

ORIGINAL RESEARCH

Cardiac Arrhythmias and Impaired Heart Rate Variability in Older Patients With Ventricular Septal Defects

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BACKGROUND: Congenital ventricular septal defects (VSDs) are considered to have benign long-term outcome when treated correctly in childhood. However, abnormal parameters are described in younger adults, including impaired heart rate variability (HRV). It is not known whether such abnormalities will deteriorate with age. Therefore, HRV and cardiac events, such as premature ventricular contraction, were evaluated in patients aged >40 years with congenital VSDs and compared with healthy peers.

METHODS AND RESULTS: A total of 30 surgically closed VSDs (51±8 years, repair at median age 6.3 years with total range 1.4–54 years) with 30 healthy controls (52±9 years) and 30 small, unrepaired VSDs (55±12 years) with 30 controls (55±10 years) were all equipped with a Holter monitor for 24 hours. Compared with healthy peers, surgically closed patients had lower SD of the normal-to-normal (NN) interbeat interval (129±37 versus 168±38 ms; $P<0.01$), SD of the average NN intervals for each 5-minute segment of a 24-hour HRV recording (116±35 versus 149±35 ms; $P<0.01$) and 24-hour triangular index (31±9 versus 44±11; $P<0.01$). SD of the NN intervals, SD of the average NN intervals for each 5-minute segment of a 24-hour HRV recording, and triangular index were comparable between unrepaired VSDs and healthy peers. SD of the NN intervals was <100 ms in 22% of surgically closed and 10% of unrepaired VSDs, whereas controls were within normal ranges. A high number of premature ventricular contractions (>200 events) was registered in 57% of surgical patients compared with 3% of controls ($P<0.01$), and 53% of unrepaired VSDs compared with 10% in controls ($P<0.01$).

CONCLUSIONS: Adults aged >40 with congenital VSDs demonstrate impaired HRV, mainly among surgically closed VSDs. More than half demonstrated a high number of premature ventricular contractions. These novel findings could indicate long-term cardiovascular disturbances. This necessitates continuous follow-up of VSDs throughout adulthood.

Key Words: adult congenital heart disease ■ cardiac arrhythmias ■ heart rate variability ■ long-term outcome ■ ventricular septal defects

With a shift in the demographics of congenital heart disease, where the number of adults now exceeds that of children, the focus is changing toward continuous care in the later decades of life of the adult patient.^{1–3} Lately, attention has also been drawn toward one of the most common congenital heart diseases, ventricular septal defect (VSD), as significant late morbidity in terms of lower functional capacity,^{4,5} reduced cardiac output during exercise,^{6,7} and disrupted

biventricular contractility^{8,9} were revealed. Interestingly, adults with VSDs in their mid-20s recently displayed abnormal heart rate variability (HRV),¹⁰ known to carry prognostic implications in predicting morbidity and mortality.¹¹ It remains to be investigated whether a possible association can be established between impaired HRV and already demonstrated abnormal cardiac parameters in the aging VSD population. In this study, HRV in older than 40 years with either a surgically closed or an

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CLINICAL PERSPECTIVE

What Is New?

- Heart rate variability is decreased and premature ventricular contractions are overrepresented in adults aged >40 years with congenital ventricular septal defects when compared with age-matched peers.
- Patients with surgically closed ventricular septal defects had more premature ventricular contractions than subjects with unrepaired, hemodynamically insignificant ventricular septal defects.

What Are the Clinical Implications?

- Decreased heart rate variability is a strong predictor of all-cause mortality, and a high percentage of premature ventricular contractions have been linked with declining ejection fraction and increase in congestive heart failure and mortality, which warrant increased awareness on the aging patient population with congenital ventricular septal defects.

Nonstandard Abbreviations and Acronyms

HRV	heart rate variability
NN	Normal-to-normal inter-beat interval
RR	interbeat interval between all successive heartbeats
SDNN	SD of the NN intervals

unrepaired VSD is studied and compared with that of age-matched healthy controls.

