International Journal of Cardiology 274 (2019) 88–92

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Heart rate variability is impaired in adults after closure of ventricular septal defect in childhood: A novel finding associated with right bundle branch block

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ARTICLE INFO

Article history:
Received 26 May 2018
Accepted 22 June 2018
Available online 25 June 2018

Keywords:
Arrhythmias
Congenital heart disease
Heart rate variability
Long-term follow-up
Ventricular septal defect

ABSTRACT

Background: Ventricular septal defects (VSDs) generally have benign long-term prognoses, but recent studies have indicated increased pulmonary vascular resistance. A potential tool for monitoring pulmonary artery pressure is heart rate variability, and therefore, the aim of this study was to assess heart rate variability in adults with a surgically repaired or unrepaired VSD.

Methods: In a long-term, follow-up study, three groups were included; VSD-patients operated in early childhood, patients with an open VSD, and controls. For each patient, 24-hour Holter monitoring was performed and heart rate variability was assessed.

Results: In total, 30 participants with a surgically closed VSD, 30 participants with an unrepaired VSD, and 36 controls were included. In the closed VSD group, there was a higher proportion of participants, who had low sNN50 ($p = 0.005$) and low sNN6% ($p = 0.017$) than in the other two groups. Similar differences were found when sNN50 was divided into increases and decreases ($p = 0.007$ and $p = 0.005$, respectively) as well as sNN6% ($p = 0.014$ and $p = 0.014$, respectively). Lastly, there was a higher proportion of patients in the closed VSD group with low rMSSD than in the other two groups ($p = 0.005$). For the closed VSD group, the proportion of participants with low total sNN50 ($p = 0.046$) and low total sNN6% ($p = 0.046$) were higher among participants with a complete right bundle branch block (RBBB) than among participants with no or an incomplete RBBB.

Conclusions: Adults who had surgical VSD closure in early childhood had impaired heart rate variability and, particularly, participants with complete RBBB had lower heart rate variability.

1. Introduction

Ventricular septal defect (VSD) is the most common congenital heart defect [1], and while around a third close spontaneously in the first years of life, the rest either undergo surgical closure or are considered hemodynamically insignificant. For both of the latter two groups, the long-term implications have traditionally been considered to be benign [2–6]. However, there is emerging evidence of late morbidity in adults with a surgically closed VSD [7–11] and also in patients with small, open defects [12–15].

In particular, studies on adults operated for VSD have indicated ncreased pulmonary vascular resistance, especially during exercise [9, 10, 16, 17]. Right ventricular thickening and an abnormal right ventricular strain pattern have also been demonstrated [9], which themselves may be adaptive to increased pulmonary hemodynamics. Most recently, our own study group has shown an abnormal right ventricular force-frequency relationship, which was directly correlated to exercise capacity [10].

It has long been known that severe left ventricular dysfunction is associated with abnormal heart rate variability (HRV) and that the degree of impaired HRV carries prognostic implications [18]. However, even relatively minor abnormalities of right ventricular function have been

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[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2018.06.097
0167-5273/

associated with abnormalities of HRV [19, 20]. For example, Tadic et al. demonstrated that minimal right ventricular remodeling was associated with impaired HRV in patients with systemic hypertension [19]. The same group showed that abnormal right ventricular strain was associated with abnormal HRV in diabetic patients [20]. There is also evidence of abnormal HRV in patients with congenital heart disease. For example, patients with atrial and ventricular septal defects have decreased HRV prior to surgical closure [21, 22], which is thought to be due to pressure and volume overload of the right ventricle altering the homeostasis of the pulmonary and systemic circulation. Whatever the mechanism, HRV has been shown to improve after transcatheter or surgical closure of atrial septal defects, for example [23].

Little is known regarding HRV in the long-term follow-up of patients with VSD, however. We hypothesized that adults, who had undergone surgical VSD-repair in early childhood and adults with small, open VSDs have abnormal HRV as a consequence of the recently demonstrated abnormalities of RV function. Therefore, the aim of this prospective cohort study was to assess HRV in adults with either a surgically repaired or a small, open VSD.

2. Methods

The Danish Data Protection Agency (chart: 1-16-02-315-16), The Regional Committee on Biomedical Research Ethics of the Central Denmark Region (chart: 1-10-72-153-16), The Danish Medicines Agency (chart: 2016061269), and the European Medicines Agency (EudraCT No. 2015-005507-89) approved the study. The study was monitored by the Good Clinical Practice Unit of Aalborg and Aarhus University Hospitals, and it is registered on clinicaltrials.gov (identifier: NCT02914652). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, revised in 2008, and all participants provided written informed consent prior to enrolment.

