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Effects of Transcatheter Closure of Atrial Septal Defects on Heart Rate Variability

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This study evaluated heart rate variability and its changes in 30 patients before and after transcatheter closure of secundum atrial septal defects. Heart rate variability data from 30 healthy volunteers with normal echocardiographic parameters and no history of atrial septal defects were included as controls. Values for the SD of all the normal RR intervals (SDNN), the SD of the means of all the 5-min segment normal RR intervals (SDANN), and the mean of all the 5-min SDs of normal RR intervals during the 24-h period (SDNN index) in patients with atrial septal defects before transcatheter closure were statistically significantly different from controls. At 6 months after closure of the defects these values were not statistically different from controls. It is concluded that transcatheter closure of secundum atrial septal defects had positive effects on heart rate variability and, consequently, may contribute to less mortality and morbidity.

KEY WORDS: Atrial septal defect; Heart rate variability; Transcatheter closure; Cardiac autonomic nervous activity; RR interval

Introduction

Secundum atrial septal defects (ASD) account for 10% of congenital heart disease cases at birth and for as much as 30% – 40% of congenital heart problems in adults.[1] The most common intervention for structural heart disease is transcatheter closure (TCC) of ASD.[2] This is a safe and effective procedure that is rapidly becoming standard treatment for secundum ASD.[2,3]

The determination of heart rate variability (HRV) is a non-invasive way of assessing the effects of the autonomic nervous system in patients with sinus arrhythmia.[4] Decreased HRV has been found in various forms of heart disease including myocardial infarction,[5] congestive heart failure,[6] coronary heart disease,[7] chronic mitral regurgitation[8] and congenital heart diseases[9] such as secundum ASD,[10,11] as well was many other medical conditions.[12,13] It is also an independent predictor of increased mortality among patients with myocardial infarction and congestive heart disease.[14]

The present cross-sectional, case–control study was designed to evaluate cardiac autonomic functions and the influence of TCC of ASD on cardiac autonomic function.

Patients and methods

STUDY POPULATION

Patients with secundum-type large ASD ('stretched' diameter > 20 mm and/or invasive QP/QS ratio > 1.5) who underwent TCC at the Department of Cardiology, Faculty of Medicine, Inonu University,

Malatya, Turkey between March 2009 and March 2010 were recruited into the study. Healthy volunteers attending the outpatient clinic for routine check-up and without any cardiac or non-cardiac disease, and who had normal physical examination and routine laboratory results, served as controls. All patients were evaluated for arrhythmia, ischaemic stroke, cardiac perforation, device erosion, embolization, thrombus formation, or for malposition of the device at 6 months after operation.

All patients and controls were required to have normal sinus rhythms to be elible for inclusion and were excluded if they had a history of symptomatic arrhythmias or syncope, were taking antiarrhythmic drugs, had recent or current treatment with diuretics or cardioactive drugs, had electrolytic or acid–base disturbances at baseline laboratory work-up, had valvular heart disease, ischaemic heart disease, cardiomyopathies or clinical evidence of heart failure. Patients with other congenital cardiac defects associated with ASD were also excluded.

The study was performed according to the principles of the Declaration of Helsinki and was approved by the Investigational Review Board of the School of Medicine at Inonu University. Written informed consent was obtained from all participating patients and controls.

ECHOCARDIOGRAPHY AND TCC

Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) were performed, using an ATL/Philips HDI-5000 echocardiography machine (Philips Medical Systems [Philips Ultrasound], Bothell, WA, USA) and a 5.0 MHz biplanar transoesophageal probe, in all patients in three different frames recorded at the same phase of the cardiac cycle as described in detail previously.[15] The following heart parameters were measured in patients before and after TCC and in controls: left ventricular ejection fraction (LVEF); left ventricular end-systolic diameter (LVESD); left atrium (LA) diameter; interventricular septum (IVS) diameter; left ventricular posterior wall (LVPW) diameter; right atrium (RA) diameter; right ventricle (RV) diameter; pulmonary artery systolic pressure (PASP); and left ventricular end-diastolic diameter (LVEDD).