METHODS

All participants gave written informed consent before inclusion. The study protocol complies with the Helsinki Declaration and was approved by the Regional Committee on Biomedical Research Ethics of the Central Denmark Region (chart: 1-10-72-185-18) and the regional data protection bank (chart: 1-16-02-290-18). The current study was a prespecified subanalysis of the original trial listed at www.clinicaltrials.gov (NCT03684161). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Adults with congenital VSDs, aged 40 to 75 years, were included at Aarhus University Hospital, Denmark, along with healthy peers, as previously specified.¹²

Inclusion criteria were a surgically closed VSD or an unrepaired VSD previously assessed as hemodynamically insignificant by cardiac catheterization or echocardiography. Healthy controls were matched on age and sex and included in an ad hoc manner through announcements on an official web page (www.forsoegsperson.dk). Exclusion criteria were existence of serious congenital cardiac lesions, spontaneous closure of VSD, associated syndromes (eg, Down syndrome), Eisenmenger physiology, or severe pulmonary disease. Patients and controls were examined in random order. The study was a cross-sectional study, with HRV assessed on the same day as bicycle exercise test,¹² echocardiography,¹³ and lung function examination.¹⁴ Therefore, the study period for all participants included HRV during both exercise and rest.

Holter Monitoring

Participants carried a 2-channel Holter monitor (Lifecard CF Digital Holter Recorder, Spacelabs Healthcare, Snoqualmie, WA) for 24 hours and registered any symptoms related to cardiopulmonary function while continuing everyday activities. The recording was examined for any cardiac arrhythmic events: a high number of premature ventricular contractions (PVCs) (defined as >200 over 24 hours), atrioventricular block (PQ intervals of ≥ 0.22 seconds), supraventricular tachyarrhythmia (≥ 1 run of ≥ 3 beats), ventricular tachyarrhythmia (≥ 1 run of ≥ 3 beats), and sinus arrest (pauses ≥ 2 seconds).

Heart Rate Variability

For the HRV time-domain measures, the interval between 2 heartbeats was analyzed as RR, describing interbeat interval between all successive heartbeats, whereas normal-to-normal interbeat interval without artifacts were labeled NN. The parameters measured included the mean RR (mean RR), the SD of the NN intervals (SDNN), the mean of the SD of all the NN named the SDNN index, and the SD of the average NN intervals for each 5-minute segment of a 24-hour HRV recording. Calculations of the square root of the mean squared difference between NN intervals were identified as rMSSD. The percentage of RR intervals differing by >50 ms was estimated and labeled pNN50. Finally, the 24-hour triangular index was included to overall describe whether an individual had a little or big variability during the recording. Analyses were performed in random order on the predefined parameters, using Pathfinder SL software (version 1.8.0.8333, Spacelabs Healthcare).

End Points

The SDNN was selected as the primary end point, as it is considered the “gold standard” of HRV time-domain

measurements in predicting cardiac risk.¹⁵ A cutoff limit of >100 ms was chosen as a normal SDNN.^{15,16} The secondary end points included SD of the average NN intervals for each 5-minute segment of a 24-hour HRV recording, square root of the mean squared difference between NN intervals, and 24-hour triangular index, as they estimate long- and short-term components of HRV as well as an overall estimate of HRV, respectively.¹⁵

Subgroup Analysis

Analysis was performed for surgically closed VSDs on HRV end points regarding those with right bundle-branch block (RBBB), which subdivided into complete RBBB defined as RSR' or RSR' configuration in lead V1 or V2 and a QRS duration ≥ 120 ms in leads I, II, III, aVL, and aVF and incomplete RBBB (QRS duration <120 ms).¹⁷

Correlation Analyses

HRV parameters were correlated with peak oxygen uptake and peak heart rate from the upright bicycle exercise test performed on the same day.¹² Furthermore, HRV parameters were correlated with peak tissue Doppler imaging values from the exercise echocardiography (isovolumetric acceleration and systolic velocities).¹³ From the resting echocardiography, analyses were applied to the HRV parameters and right ventricle fractional area change and tricuspid annular plane systolic excursion. HRV parameters among patients with surgically closed VSDs were correlated with age, year, and type of operation (atriotomy or ventriculotomy). For unrepaired VSDs, analyses were applied between the current peak Doppler gradient across the defect and the HRV parameters.

Statistical Considerations

Continuous data are presented as mean with SD or medians with 95% CIs as appropriate and binary data are presented as absolute numbers and percentages of participants. For normally distributed data, differences between groups were assessed using unpaired Student *t* test with either equal or unequal variance, as tested by the variance-comparison test. The number of prespecified comparisons posed a risk of committing a type 1 error. A lower than normal *P*-value was chosen to compensate for the multiple comparisons. *P*<0.01 were considered statistically significant. Correlation analyses were made using Pearson's sample correlation *r*. The current study was a prespecified subanalysis of an exercise study with a primary end-point of exercise capacity. Therefore, sample size calculations were based on a previous exercise study on younger adults with closed VSDs,⁴ where a difference in peak oxygen uptake of 80% was expected. With a significance level of 5% and a power of 90%, at least 19 participants in each group were needed. We included 30 in each group to account for missing values or dropouts. Statistical analyses and drawing of plots were performed using StataC 11.2 (StataCorp LP, College Station, TX) and Prism 7 (GraphPad Software, La Jolla, CA).