2.1. Design

In a long-term, follow-up study, participants were included at Aarhus University Hospital, Denmark. This report presents a substudy of a double-blinded, cross-over trial in which participants inhaled 900 μg of salbutamol (Ventoline®) or placebo (Evohaler®) in a randomized order at two separate visits with 2 to 14-days interval. In the original study, the aim was to assess ventilatory function in VSD-patients, including the potential effects of inhaled salbutamol. As a substudy, participants were equipped with a Holter monitor, and hence, this report only includes placebo data none of which have been presented elsewhere.

2.2. Study population

Inclusion criteria were 1) operated VSD-patients who had undergone surgical closure of a congenital, isolated VSD through right atrial approach at Aarhus University Hospital between 1990 and 1997, 2) patients from 18 to 40 years of age with a small, unrepaired VSD followed at our local or a regional outpatient clinic with echocardiographic follow-ups, 3) a healthy control group consisting of age- and gender-matched controls enrolled through flyers and announcements on government, official webpages. Exclusion criteria were coexistence of other congenital cardiac defects than VSD, associated syndromes, e.g. Down's syndrome, documented arrhythmia, cardiac or pulmonary disease including any valve pathology, and missing patient chart. Details of the surgical procedures are previously described [7].

2.3. Holter monitoring

At each visit, the participant was equipped with a 2-channel Holter monitor (Lifecard CF Digital Holter Recorder, Spacelabs Healthcare, WA, US), which was worn for 48-hours after the first visit and 24 h after the second visit. The recordings were analyzed using Pathfinder SL software (Spacelabs Healthcare, WA, US) and all measurements were expressed as 24-hour values.

The Holter recordings were analyzed for presence of arrhythmic events including premature ventricular contractions, supraventricular and ventricular tachyarrhythmia (defined as ≥1 runs of ≥3 beats), sinus arrest (defined as pauses of ≥2 s), and atrioventricular block (defined as PQ intervals of ≥0.22 s). Right bundle branch block (RBBB) was subdivided into *complete RBBB* defined as RSr' or RSR' configuration in leads V_1 or V_2 and a QRS duration ≥120 ms in leads I, II, III, aVL, and aVF and *incomplete RBBB* (QRS duration <120 ms) [24].

HRV analyses were performed for the first 24 h after each visit and included the following parameters: **1**) number of pairs of adjacent NN intervals differing by >50 ms per 24 h, standardized for invalid intervals (sNN50); **2**) number of pairs of adjacent NN intervals differing by >6% per 24 h, standardized for invalid intervals (sNN6%); **3**) standard deviation of all normal sinus intervals (SDNN); **4**) standard deviation of all normal sinus intervals for all 5 min segments (SDNNi); **5**) standard deviation of the averaged normal sinus intervals for all 5 min segments (SDANN); **6**) root mean square of the successive normal sinus interval difference (rMSSD); **7**) integral of the density distribution divided by the maximum of the density distribution i.e. total number of NN intervals divided by number of NN intervals in the modal bin (triangular index).

2.4. Endpoints

Our primary endpoint was low sNN50 defined as the proportion of participants with a sNN50 lower than a predefined threshold (mean value in the control group − 1 standard deviation). Secondary endpoints were similarly defined as the proportions of participants with low sNN6%, low SDNN, low SDNNi, low SDANN, low rMSSD, and low triangular index.

2.5. Statistical analyses

Continuous data are presented as means ± standard deviations or median with 95% confidence intervals (CI), as appropriate, and binary data are presented as absolute numbers and percentages of participants. Differences between groups were assessed using one-way analyses of variance (ANOVA) or Students *t*-tests, as appropriate, for continuous data and chi-squared tests for binary data. *p*-Values < 0.05 were considered statistically significant, all *p*-values are two-sided. Descriptive data were stored in Microsoft Excel 2016 (Microsoft Corp., CA, USA) and statistical analyses were performed using Stata/IC 12.1 for Mac (Stata Corp., TX, USA).

2.5.1. Sample size justification

The sample size was determined by the number of participants included in the original study, wherefore no formal sample size calculation was performed for this substudy.

3. Results

In the period from November 2016 to June 2017, 96 participants were enrolled of which 30 participants had a surgically closed VSD, 30 participants had an unrepaired VSD and 36 participants were healthy controls as detailed in Fig. 1. In the operated group, the median age at surgery was 1.4 years (95% CI 0.9–2.4 years). All participants completed both study visits and no serious adverse events were observed. In the closed VSD group, 9 participants had complete RBBB and 21 participants had either no or incomplete RBBB, whereas there were no participants in either the open VSD group or in the control group with complete RBBB. Basic characteristics for all the enrolled participants are shown in Table 1, there was no significant difference between the groups.

