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Original Article

Serial assessment of variability in heart rate in children with the Fontan circulation

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Abstract Autonomic nervous control of the heart can be studied by analysing variability in heart rate. Although earlier studies have shown reduced variability in patients with the Fontan circulation, we are not aware of any previous study examining longitudinal changes in such children. We have examined 13 patients who had undergone total cavopulmonary connection, and 37 healthy controls matched for age and gender. The examinations included complete echocardiography, and 24-hour ambulatory electrocardiogram for analysis of the parameters for variability in heart rate. After the Fontan procedure, three follow-up examinations were performed at a mean of 4.4 years, 5.6 and 7.2 years. Reduced variability was found in those with the Fontan circulation. A significant difference was found between patients and their controls with respect to high-frequency power at the second, p equal to 0.05, and third, p equal to 0.03, examination. The ratio of low-to-high-frequency components progressively increased in those with the Fontan circulation, a phenomenon that led to a significant difference, p equal to 0.03, at the third examination. Our study shows that, in patients with the Fontan circulation, routine ambulatory electrocardiographic monitoring including analysis of variability in heart rate, detects over time a progressive sympatovagal imbalance.

Keywords: Total cavopulmonary connection; sinus node dysfunction; heart rate variability

Over the last few decades, the spectrum of patients surviving complex cardiac anomalies has changed. Previously judged to be inoperable, a variety of patients having functionally single ventricles, including those with hypoplasia of the left heart, are now being offered a modified Fontan operation as a permanent palliation.[1,2] The surgical techniques have been modified significantly over the past 25 years. In 1979, Kreutzer et al.[3] introduced the atriopulmonary connection, including atrial suturing, atrial distension, and elevation of atrial pressure. These latter features are associated with sinus nodal dysfunction. Today, the most common surgical approach is to create a total cavopulmonary connection, or a total extra cardiac connection.[4,5] By creating a lateral tunnel close to the sinus node, the total cavopulmonary connection may also lead to an impairment of the blood supply to the sinus node. Kürer et al.,[6] for example, showed sinus nodal abnormalities in more than half of the patients they studied with the Fontan circulation. In 1995, Kavey et al.[7] demonstrated a high loss of sinus rhythm in a 2-year follow-up study of patients with the total cavopulmonary connection. Other authors[8,9] have found altered sinuatrial nodal function in this group of patients, indicating a risk for developing arrhythmias. Sinus nodal dysfunction, and arrhythmias, are two of the reasons underscoring the introduction of the extracardiac connection[5] for creation of the Fontan circulation.

Analysis of variability in heart rate is a non-invasive method for studying cardiovascular autonomic control, showing how the sympathetic and parasympathetic system regulates the beat-to-beat fluctuations

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in heart rate. Such variability has also been found to be impaired in cardiac diseases.[10] Massin et al.[11] found that a reduction in the variability was not linked to haemodynamic data in children with congenital heart disease. In 1999, Butera et al.[12] showed that patients with both total cavopulmonary and atriopulmonary connections had significantly reduced variability in their heart rate, and suggested that surgery alters the intracardiac nervous system. In routine follow-up of our patients, we observed that patients palliated by construction of the Fontan circulation had reduced variability, a reduction that seemed to increase over time. An earlier study[13] showed that patients older than 10 years have reduced variability compared to younger patients. Thus, we hypothesized that patients palliated by construction of the Fontan circulation would have a progressive reduction in variability of their heart rate over time. The purpose of this study was to assess longitudinal changes in such variability in these patients.

Material and methods

We studied 50 children and youths. The group of patients represents all survivors of construction of Fontan circulation between 1993 and 1997. These 13 patients, seven male and six female, were referred to our division of paediatric cardiology for follow-up. Their mean age at the time of construction of the total cavopulmonary connection was 6.2 years, with a range from 1.6 to 13.5 years, and standard deviation of 4.5 years. Of the patients, 5 had tricuspid atresia, four with concordant and one with discordant ventriculo-arterial connections, three had pulmonary atresia, two had double inlet left ventricle with discordant ventriculo-arterial connection, one with unbalanced atrioventricular septal defect, one with mitral atresia, and one with a large ventricular septal defect functioning as a single ventricle in the setting of discordant ventriculo-arterial connections. All patients had undergone a total cavopulmonary connection. In all 13 patients, the predominant rhythm was sinus, but one patient had periods of nodal rhythm. Inhibitors of angiotensin converting enzyme were prescribed for 5 patients, and digoxin for one. Of the patients, 2 were medicated with both digoxin and inhibitors of angiotensin converting enzyme. None of the patients were beta-blockaded. During the study, the medication was held constant.