RESULTS

Study Population

A total of 30 patients with surgically closed VSDs and 30 healthy peers along with 30 patients with small, unrepaired VSDs and 30 healthy peers were enrolled between September 2018 and August 2019. Table 1 describes demographics and clinical characteristics, with types of VSDs classified as described by Jacobs

Table 1. Demographics in Patients With Surgically Closed or Unrepaired VSDs and Healthy Peers

	Closed VSDs (n=30)	Healthy controls (n=30)	Open VSDs (n=30)	Healthy controls (n=30)
Age, y	51±8	52±9	55±12	55±10
Body mass index	28±4	26±4	27±7	26±4
Body surface area, m ²	2.0±0.2	2.0±0.2	1.9±0.3	1.9±0.2
Men, n (%)	15 (50)	15 (50)	13 (43)	13 (43)
Lean body mass, %	72±8	75±6	72±8	74±5
Systolic blood pressure, mm Hg	122±19	129±24	129±17	128±17
Diastolic blood pressure, mm Hg	80±11	86±17	82±11	85±18
Smoking status, smoker/ex-smoker/never, n	2/11/17	2/13/15	3/9/18	2/14/14
NYHA class I/II/III, n	21/7/2	29/1/0	23/7/0	29/1/0
Prescription medicine, n	14	16	18	12
Type of VSD, perimembranous/muscular/inlet/outlet, n	18/1/1/4*		17/7/4/2	

Mean±SD or total number with (percentage). NYHA indicates New York Heart Association; and VSD, ventricular septal defect.

*Missing information in 6 surgically closed patients.

et al.¹⁸ No demographic differences existed between patients and healthy peers. Regarding cardiac-related prescription medication, 20% of surgically closed patients used antihypertensive medication compared with 17% of matched controls, and 27% of unrepaired VSDs compared with 20% of their controls. Surgically closed VSDs and unrepaired VSDs used anticoagulants (13% and 20%, respectively) and antiarrhythmic medication (3% and 7%, respectively), with none in the 2 control groups.

All surgically closed VSDs were operated through median sternotomy between 1964 and 2015 at a median age of 6.3 years (total range, 1.4–54 years), with 20 patients operated at <10 years of age (median, 5.5 years; total range, 1.4–8.6 years) and 10 patients operated at >10 years of age (median, 31 years; total range, 17–54 years). All patients were discharged from follow-up at a median age of 8 years (total range, 2–54 years). Interestingly, 60% of these patients were eventually referred back for checkup ≥ 1 times, with the most common causes being palpitations ($n=10$), chest pain ($n=4$), and syncope ($n=2$). Currently, 2 patients are followed in outpatient clinics, whereas the remaining 28 were last seen 16 years ago (total range, 4–43 years). Other cardiac congenital abnormalities were present, comprising 3 patients with closed persistent ductus arteriosus, 4 with closed atrial septal defect, 1 with closed aortopulmonic fistula, 1 with mitral valve disease, 1 with aortic insufficiency, and 1 with bicuspid aortic valve that had resulted in a mechanical valve. No significant residual VSD was found, assessed by echocardiography on the day of enrollment.

None of the unrepaired VSDs had closed spontaneously as evaluated by auscultation and echocardiography on the day of enrollment. The mean gradient across the defect was 97 ± 25 mm Hg (range, 54–139 mm Hg). Regarding other congenital cardiac

abnormalities among unrepaired patients, 1 patient had a bicuspid aortic valve, and 1 patient had a subvalvular membrane. Of patients with unrepaired VSD, 83% had been discharged from follow-up at a median age of 19 years (range, 6–24 years). Following discharge, 80% were referred back ≥ 1 times, with the most frequent causes being chest pain ($n=17$), palpitations ($n=8$), syncope ($n=3$), and aortic insufficiency ($n=1$). Interestingly, 17% of unrepaired VSDs had experienced an episode of infectious endocarditis after initially being discharged. Currently, 7 unrepaired VSDs are followed with intervals of 3 to 5 years, with the remaining 23 patients last seen 15 years ago (total range, 6–32 years).