Heart rate variations and arrhythmic events over 24 h are displayed in Table 2.There was a higher proportion of participants in the closed VSD group with a high number of premature ventricular contractions than in the two other groups ($p < 0.001$), but there were no differences between the three groups in terms of heart rate variations or proportions of participants with supraventricular tachycardia ($p = 0.128$), ventricular tachycardia ($p = 0.708$), sinus pause ($p = 0.553$), or atrioventricular block ($p = 0.174$).

HRV for the three groups is shown in Table 3. There was a higher proportion of patients in the closed VSD group with low total sNN50 ($p = 0.005$) and low total sNN6% ($p = 0.017$) than in the other two groups. A similar pattern was observed when sNN50 was divided into increases and decreases ($p = 0.007$ and $p = 0.005$, respectively) as well as sNN6% ($p = 0.014$ and $p = 0.014$, respectively). We also found a higher proportion of patients in the closed VSD group with low rMSSD than in the other two groups ($p = 0.005$), but there were no differences between the groups in terms of SDNN ($p = 0.400$), SDNNi ($p = 0.059$), SDANN ($p = 0.602$), or triangular index ($p = 0.400$).

For the closed VSD group, HRV was then analyzed according to the presence of a complete RBBB (Supplementary Table 1). The proportion of participants with low total sNN50 ($p = 0.046$) and low total sNN6% ($p = 0.046$) was higher among patients with complete RBBB compared to those with no or incomplete RBBB. There were no differences between these two subgroups in terms of rMSSD, SDNN, SDNNi, SDANN, or triangular index.

Participants with a closed VSD without complete RBBB were then compared with the control group (Supplementary Table 2). A higher proportion of participants with a closed VSD without complete RBBB had low sNN50 (decreases) compared with the control group, but otherwise there were no differences in HRV between these two groups. As seen, 38% and 17%, respectively, had low total sNN50 ($p = 0.070$), and 38% and 19%, respectively, had low total sNN6% ($p = 0.198$).

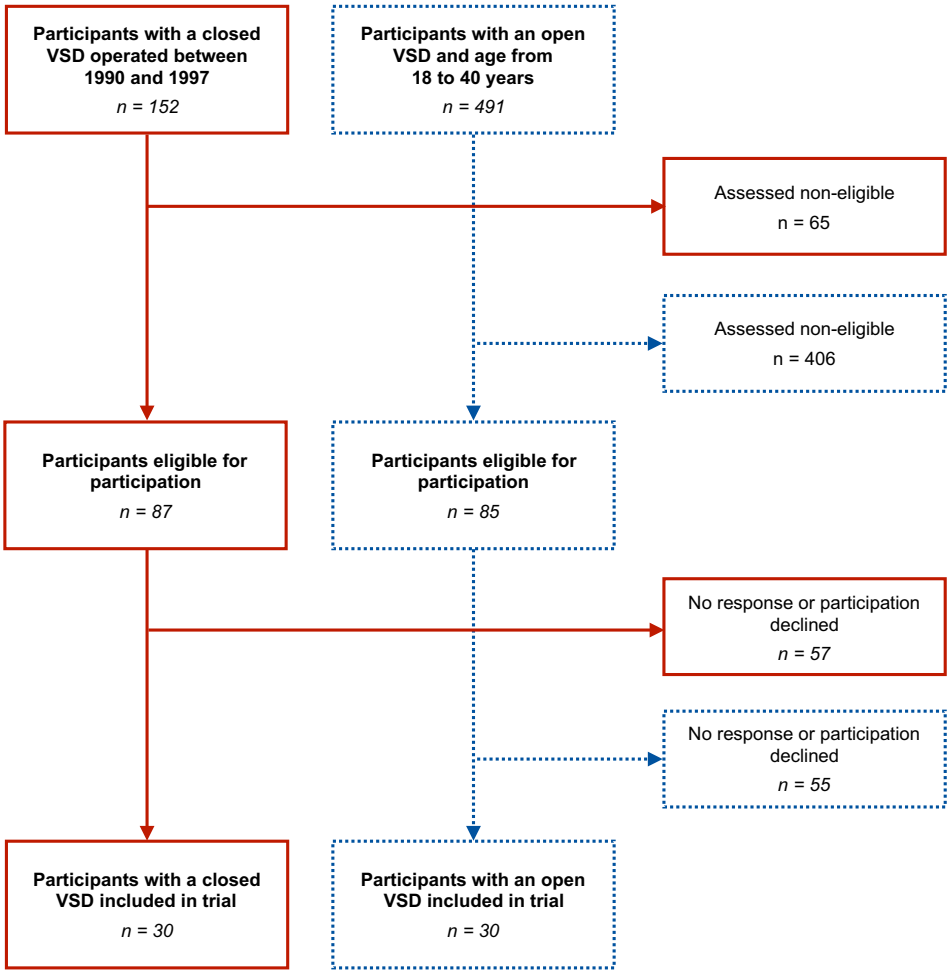

Fig. 1. Patient flow chart Flow of VSD participants through the study period. VSD, ventricular septal defect.