The TCC procedure was performed under TEE monitoring using the Occlutech Figulla ASD Occluder (FSO) (Occlutech, Jena, Germany), as described previously.[15,16] Aspirin (3 – 5 mg/kg) was administered 24 h before the operation and continued daily for 6 months afterwards.

DETERMINATION OF HRV

Ambulatory 24-h Holter recordings before and 6 months after ASD closure were used to determine HRV. Six-channel, 24-h ambulatory electrocardiographic recordings (DMS 300-7 HolterReader; DMS, Stateline, NV, USA) were obtained for all patients and controls. Before automatic analysis of the tapes with the Holter program (CardioScan 12.0 DM software; DMS), all electrocardiographic recordings were visually reviewed by an experienced cardiologist (H.P.) and edited to delete artifacts. All data were also reviewed by the same cardiologist. There had to be ≥ 23 h of analysable data for the 24-h recording to be accepted for the study. The following time-domain HRV indices were determined: the SD of all the normal RR intervals (SDNN); the SD of the means of all the 5-min segment normal RR intervals (SDANN); the mean of all the 5-min SDs of normal RR intervals during the 24-h period (SDNN index); the root-mean square of differences between

adjacent normal RR intervals during the 24-h period (rMSSD); the number of successive normal RR intervals > 50 ms during the 24-h period (sNN50); and the percentage differences between adjacent normal RR intervals that are > 50 ms during the 24-h period (pNN50). Among them, rMSSD, sNN50 and pNN50 primarily reflect parasympathetically-mediated changes in heart rate.[17] The other time-domain variables reflect a mixture of parasympathetic, sympathetic and other physiological influences.

STATISTICAL ANALYSES

Statistical analyses were carried out using the SPSS® statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Continuous variables were expressed as mean ± SD and categorical variables were expressed as numbers and percentages. The continuous variables were determined for normality by the Shapiro–Wilk test and found to have a normal distribution. Independent *t*-tests and paired *t*-tests were used for between-group comparisons. Mann–Whitney *U*-tests and χ^2 tests was used for comparison of categorical variables where appropriate. A *P*-value < 0.05 was considered to be statistically significant.

Results

In total, 30 patients (four men, 26 women; mean ± SD age 34 ± 13 years, age range 18 – 64 years) with secundum type large ASD underwent TCC and 30 healthy volunteers (six men, 24 women; mean ± SD age 29 ± 6 years, age range 19 – 40 years) served as controls. There were no statistically significant differences in sex or age between the two groups. The mean ± SD diameter of the ASD was 15.6 ± 6.8 mm (range 5 – 30 mm) and mean ± SD QP/QS ratio was 1.9 ± 0.4 (range 1.4 – 3.3). Two of the patients with ASD had a history of cerebrovascular accident.

The HRV parameters were compared between patients before and after TCC and with controls. The values for SDNN, SDANN and SDNN index in patients with ASD before LCC were statistically significantly different from controls ($P \leq 0.005$) whereas, after TCC, there was no statistically significant difference between patients and controls (Table 1).

The LVEF, LVEDD, LVESD and IVS values were not statistically significantly different among patients with ASD before or after TCC or compared with controls (Table 2). Although there was no statistical difference in LVESD, it tended to a slight increase after TCC. Compared with patients with ASD before TCC, LA diameter, LVPW, RA diameter, RV diameter and PASP were significantly improved after TCC ($P \leq 0.011$; Table 2). Values for LA diameter, LVPW and RV diameter were not statistically significantly different from the control group after LCC, whereas RA diameter and PASP remained statistically significantly higher than the control group ($P = 0.001$; Table 2).

Discussion

An isolated ASD results in left-to-right shunting which, when significant, leads to RA/RV and pulmonary arterial dilation.[18] It is now accepted that long-standing right heart, pulmonary arterial and venous volume overload and dilation in the setting of an ASD is detrimental and leads to morbidity (heart failure, arrhythmia and thromboembolic events) and increased mortality.[19,20] Patients with ASD have increased RA, LA and RV diameters compared with individuals without ASD[21,22] and this was also shown in the present study.