Holter Monitoring

Heart rate variations and arrhythmic events during Holter monitoring are displayed in Table 2. No differences were demonstrated among the 4 groups regarding heart rates. Both surgically closed and unrepaired VSDs had higher numbers of PVCs compared with their controls ($P<0.01$). For participants with >200 PVCs, the percentage of PVC of total number of beats, the PVC burden, was $1.4\pm 2\%$ in surgically closed VSDs compared with $0.7\pm 0.5\%$ in controls ($P=0.07$) and $2.8\pm 3\%$ in unrepaired VSDs compared with $1.0\pm 0.6\%$ in controls ($P=0.63$). Regarding other events, a number of the patients with VSD had ventricular tachyarrhythmias, sinus pauses, and atrioventricular block; however, none were significantly different from controls. Considering subjective incidents, 7% of surgical patients registered incidents (chest pain) compared with 3% of their controls (dyspnea), whereas 17% of unrepaired patients with VSD registered incidents (chest pain and palpitations) compared with 3% of controls (dyspnea).

Table 2. Heart Rate Variations and Events for Patients With Surgically Closed or Unrepaired VSDs and Healthy Peers

	Closed VSDs (n=30)	Healthy controls (n=30)	P Value	Open VSDs (n=30)	Healthy controls (n=30)	P Value
Heart rate						
Minimum, beats/min	57 \pm 9	52 \pm 7	0.02	55 \pm 8	52 \pm 8	0.14
Mean, beats/min	75 \pm 10	80 \pm 19	0.39	75 \pm 9	77 \pm 20	0.64
Maximum, beats/min	159 \pm 18	160 \pm 27	0.86	159 \pm 19	161 \pm 21	0.73
Events						
High number of PVC,* n (%)	17 (57)	1 (3)	<0.01	16 (53)	4 (13)	<0.01
Supraventricular tachyarrhythmia, n (%)	8 (27)	14 (47)	0.11	14 (47)	12 (40)	0.60
Ventricular tachyarrhythmia, n (%)	4 (13)	1 (3)	0.16	4 (13)	0 (0)	0.04
Sinus pauses, n (%)	3 (10)	0 (0)	0.07	2 (7)	0 (0)	0.15
Atrioventricular block, n (%)	3 [†] (10)	0 (0)	0.30	2 [†] (7)	0 (0)	0.15
Subjective incidents, n (%)	2 (7)	1 (3)	0.56	5 (17)	1 (3)	0.08

Mean \pm SD or total number with (percentage). PVC indicates premature ventricular contractions; and VSD, ventricular septal defect.

*Defined as >200 PVCs during the recording.

[†]All atrioventricular blocks were first-degree blocks of which none had a pacemaker.

Table 3. Time-Domain Measures of Heart Rate Variability in Patients With Surgically Closed or Unrepaired VSDs and Healthy Peers

	Closed VSDs (n=27)	Healthy controls (n=30)	P Value	Open VSDs (n=30)	Healthy controls (n=30)	P Value
Analyzed ECG, %	93±9	95±6	0.27	93±9	96±5	0.09
Mean RR, ms	797±95	799±158	0.97	814±93	816±133	0.95
SDNN, ms	129±37	168±39	<0.01	145±39	163±40	0.08
SDNNi	44±15	59±18	<0.01	50±12	56±18	0.13
SDANN, ms	116±35	149±35	<0.01	129±36	145±36	0.11
rMSSD, ms	23±12	30±15	0.05	25±8	29±15	0.15
pNN50, %	5.4±7	8.8±9	0.11	5.3±4	8.4±9	0.10
24-h triangular index	31±9	45±10	<0.01	40±11	44±12	0.16

Mean±SD. pNN50 indicates percentage of RR intervals differing by more than 50 ms; rMSSD, square root of the mean squared difference between normal-to-normal interbeat intervals; RR, interbeat interval between all successive heartbeats; SDANN, SD of the average normal-to-normal interbeat intervals for each 5-minute segment of a 24-hour HRV (heart rate variability) recording; SDNN, SD of the normal-to-normal interbeat intervals; SDNNi, SDNN index; and VSD, ventricular septal defect.

None of the subjective incidents coincided with particular events on the ECG explaining the symptoms of the participant.