4. Discussion

In this long-term follow-up study, adults who had surgical VSD closure in early childhood have a significantly impaired HRV compared with adults with small, hemodynamically insignificant VSDs and healthy controls. It was also clear that HRV impairment is more pronounced in patients with complete RBBB compared to those with no or incomplete RBBB, although HRV in the latter group was still impaired compared to unoperated patients and healthy controls. These novel findings add to the increasing number of reports suggesting that surgical repair of VSD, even when performed decades earlier, is associated with measurable abnormalities of cardiopulmonary performance and challenge the notion that the long-term outcome of such surgery is benign. Indeed, given that anticipated survival of these patients may span many decades, it is perhaps premature to suggest that they do not require specialist follow-up [25–27].

Table 1
Characteristics of participants with surgically closed VSDs, open VSDs and healthy controls.

	Closed VSDs n = 30	Open VSDs n = 30	Controls n = 36
Demographics			
Age, years	24 ± 2	27 ± 6	26 ± 5
Male sex, n (%)	17 (57)	17 (57)	18 (50)
Weight, kg	71 ± 12	75 ± 13	71 ± 11
Height, cm	174 ± 10	174 ± 9	175 ± 8
Body mass index, kg/m^2	24 ± 3	25 ± 3	23 ± 3
Fat free mass, kg	54 ± 11	56 ± 12	56 ± 10
Smoking status			
Non-smokers, n (%)	23 (77)	24 (80)	32 (89)
1–7 cigarettes/week, n (%)	3 (10)	2 (7)	2 (6)
8–20 cigarettes/week, n (%)	1 (3)	3 (10)	1 (3)
>21 cigarettes/week, n (%)	3 (10)	1 (3)	1 (3)

Data reported as means ± standard deviations or absolute numbers and percentages of patients.
VSD, ventricular septal defect.

While this proof-of-principle study was not designed to explore mechanisms, our data suggest possible areas for future investigation. As discussed above, we showed that postoperative RBBB has a negative, independent effect on HRV. Our group has previously shown that postoperative RBBB is associated with a blunted heart rate response to exercise [28], and in a recently conducted review, chronotropic incompetence was found to be more common in operated patients with postoperative RBBB than in those without [29]. While it is possible that there is a causal relationship between RBBB and these outcomes, it is perhaps more likely that RBBB is a surrogate for other pathophysiologic processes e.g. greater RV damage, worse RV function, and abnormal HRV is, in turn, a reflection of underlying dysfunction rather than a consequence of disturbed conduction. Indeed, there is increasing evidence that even subtle degrees of RV dysfunction, in the absence of conduction disturbance, is associated with abnormal HRV [19, 20]. Going along with this hypothesis, we also showed impaired HRV in patients with no or incomplete RBBB. While clearly, we cannot address the mechanisms underlying this suggestion, it is noteworthy that impaired

Table 2
Heart rate variations and events over 24 h for participants with surgically closed VSDs, open VSDs and healthy controls.

	Closed VSDs n = 30	Open VSDs n = 30	Controls n = 36	P-value
Heart rate variations				
Minimum heart rate, beats/min	49 ± 8	51 ± 7	50 ± 9	0.879
Mean heart rate, beats/min	72 ± 8	75 ± 10	73 ± 9	0.555
Maximum heart rate, beats/min	140 ± 23	141 ± 25	150 ± 26	0.212
Events				
High number of PVCs, n (%)	9 (30)	2 (7)	0 (0)	<0.001*
Supraventricular tachyarrhythmia, n (%)	6 (20)	1 (3)	4 (11)	0.128
Ventricular tachyarrhythmia, n (%)	2 (7)	2 (7)	1 (3)	0.708
Sinus pause, n (%)	3 (10)	1 (3)	2 (6)	0.553
Atrioventricular block, n (%)	3 (10)	2 (7)	0 (0)	0.174

Data reported as means ± standard deviations or absolute numbers and percentages of patients.
High number of PVCs was defined as >200 over 24 h. Supraventricular and ventricular tachyarrhythmia were defined as ≥1 runs of ≥3 beats, sinus pause was defined as pauses of ≥2 s, and atrioventricular block was defined as PQ intervals of ≥0.22 s.
VSD, ventricular septal defect; PVC, premature ventricular contractions.
* Marks a statistically significant difference.