All examinations were performed according to the local protocol for routine follow-up for patients with the Fontan circulation. Clinical examination, complete echocardiographic examination, and 24-hour ambulatory electrocardiographic monitoring were performed as late follow-up examinations. After the final operation, progressive examinations were performed, first, at a mean of 4.5 years, with a standard deviation of 0.7 years, and a median of 4.5 years, followed by a mean of 5.6 years, with standard deviation of 0.8 years, and median of 5.7 years, and finally at a mean of 7.2 years, with a standard deviation of 0.7 years, and a median of 7.4 years.

The patients were compared with a group of 37 healthy children and youths matched for age and gender. Both groups were selected from the same region. The study protocol was approved by the Ethics Committee of the Medical Faculty and informed consent was obtained.

Echocardiography

Complete cross-sectional and Doppler echocardiographic transthoracic examinations were performed in both patients and controls. Global ventricular function was semi-quantitatively assessed in all projections and graded as poor, fair or good.

Ambulatory 24-hour electrocardiogram

All patients and their controls underwent standard 24-hour ambulatory electrocardiographic monitoring during daily activity using the Tracker III, the Sherpa recorder (Reynolds Medical Ltd, Herts, England), or the DL 700 Digital Holter Recorder (Braemer Inc, Burnsville, MN, USA). We used 4 electrodes, one in V2-position, one in V5-position, and two as references underneath the right clavicle. All the recordings were analysed using a Holter system for personal computers (Danica, Borlänge, Sweden), and the electrocardiogram was digitised at 128 samples per second. We analysed either the V2 or V5 channels. One analyst reviewed all the data.

Variability in heart rate

Frequency-domain indexes of variability were determined based on normal-to-normal intervals, that is all intervals between adjacent QRS complexes resulting from sinus nodal depolarization. The 24-hour mean-normal-to-normal interval was measured as the mean of all normal-to-normal intervals over the length of the analysis.

The frequency-domain analysis of the beat-to-beat fluctuations in R–R intervals was performed using the fast Fourier Transformation algorithm, where we averaged the spectrums for successive segments of 205 seconds. Spectral power was determined in three frequency regions of interest, namely very low frequencies between 0.003 and 0.04 hertz, low frequencies from 0.04 to 0.15 hertz, and high frequencies from 0.15 to 0.4 hertz.

The high-frequency component is associated with vagal tone, the low-frequency component is associated

Table 1. Systemic ventricular function and functional class (New York Heart Association, NYHA) in the patients at their three follow-up examinations.

Examination		I (n = 13)	II (n = 13)	III (n = 11)
Years postoperatively mean (SD; median)		4.5 (0.7; 4.5)	5.6 (0.8; 5.7)	7.2 (0.7; 7.4)
NYHA functional class	I	11	10	8
	II	1	2	1
	III	1	1	1
	IV	0	0	1
Systemic ventricular function	Good	11	11	9
	Fair	2	1	1
	Poor	0	1	1

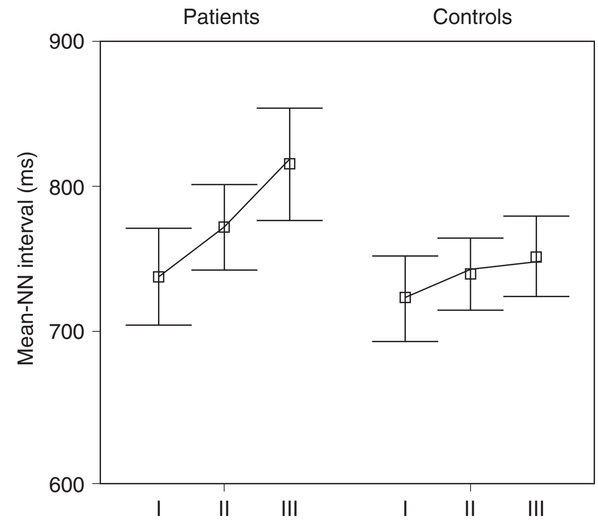

Figure 1.
Comparison of mean-NN between patients and controls. Mean-NN: mean of all normal-normal intervals; I: first follow-up; II: second follow-up; III: third follow-up.