Heart Rate Variability

Three patients with surgically closed VSDs were excluded because of pacemaker (n=1) and permanent

atrial fibrillation (n=2). For the study population, the HRV time-domain measures are presented in Table 3, with differences seen in the group of surgically closed VSDs when compared with their healthy peers. Scatter plots on SDNN, SD of the average NN intervals for each 5-minute segment of a 24-hour HRV recording, and triangular index are displayed in Figure 1, along with examples on HRV from 3 different subjects

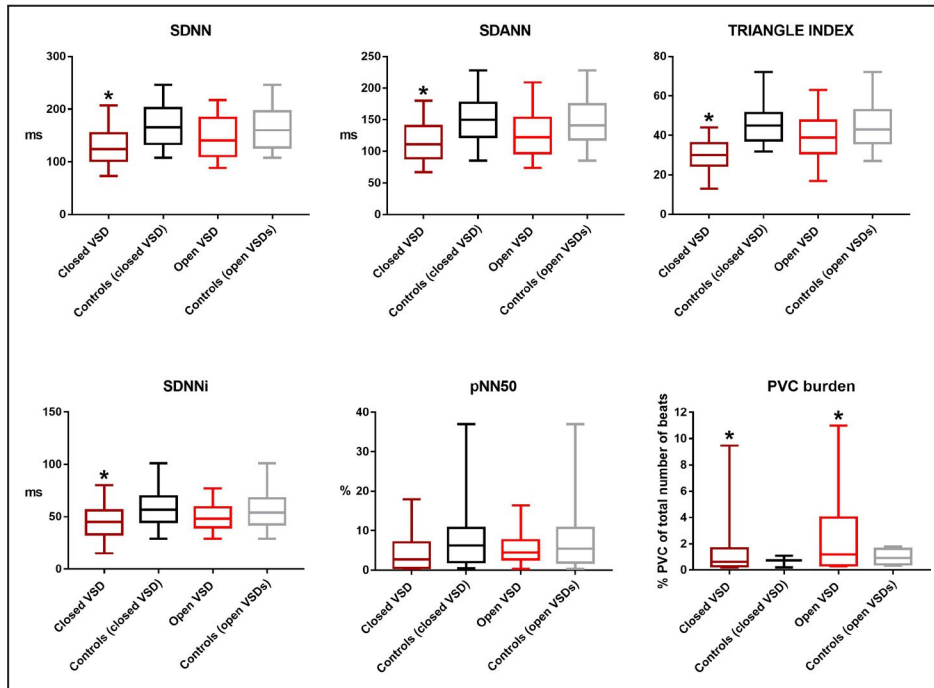


Figure 1. Box plots depicting heart rate variability in patients with surgically closed VSDs and their controls, as well as patients with unrepaired VSDs and their controls.

Asterisk indicating significant differences ($P<0.01$) between patient group and their healthy, matched controls. PVC burden: depicting % premature ventricular contractions of total number of beats for participants with >200 premature ventricular contractions. pNN50 indicates percentage of RR intervals differing by more than 50 ms; PVC, premature ventricular contraction; SDANN, SD of the average normal-to-normal interbeat intervals for each 5-minute segment of a 24-hour HRV recording; SDNN, SD of the normal-to-normal interbeat intervals; SDNNi, SDNN index; and VSD, ventricular septal defect.