The 'ideal' ASD treatment should aim at both eliminating the intracardiac shunt and

TABLE 1:
Comparison of heart rate variability (HRV) parameters in the control group and before and 6 months after transcatheter closure (TCC) of secundum atrial septal defect in the patient groups

	Patient group		
HRV parameter	Control group (n = 30)	Before TCC (n = 30)	After TCC (n = 30)
SDNN (ms)	139.2 ± 30.3	103.9 ± 29.4[a]	131.1 ± 41.3[b]
SDANN (ms)	125.5 ± 30.3	91.2 ± 29.4[a]	119.8 ± 42.7[b]
SDNN index (ms)	60.6 ± 12.7	45.6 ± 18.7[c]	54.3 ± 15.5[d]
rMSSD (ms)	31.1 ± 7.9	27.1 ± 16.1	31.5 ± 13.8
pNN50 (%)	10.0 ± 5.7	9.0 ± 9.5	10.8 ± 8.4

Data presented as mean ± SD
[a]P = 0.001 versus control; [b]P = 0.0001 versus before TCC; [c]P = 0.005 versus control; [d]P = 0.004 versus control); independent and paired t-tests.
SDNN, the SD of all the normal RR intervals; SDANN, SD of the means of all the 5-min segment normal RR intervals; SDNN index, the mean of all the 5-min SDs of normal RR intervals during the 24-h period; rMSSD, the root-mean square of differences between adjacent normal RR intervals during the 24-h period; pNN50, the percentage differences between adjacent normal RR intervals that are > 50 ms during the 24-h period.

reversing the geometric change caused by cardiac overload.[21] Transcatheter ASD device occlusion has become the treatment of choice for most secundum ASDs and appears to be beneficial, with improvements in life quality and functional capacity, reduction of pulmonary artery pressure[23] and tricuspid regurgitation,[24] and minimal complications[25,26] such as atrial tachyarrhythmias.[27] After TCC, the heart remodels and pulmonary artery pressure decreases.[23] In some patients with ASD, dilation of the RV may subside for up to 5 years after ASD closure.[28] Others have reported progressive normalization of RV size during the first 24 months after surgical or device closure.[29 – 32] In the present study, RV diameter and PASP had decreased significantly 6 months after TCC compared with values measured before TCC in patients with ASD.

Impaired cardiac autonomic nervous system activity is associated with an increased risk of sudden cardiac death in congenital cardiac disease.[33] HRV is a non-invasive method for investigating the effects of the autonomic nervous system in patients with sinus rhythm. A decrease in HRV is proportional to end-diastolic pressure in the RV, so that RV volume overload possibly induces ventricular baroreceptor dysfunction and this directly influences sympathicovagal balance.[34] Horner *et al.*[35] have shown in pig hearts that increased mechanical stretch of the volume-overloaded RA on the sino-atrial nodal area could alter HRV by a direct effect on diastolic depolarization within sino-atrial pacemaker cells via stretch-activated channels or a reflex-mediated response to afferent signals via neuronal stretch receptors. Atrial arrhythmias in ASD patients are the by-product of long-standing RA dilation and stretch.[36] Atrial tachyarrhythmias are common among adults with secundum ASD and contribute to substantial cardiac morbidity[37 – 39] Edwards *et al.*[40] have shown that atrial stretch is the principal stimulus for atrial natriuretic peptide secretion. These findings strengthen the likelihood that reduction in volume and

TABLE 2:
Comparison of echocardiographic parameters in the control group and before and 6 months after transcatheter closure (TCC) of secundum atrial septal defect in the patient groups