with both sympathetic and vagal activity, while the very low frequency is associated with more long-term fluctuations in heart rate.[10]

We calculated the total power between 0.003 and 0.4 hertz, and the ratio of low-to-high-frequency components. All spectral indexes were calculated as average data over the complete recording period, up to 24 hours. The low- and high-frequency indexes were logarithmically transformed and presented in figures as mean values and standard errors of the mean.

Statistical analysis

The SPSS software (SPSS, Chicago, IL) was used for statistical analysis. Non-parametric statistical methods were used for all statistical comparisons. The development of variability in heart rate within the patients was investigated with a Friedman test. In addition, the different recordings from each patient were compared with the corresponding control subjects using the Mann Whitney U-test. The level of statistical significance was defined as a p-value of less than 0.05, two sided.

Results

We examined 13 patients at the first and second follow-up. At the third examination, two patients were not available for follow-up, one having moved, while the other had been diagnosed with acute myeloblastic leukemia. This resulted in 37 examinations being available for examination. Each examination was matched with a healthy control, resulting in 37 healthy controls.

Echocardiography and functional state

In the majority of the 13 patients, the echocardiographic evaluations revealed good systemic ventricular function (Table 1). We observed decreasing ventricular function during this period in 1 patient, who underwent cardiac transplantation three months after the last examination. Another patient developed clinical symptoms from sinus nodal dysfunction, and a pacemaker was implanted twelve months after the last examination. Her ventricular function remained good. Most of the patients were in classes I and II in the functional grading of the New York Heart Association, 12 of 13 at the first examination, and 9 of 11 at the last examination. As expected, all controls produced normal findings.

Variability in heart rate

We were unable to find any significant change in the mean of all normal-to-normal intervals during follow-up. In those with the Fontan circulation, however, there was a tendency towards a larger increase in the mean of all normal-to-normal intervals (Fig. 1).

The power of the high-frequency component decreased over time (p equal to 0.04), but the other indexes for frequency domain in those patients with three recordings showed no statistically significant change over time. Low-frequency power, however, was more than 50 percent higher in two patients at the third examination as compared with the first. Although the controls showed a successive increase in low-frequency power at a higher level, we could not find any significant difference between patients and controls (Fig. 2). Comparing power in the high-frequency region, a statistically significant lower power was found in the patients at their second

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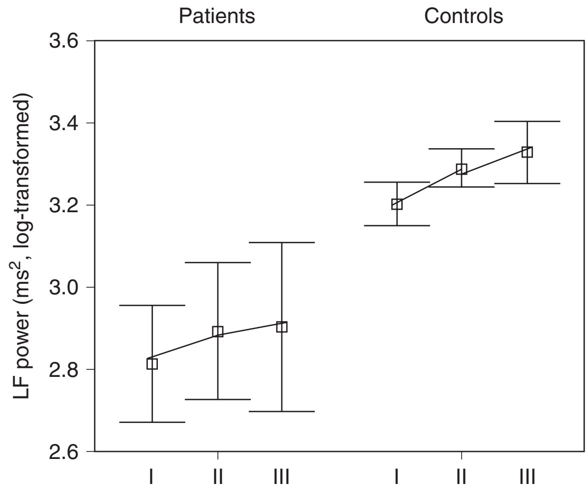

Figure 2.
Low-frequency component in the patient group compared to the control group during follow-up. LF: power in low-frequency region 0.04–0.15 hertz (ms^2).