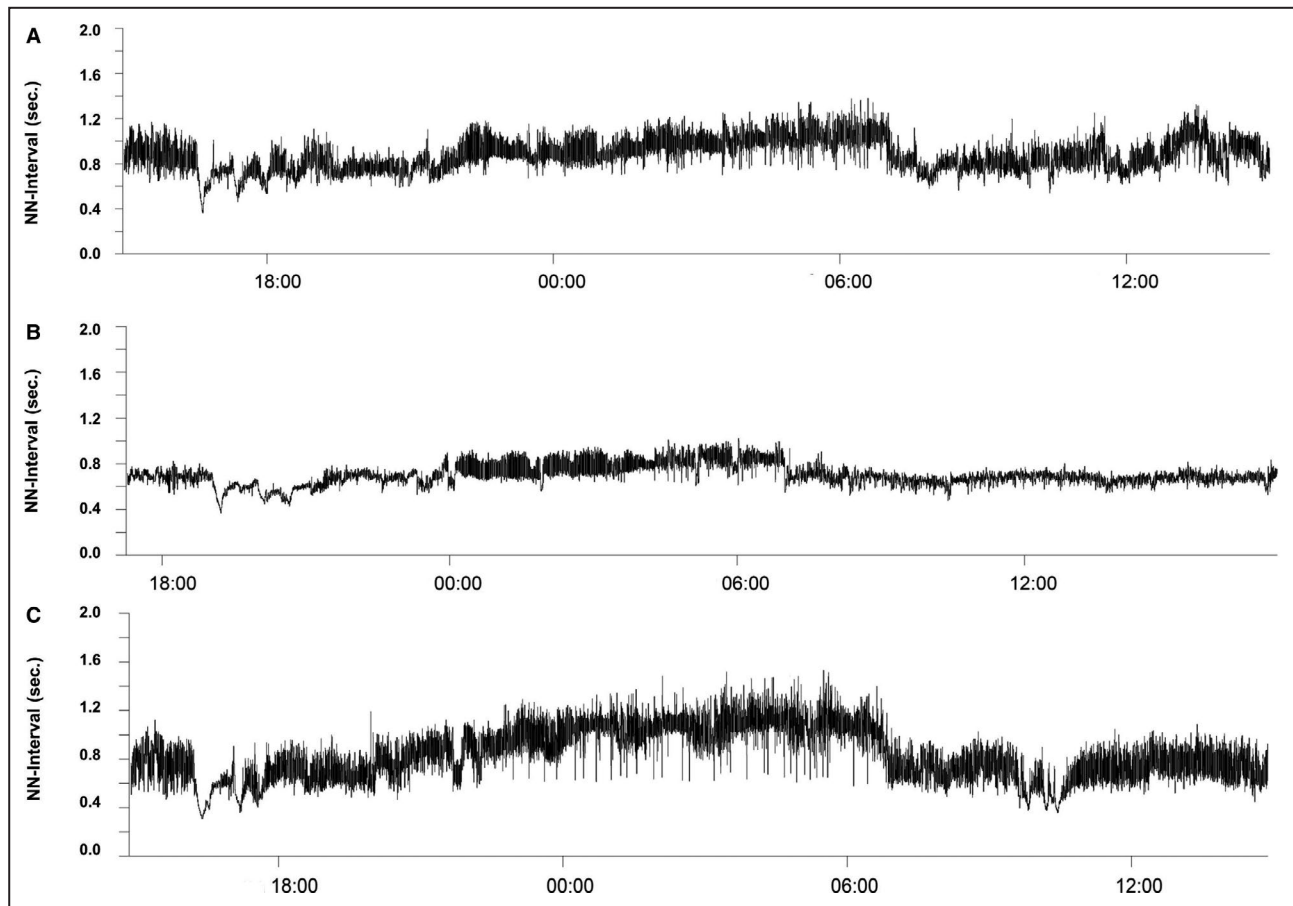


Figure 2. Examples on NN interval time series on the total study period of 24 hours in (A) a patient with a surgically closed VSD (42.5-year-old man; SDNN, 134.2; triangular index, 38.9), (B) a patient with an unrepaired VSD (48.3-year-old man; SDNN, 89.1; triangular index, 16.8), and (C) a healthy control (43.1-year-old man; SDNN, 203.6, triangular index, 48.8). NN indicates normal-to-normal; SDNN, SD of the normal-to-normal interbeat intervals; and VSD, ventricular septal defect.

in Figure 2. Regarding the primary end point, 22% of surgically closed VSDs and 10% of unrepaired VSDs demonstrated SDNN <100 ms, whereas all of the controls had normal SDNN. Considering differences between surgically closed and unrepaired VSDs, the surgical patients demonstrated lower triangular index compared with unrepaired VSDs (31 ± 9 versus 40 ± 11 ; $P<0.01$), with all remaining time-domain measures being comparable.

Subgroup Analysis

Of all surgically closed patients, 17 had complete RBBB, 5 had incomplete RBBB, and 8 had no RBBB. No differences could be demonstrated between surgically closed VSDs with complete RBBB and surgical patients with either incomplete or no RBBB regarding peak heart rate ($P=0.83$), SDNN ($P=0.87$), SDNN index ($P=0.77$), SD of the average NN intervals for each 5-minute segment of a 24-hour HRV recording ($P=0.55$), square root of the mean squared

difference between NN intervals ($P=0.56$), triangular index ($P=0.250$), or percentage of RR intervals differing by >50 ms ($P=0.73$). One unrepaired VSD had complete RBBB, whereas none of the healthy controls had RBBB.