Echocardiographic parameter	Control group (I) (*n* = 30)	Patient group: Before TCC (II) (*n* = 30)	Patient group: After TCC (III) (*n* = 30)	Statistical significance[a]: I versus II	Statistical significance[a]: II versus III	Statistical significance[a]: I versus III
LVEF (%)	61.4 ± 6.6	64.9 ± 4.4	64.8 ± 3.6	NS	NS	NS
LVEDD (mm)	44.8 ± 1.4	44.1 ± 3.5	44.1 ± 2.9	NS	NS	NS
LVESD (mm)	29.3 ± 2.8	26.2 ± 3.3	27.5 ± 3.3	NS	NS	NS
LA diameter (mm)	31.1 ± 2.1	33.7 ± 4.3	32.7 ± 3.8	$P = 0.02$	$P = 0.011$	NS
IVS (mm)	10.3 ± 0.8	10.1 ± 0.5	10.6 ± 0.3	NS	NS	NS
LVPW (mm)	10.3 ± 0.8	9.2 ± 0.7	10.3 ± 0.8	$P = 0.001$	$P = 0.001$	NS
RA diameter(mm)	26.2 ± 2.3	37.1 ± 6.0	33.7 ± 5.0	$P = 0.001$	$P = 0.001$	$P = 0.001$
RV diameter (mm)	38.8 ± 2.5	43.1 ± 7.0	39.3 ± 5.7	$P = 0.015$	$P = 0.001$	NS
PASP (mm/Hg)	25.8 ± 3.9	38.0 ± 5.3	32.3 ± 4.3	$P = 0.001$	$P = 0.001$	$P = 0.001$

Data presented as mean ± SD.
[a]Independent and paired *t*-tests.
LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, ventricular end-systolic diameter; LA, left atrium; IVS, interventricular septum diameter; LVPW, left ventricular posterior wall diameter; RA, right atrium; RV, right ventricle; PASP, pulmonary artery systolic pressure; NS, not statistically significant ($P > 0.05$).

pressure as well as neurohumoural factors influence improvement in HRV. Previous studies have demonstrated that vagal activity and indices of HRV are reduced in ASD, with the change dependent on the extent of haemodynamic disturbances, expressed by variables such as elevated RV filling pressure and pulmonary arterial hypertension.[34,41] Similarly, in the present study, indices of vagal activity, such as SDNN, SDANN and SDNN index values, were reduced in the ASD group compared with the control group, whereas there were no changes in rMSSD and pNN50 values, which are indices of parasympathetic system activity.

As in the present 6-month study on adults, HRV evaluated in a paediatric population with ASD following TCC reported significant improvement 3 months after TCC.[11] Decreases in cardiac parameters and improvements in time-domain HRV parameters in patients with ASD were found in the present study. The HRV parameters may be improved as a result of reduced blood volumes in the RA and RV after TCC causing a decrease in RA and RV diameters.[42]

For technical reasons, only the time-domain parameters of HRV were used in the present study. The study would have been improved by inclusion of frequency-domain parameters; however, as time-domain and frequency-domain parameters are related to each other, with a change in one of them generally suggestive of a change in the other,[43] the present study still has value. In addition, a study of healthy subjects found that the time-domain HRV was better for indicating vagal activity.[44]

In conclusion, the present study demonstrated that TCC of isolated secundum ASD using the novel design of the FSO device was safe and effective during the first 6 months of follow-up, and that this procedure had positive effects on HRV, potentially leading to less mortality and morbidity. These short-term findings should be evaluated in further long-term prospective studies with larger numbers of patients.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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References

1 Abd El Rahman MY, Hui W, Timme J, *et al*: Analysis of atrial and ventricular performance by tissue Doppler imaging in patients with atrial septal defects before and after surgical and catheter closure. *Echocardiography* 2005; **22:** 579 – 585.
2 Du ZD, Hijazi ZM, Kleinman CS, *et al*: Comparison between transcatheter and surgical closure of secundum atrial septal defects in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol* 2002; **39:** 1836 – 1844.
3 Marie Valente A, Rhodes JF: Current indications and contraindications for transcatheter atrial septal defect and patent foramen ovale device closure. *Am Heart J* 2007; **153(4 suppl):** 81 – 84.
4 Heart rate variability, standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; **93:** 1043 – 1065.
5 Kleiger RE, Miller JP, Bigger JT, *et al*: Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; **59:** 256 – 262.
6 Brouwer J, Van Veldhuisen DJ, Man in'T Veld AJ, *et al*: Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. The Dutch Ibopamine Multicenter Trial Study Group. *J Am Coll Cardiol* 1996; **28:** 1183 – 1189.
7 Rich MW, Saini JS, Kleiger RE, *et al*: Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. *Am J Cardiol* 1988; **62:** 714 – 717.

