limitation of our study is that we did not demonstrate the relation between abnormalities of heart rate variability and the occurrence of rhythm disturbances in cavopulmonary connections. However, dysfunction of the autonomic nervous system might be a risk factor for arrhythmias in these patients. Therefore surgical strategies preserving the intracardiac autonomic nervous system should be considered. We have shown here that partial cavopulmonary connection leads to less altered heart rate variability, probably because damage to the intracardiac autonomic nervous system is reduced. Similarly, the construction of a total cavopulmonary connection by using an extracardiac conduit might also preserve intracardiac ganglia, but further studies are needed to resolve these issues.

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