Correlation Analyses

A negative correlation was found between a low resting heart rate and SDNN for all 4 groups, which is displayed in Figure 3. Furthermore, a positive tendency was seen regarding those with first-degree atrioventricular blocks or sinus arrests and SDNN for surgically closed VSDs ($r=0.41$; $P=0.03$) and unrepaired VSDs ($r=0.40$; $P=0.03$). For the surgically closed VSDs, no correlations were demonstrated between HRV parameters and age at operation, year of operation, or surgical approach (atriotomy or ventriculotomy). For the unrepaired VSDs, no association was established between the current gradient across open defect and HRV measurements. Regarding analyses between HRV parameters and peak oxygen uptake as well as

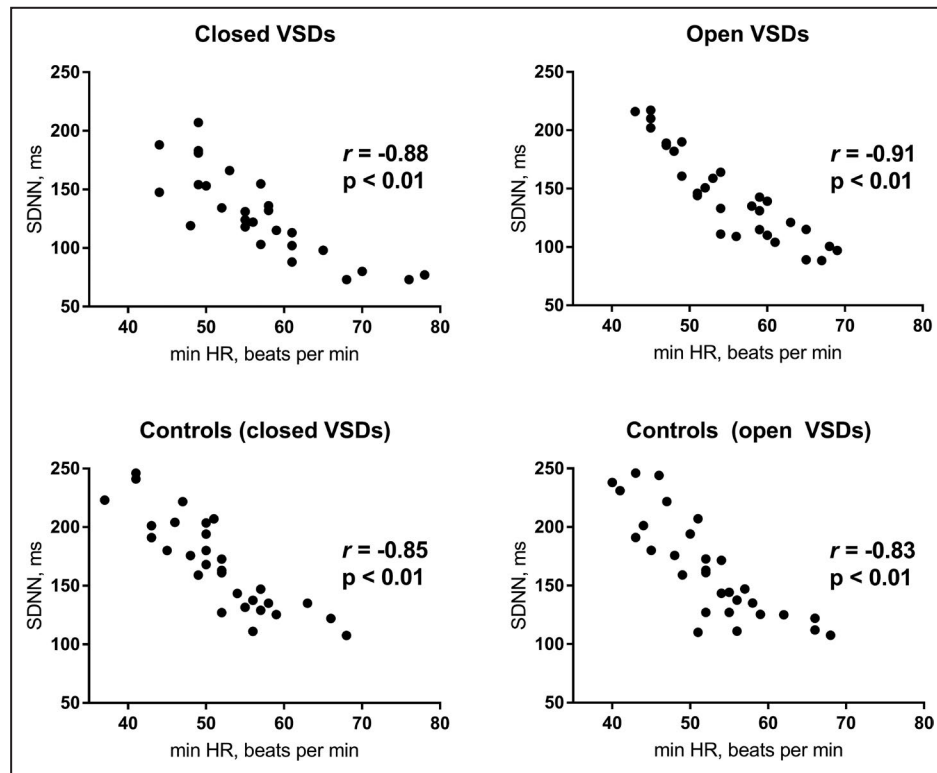


Figure 3. Correlations between a low resting heart rate and SDNN for patients with surgically closed VSDs and their controls, as well as for patients with unrepaired VSDs and their controls.

HR indicates heart rate; SDNN, SD of the normal-to-normal interbeat intervals; and VSD, ventricular septal defect.

peak heart rate from the upright bicycle test,¹² no correlations were seen for patients or healthy controls, except in unrepaired VSDs when considering peak oxygen uptake and SDNN index ($r=0.47$, $P<0.01$) as well as triangular index ($r=0.42$; $P<0.01$). Considering correlation analyses between HRV parameters and resting and exercise echocardiography,¹³ no association was demonstrated.

DISCUSSION

This is the first study to assess HRV in adults past the age of 40 years with a congenital VSD. The most pronounced difference was seen in patients with surgically closed VSDs where a number of reduced time-domain measures are presented when compared with their healthy peers. Reduced HRV could indicate an autonomic imbalance in the patients. We speculate that the dissection in the vicinity of the larger vessels, for placing the aorta clamp and snaring the caval veins, may damage parts of the vagal nerve that innervates the sinoatrial node and thus cause reduced chronotropic response and perhaps overall impaired HRV. In a recent study, patients with VSDs in their mid-20s likewise

demonstrated reduced time-domain measures, with the most predominant findings in the surgically closed defects.¹⁰ Nevertheless, both surgical intervention and catheter-device closure improve the lower HRV following 3 months after intervention.¹⁹ In our study, the patients with unrepaired VSDs also demonstrated a degree of reduced HRV, although not to the same extent as in the surgically closed VSDs. One of the most interesting parameters of this study is the SDNN measure, which is established as a strong correlate with cardiac mortality in patients suffering from acute myocardial infarction.^{16,20} An SDNN >100 ms is considered to be a reflection of “normal health.”^{15,16} None of the healthy older controls in our study demonstrated abnormal SDNN, whereas 22% of our surgically closed patients and 10% of unrepaired VSDs presented with SDNN <100 ms.