8 Stein KM, Bores JS, Hochreiter C, *et al*: Prognostic value and physiological correlates of heart rate variability in chronic severe mitral regurgitation. *Circulation* 1993; **88:** 127 – 135.
9 Heragu NP, Scott WA: Heart rate variability in healthy children and in those with congenital heart disease both before and after operation. *Am J Cardiol* 1999; **83:** 1654 – 1657.
10 Massin MM, Derkenne B, von Bernuth G: Heart rate behavior in children with atrial septal defect. *Cardiology* 1998; **90:** 269 – 273.
11 Białkowski J, Karwot B, Szkutnik M, *et al*: Comparison of heart rate variability between surgical and interventional closure of atrial septal defect in children. *Am J Cardiol* 2003; **92:** 356 – 358.
12 Yokusoglu M, Ozturkt S, Uzun M, *et al*: Heart rate variability in patients with allergic rhinitis. *Mil Med* 2007; **172:** 98 – 101.
13 Yokusoglu M, Nevruz O, Baysan O, *et al*: The altered autonomic nervous system activity in iron deficiency anemia. *Tohoku J Exp Med* 2007; **212:** 397 – 402.
14 Bigger JT Jr, Fleiss JL, Steinman RC, *et al*: Frequency domain measures of heart rate variability and mortality after myocardial infarction. *Circulation* 1992; **85:** 164 – 171.
15 Podnar T, Martanovic P, Gavora P, *et al*: Morphological variations of secundum-type atrial septal defects: feasibility for percutaneous closure using Amplatzer septal occluders. *Catheter Cardiovasc Interv* 2001; **53:** 386 – 391.
16 Veldtman GR, Razack V, Siu S, *et al*: Right ventricular form and function after percutaneous atrial septal defect device closure. *J Am Coll Cardiol* 2001; **37:** 2108 – 2113.
17 Kleiger RE, Stein PK, Bosner MS, *et al*: Time domain measurements of heart rate variability. *Cardiol Clin* 1992; **10:** 487 – 498.
18 Davlouros PA, Niwa K, Webb G, *et al*: The right ventricle in congenital heart disease. *Heart* 2006; **92(suppl I):** i27 – i38.
19 Swan L, Gatzoulis MA: Closure of atrial septal defects: is the debate over? *Eur Heart J* 2003; **24:** 130 – 132.
20 Murphy JG, Gersh BJ, McGoon MD, *et al*: Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med* 1990; **323:** 1645 – 1650
21 Ding J, Ma G, Huang Y, *et al*: Right ventricular remodeling after transcatheter closure of atrial septal defect. *Echocardiography* 2009; **26:** 1146 – 1152.
22 Pascotto M, Santoro G, Cerrato F, *et al*: Time-course of cardiac remodeling following transcatheter closure of atrial septal defect. *Int J Cardiol* 2006; **112:** 348 – 352.
23 Balint OH, Samman A, Haberer K, *et al*: Outcomes in patients with pulmonary hypertension undergoing percutaneous atrial septal defect closure. *Heart* 2008; **94:** 1189 – 1193.
24 Yalonetsky S, Lorber A: Percutaneous closure of a secundum atrial septal defect in elderly patients. *J Invasive Cardiol* 2007; **19:** 510 – 512.
25 Majunke N, Bialkowski J, Wilson N, *et al*: Closure of atrial septal defect with the Amplatzer septal occluder in adults. *Am J Cardiol* 2009; **103:** 550 – 554.
26 Patel A, Lopez K, Banerjee A, *et al*: Transcatheter closure of atrial septal defects in adults ≥ 40 years of age: immediate and follow-up results. *J Interv Cardiol* 2007; **20:** 82 – 88.
27 Silversides CK, Haberer K, Siu SC, *et al*: Predictors of atrial arrhythmias after device closure of secundum type atrial septal defects in adults. *Am J Cardiol* 2008; **101:** 683 – 687.
28 Meyer RA, Korfhagen JC, Covitz W, *et al*: Long-term follow-up study after closure of secundum atrial septal defect in children: an echocardiographic study. *Am J Cardiol* 1982; **50:** 143 – 148.
29 Kort HW, Balzer DT, Johnson MC: Resolution of right heart enlargement after closure of secundum atrial septal defect with transcatheter technique. *J Am Coll Cardiol* 2001; **38:** 1528 – 1532.
30 Schussler JM, Anwar A, Phillips SD, *et al*: Effect on right ventricular volume of percutaneous Amplatzer closure of atrial septal defect in adults. *Am J Cardiol* 2005; **95:** 993 – 995.
31 Santoro G, Pascotto M, Sarubbi B, *et al*: Early electrical and geometric changes after percutaneous closure of large atrial septal defect. *Am J Cardiol* 2004; **93:** 876 – 880.
32 Santoro G, Pascotto M, Caputo S, *et al*: Similar cardiac remodelling after transcatheter atrial septal defect closure in children and young adults. *Heart* 2006; **92:** 958 – 962.
33 Lammers A, Kaemmerer H, Hollweck R, *et al*: Impaired cardiac autonomic nervous activity predicts sudden cardiac death in patients with operated and unoperated congenital cardiac disease. *J Thorac Cardiovasc Surg* 2006; **132:** 647 – 655.
34 Massin MM, Derkenne B, von Bernuth G: Heart rate behavior in children with atrial septal defect. *Cardiology* 1998; **90:** 269 – 273.
35 Horner SM, Murphy CF, Coen B, *et al*: Contribution to heart rate variability by mechanoelectric feedback. Stretch of the sinoatrial node reduces heart rate variability. *Circulation* 1996; **94:** 1762 – 1767.
36 Webb G, Gatzoulis MA: Atrial septal defects in the adult: recent progress and overview. *Circulation* 2006; **114:** 1645 – 1653.
37 Attie F, Rosas M, Granados N, *et al*: Surgical treatment for secundum atrial septal defects in patients > 40 years old. A randomized clinical trial. *J Am Coll Cardiol* 2001; **38:** 2035 – 2042.
38 Konstantinides S, Geibel A, Olschewski M, *et al*: A comparison of surgical and medical therapy for atrial septal defect in adults. *N Engl J Med* 1995; **333:** 469 – 473.