HRV, characteristic of congestive heart failure, is associated with modulation of vagal tone [30] and abnormalities of adrenoreceptor responses to endogenous stimulation [31]. We cannot exclude a more direct effect of surgery however. A number of studies, have shown that surgical VSD closure is associated with persisting chronotropic impairment [32–34] and this, in turn, has been ascribed to autonomic denervation in the proximity of the aorta [35, 36].

No matter what the cause, impaired HRV can now be added to the list of subtle, but potentially important, abnormalities that are seen in the late follow-up of patients who have undergone repair of VSD in early childhood. While the functional implications of these abnormalities are minimal at present (the vast majority of patients are entirely asymptomatic] it is unclear what impact these modest hemodynamic burdens may have both cumulatively and when present over the lifetime of our patients. Current recommendations suggest that these patients do not require specialist follow-up [25–27]. However, we would suggest that, on the basis of current evidence, these patients do warrant continued (albeit intermittent) follow-up in adult congenital heart clinics, not only for clinical surveillance, but also to facilitate ongoing studies of the mechanisms of their potentially modifiable pathophysiology.

Table 3
Heart rate variability over 24 h for participants with surgically closed VSDs, open VSDs and healthy controls.

	Closed VSDs n = 30	Open VSDs n = 30	Controls n = 36	P-value
Mean RR, ms	816 ± 93	803 ± 100	805 ± 85	0.857
Low sNN50 (total), n (%)	15 (50)	6 (20)	6 (17)	0.005*
Low sNN50 (increases), n (%)	14 (46)	6 (20)	5 (14)	0.007*
Low sNN50 (decreases), n (%)	15 (50)	8 (27)	5 (14)	0.005*
Low sNN6% (total), n (%)	15 (50)	6 (20)	8 (22)	0.017*
Low sNN6% (increases), n (%)	14 (47)	5 (17)	7 (19)	0.014*
Low sNN6% (decreases), n (%)	14 (47)	6 (20)	6 (17)	0.014*
Low SDNN, n (%)	6 (20)	7 (23)	4 (11)	0.400
Low SDNNi, n (%)	11 (37)	5 (17)	5 (14)	0.059
Low SDANN, n (%)	6 (20)	5 (17)	4 (11)	0.602
Low rMSSD, n (%)	13 (43)	5 (17)	4 (11)	0.005*
Low triangular index, n (%)	7 (23)	6 (20)	4 (11)	0.400

Data reported as means ± standard deviations or absolute numbers and percentages of participants with heart rate variability lower than a predefined threshold (mean value in the control group − 1 standard deviation).
VSD, ventricular septal defect; sNN50, number of pairs of adjacent NN intervals differing by >50 ms per 24 h, standardized for invalid intervals; sNN6%, number of pairs of adjacent NN intervals differing by >6% per 24 h, standardized for invalid intervals; SDNN, standard deviation of all normal sinus intervals; SDNNi, standard deviation of all normal sinus intervals for all 5 min segments; SDANN, standard deviation of the averaged normal sinus intervals for all 5 min segments; rMSSD, root mean square of the successive normal sinus interval difference; triangular index, integral of the density distribution divided by the maximum of the density distribution i.e. total number of NN intervals divided by number of NN intervals in the modal bin.
* Marks a statistically significant difference.

4.1. Limitations

The median surgical age is higher then would be expected in contemporary cohorts, but nevertheless reflective of practice 25 years ago and relevant to the large number of patients operated in that era. No sample size calculation was performed for this substudy, hence, there is a risk of reporting statistically significant but clinically irrelevant results. However, we found a prevalence of low HRV that was more than twice as high in the operated group than in the two other groups. Similarly, due to the missing sample size calculation there is a risk of type 2 errors, therefore, we urge caution in statistical interpretation, particularly of the subdivision of VSD operated patients.

In conclusion, adults who had surgical VSD closure in early childhood have a significantly impaired HRV compared with adults with small, hemodynamically insignificant VSDs and healthy controls. Long-term surveillance for possible clinically relevant sequalae, and future studies of underlying mechanisms, with higher patient numbers and longer period of follow-up, appears to be warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.06.097.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

Karen Elise Jensen's Fund, Aase and Ejnar Danielsen's Fund, and Aarhus University funded this study.

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