Another interesting finding is the markedly higher proportion of PVCs, with 57% detected in surgically closed VSDs and 53% in unrepaired VSDs. For comparison, 30% of younger adults with surgically closed VSDs and 7% of unrepaired VSDs, all in their mid-20s, presented with a high number of PVCs, whereas healthy peers had none.¹⁰ Although

the significance of a high number of PVCs is far from fully understood, it does justify a noteworthy finding by Dukes et al from 2015.²¹ A total of 1429 healthy subjects aged >65 years with initial normal left ventricular ejection fraction and no history of congestive heart failure were followed with serial 24-hour Holter monitoring for ≈15 years, where a high percentage of PVC was associated with declining ejection fraction, increase in congestive heart failure, and increase in mortality. The specificity for prediction of congestive heart failure exceeded 90% when PVCs included at least 0.7% of total ventricular beats of 24-hour recordings. Furthermore, the positive predictive value for the 15-year risk of incident congestive heart failure was >50% for PVC percentages between 1.24% and 3.55%. These are quite striking results considering that more than half of our patients have a mean PVC proportion of $1.4 \pm 2\%$ in surgically closed VSDs and $2.8 \pm 3\%$ in unrepaired VSDs. Moreover, our patients have a younger mean age than those investigated in the study by Dukes et al, so it is particularly concerning that such a large proportion of patients already demonstrate a relatively high percentage of PVCs, without receiving follow-up. Only 15% of our studied patients are currently followed in outpatient clinics, with the majority discharged for many years.

Reduced HRV is an established strong predictor of all-cause mortality.^{22,23} Others have likewise found poorer outcomes with regard to life expectancy in these simple defects when compared with the general population. In a register-based study from 2016, 1241 patients with simple congenital defects, diagnosed between 1963 and 1973, alive at age 15 years, were followed until 2013, at a median age of 47 years.²⁴ Adults with VSDs had increased mortality compared with the control population (adjusted hazard ratio, 2.08) with one of the most frequent events for critical cardiac morbidity, besides (re)operation, being heart failure or ventricular tachyarrhythmia. The most common cause of death was “sudden unexpected death.” Only 20% were seen in outpatient clinics, much like our current patient population. In another nationwide register-based study, Larsen et al¹ focused on long-term survival following interventional treatment in congenital heart diseases for 3 different time periods. As our current surgical patient population had undergone intervention at a median year of 1978, it is particularly noteworthy that VSDs with intervention between 1977 and 1989 had a long-term survival of 79% compared with 97% in the matched background population. Although survival improves for those born and operated in the later years, it still remains lower than the background population.

Limitations

The study design presents a limitation, as it was not possible to establish whether patients will further progress in terms of impairment. It would be interesting to follow these patients with serial monitoring to investigate the specific development of HRV time-domain measures. According to well-established recommendations, strenuous physical exercise should not be performed during the 24 hours recordings for the HRV analysis.¹⁵ All participants underwent a bicycle exercise test, which could present a limitation in the interpretation of the results. Nevertheless, as this was the case for all participants, the time-domain differences seen between patients and controls as well as the higher prevalence of certain events in patients compared with controls still present interesting findings with the same clinical relevance as discussed. A risk of selection bias should be considered, as patients are invited on the basis of their diagnosis, whereas controls are found through announcements and thereby seek participation on their own initiative. It is therefore critical to ensure good matching between groups on as many measurable parameters as possible, as presented in the demographics of the study. The high percentage of endocarditis is unexpected and unexplained, and the impact on HRV and on the frequency of ventricular ectopy is unknown. Finally, treatment and management of VSDs have improved over the past decades, necessitating careful interpretation, as our study population is a reflection of previous management. Still, our patients represent a large group of adults with congenital VSDs that in the coming years most likely will need increased surveillance and treatment.

CONCLUSIONS

Adult patients past the age of 40 years with either a surgically closed or unrepaired VSD demonstrate an impaired HRV and a high proportion of PVCs when compared with their healthy peers. Since both impaired HRV and a high proportion of PVCs are associated with increased risk of congestive heart failure and all-cause mortality, these novel findings may suggest long-term cardiovascular disturbances, and consequently favor the increasing awareness that a congenital VSD has an impact on later outcome in adulthood warranting continuous follow-up at specialized centers.

ARTICLE INFORMATION

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Disclosures

None.

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