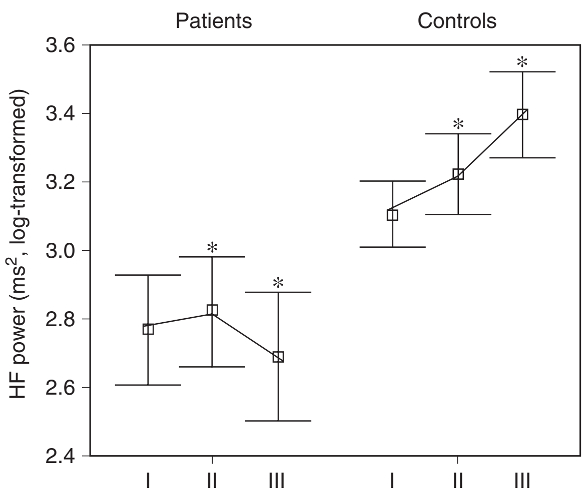

Figure 3.
Comparison between patients and healthy controls regarding power of the high-frequency component. $^*p = 0.01$ patients versus controls. HF: power in high-frequency region 0.15–0.4 hertz (ms^2).

(p equal to 0.05), and third (p equal to 0.03), examinations (Fig. 3).

There was a progressive increase in the ratio of low-to-high-frequency components in those with the Fontan circulation, an increase that led to a statistically significant difference (p equal to 0.03) at the third examination (Fig. 4). There was a tendency that total power was higher in controls at the second (p equal to 0.10) and third (p equal to 0.10) examinations. There were no statistically significant differences in very low-frequency power between those with the Fontan circulation and their controls at any examination.

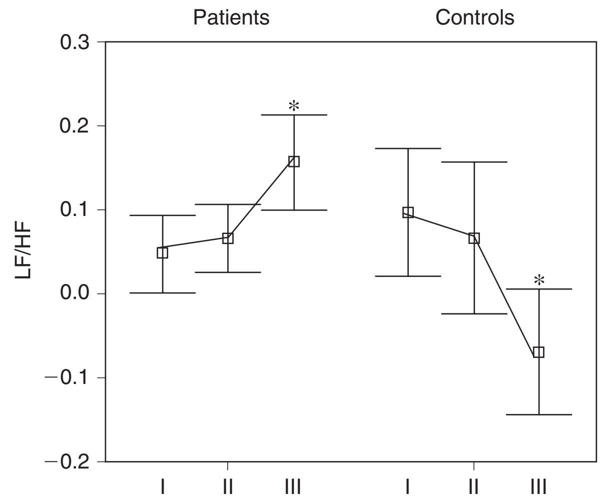

Figure 4.
Ratio of low-to-high-frequency (LF/HF) components in the patients compared to their controls. $^*p = 0.01$ patients versus controls.

Discussion

Our prospective study reveals increasing sympatovagal imbalance and bradycardia over time in patients with a Fontan circulation. Bradycardia is common in this group of patients. In many earlier studies, the presence of bradycardia was held to indicate sinus nodal dysfunction.[6,7,11,14] Although our study agrees with this, we also found a tendency towards more increasing mean-normal-to-normal intervals over time compared to the healthy controls. This occurred even though vagal tone decreased, not showing the expected increase as found in the controls. Although the differences in mean-normal-to-normal intervals between the patients and their controls were not significant, further longitudinal studies are needed to describe the development of age-adjusted bradycardia, reflecting the sinus nodal dysfunction in this group of patients.

Many authors[8,12,14,15] have discussed the fact that surgery to the caval veins and right atrium may alter the electrical stability of the heart. Most of the parasympathetic ganglions are located in relation to the atrial walls and at the junction of superior caval vein and the right atrium. The sinus node and the atrioventricular node, innervated from these ganglions, could easily be affected by the surgical manoeuvres needed to produce the Fontan circulation. A more common late decline in sinus nodal dysfunction in patients with an intermediate cavopulmonary connection is reported by at least 2 groups before the final Fontan operation.[8,14] Cohen et al.[14] also showed a progressive sinus nodal dysfunction in these patients. The late decline in sinus nodal function could be due to a combination of injury directly to the ganglions, and/or indirectly by affecting the vascularisation, injuries that may result in progressive fibrosis. The surgical approach with an extracardiac connection following a bidirectional Glenn anastomosis may decrease the risk of developing sinus nodal dysfunction.[5] Although one group[16] was unable to find any early difference in sinus nodal dysfunction after the extracardiac conduit compared with the lateral tunnel in patients with the Fontan circulation, further studies are needed to investigate the late results.