39 Gatzoulis MA, Freeman MA, Siu SC, *et al*: Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med* 1999; **340:** 839 – 846.
40 Edwards BS, Zimmerman RS, Schwab TR, *et al*: Atrial stretch, not pressure, is the principal determinant controlling in the acute release of atrial natriuretic factor. *Circ Res* 1988; **62:** 191 – 195.
41 Ferguson JJ 3rd, Miller MJ, Aroesty JM, *et al*: Assessment of right atrial pressure–volume relations in patients with and without an atrial septal defect. *J Am Coll Cardiol* 1989; **13:** 630 – 636.
42 Finley JP, Nugent ST, Hellenbrand W, *et al*: Sinus arrhythmia in children with atrial septal defect: an analysis of heart rate variability before and after surgical repair. *Br Heart J* 1989; **61:** 280 – 284.
43 Vaishnav S, Stevenson R, Marchant B, *et al*: Relation between heart rate variability early after acute myocardial infarction and long-term mortality. *Am J Cardiol* 1994; **73:** 653 – 657.
44 Pluim BM, Swenne CA, Zwinderman AH, *et al*: Correlation of heart rate variability with cardiac functional and metabolic variables in cyclists with training induced left ventricular hypertrophy. *Heart* 1999; **81:** 612 – 617.

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