Reduced variability in heart rate in patients with the Fontan circulation has been previously been reported.[12,13,17,18] Our study shows reduced variability, with decreased high-frequency power, as compared to healthy controls. When following these parameters prospectively, we found a difference in separate parameters. At follow-up, the high-frequency component failed to reveal the expected increase, resulting in a progressive increase in the ratio of low-to-high-frequency components, and demonstrating a sympatovagal imbalance. In healthy individuals, an increase in the ratio of low-to-high-frequency components is normally associated with an increased sympathetic activity, and/or decreased vagal activity.[10] It is stated that most authors view low-frequency power as reflecting both sympathetic and vagal activity.[10] The mechanism behind this marked increase in the low-frequency component found in some patients in this study, and its clinical significance, is not yet clear, but it will be investigated further. The major contributor to the high-frequency component is parasympathetic or vagal activity.[10] The absence of the expected increase in the high-frequency component indicates an affect on the parasympathetic and vagal activity. We believe that this is the most important finding in our study, indicating that the surgery required to produce the Fontan circulation may affect the parasympathetic nervous system, a situation that could explain both sinus nodal dysfunction with bradycardia and the absence of the expected increase of the power in the high-frequency range.

The limitation of our study is the small number of patients we were able to examine, although the serial assessments resulted in 37 examinations. Our group of patients, nonetheless, represents a cohort of all survivors undergoing the total cavopulmonary connection performed between 1993 and 1997. This group was referred back for follow-up, and the group is homogenous regarding surgical technique. It was not possible to follow the healthy controls during the same period. Previous studies have shown that variability in heart rate increases with age in healthy children within the same age interval.[19–21] Thus, the results from our controls correspond well with the expected development of variability in heart rate reported in earlier studies. Regarding medication, the patients were far from uniform, with 5 receiving inhibitors of angiotensin converting enzyme, one receiving digoxin, and two on a combination of inhibitors of angiotensin converting enzyme and digoxin. There is controversy regarding the effect of inhibitors of angiotensin converting enzyme on variability in heart rate,[22] although it is accepted that digoxin increases the variability in heart rate, most markedly in the high-frequency component.[22] In our study, we found a significant lower high-frequency power in those with the Fontan circulation. Furthermore, all medication was held constant during the serial follow-up.

A reduced variability in heart rate has been observed in patients with cardiac failure.[10] The reduction in time-domain indexes seems to mirror the severity of the disease, whereas the relationship between spectral indexes and ventricular dysfunction seems to be more complex.[10] Cardiac failure is characterised by sympathetic activation, such as faster heart rate. Our patients showed a tendency towards increasing mean-normal-to-normal intervals, leading to a relative bradycardia. Only one patient had a clearly progressive and severe heart failure. This patient underwent cardiac transplantation three months after the last examination. The other patients remained stable.

We believe that the finding of a progressive increase over time in the ratio of low-to-high-frequency components, with a lack of an expected increase in high-frequency power, reflects the progressive sinus nodal dysfunction in this group of patients. The physiological consequences of bradycardia in such patients are important, because it limits cardiac output. Cardiac output may also be affected by sinus nodal dysfunction because of the lack of an atrial kick in patients with a rather fixed stroke volume. Decline in sinus nodal function with symptomatic bradycardia requires pacemaker therapy. Implantation of antibradycardiac pacing improves atrioventricular synchrony and cardiac output, and may decrease the risk of developing late atrial arrhythmias. In patients who have been converted to the Fontan circulation, routine follow-up with 24-hour ambulatory electrocardiographic monitoring, including analysis of the variability in heart rate, could be an effective method with which to detect a progressive sympatovagal imbalance. Such follow-up could optimise the timing of intervening with antibradycardiac pacing.

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