

Association of cardiac adaptations with NT-proBNP levels after percutaneous closure of atrial septal defect

Perkütan atriyal septal defekt kapatılması sonrası kardiyak adaptasyonunun NT-proBNP düzeyi ile ilişkisi

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ABSTRACT

Objective: The aim of this study was to evaluate the early effects of transcatheter closure of secundum atrial septal defect (ASD) on atrial and ventricular diameters and functions evaluated by transthoracic echocardiography, and to assess the relation of morphological changes to N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.

Methods: Twenty-two patients with secundum-type ASD referred for percutaneous closure were included in the study as well as 22 healthy individuals who served as a control group. TTE and concurrent blood sampling were performed prior to and 24 hours and 30 days after the closure procedure.

Results: At follow-up 24 hours and 30 days after the closure, the right atrial (RA) area, right ventricular (RV) area, RV end-diastolic volume (EDV), and RV end-systolic volume (ESV) decreased, while left ventricle (LV) EDV (LVEDV), LVESV, and LV stroke volume (LVSV) increased. Global RV systolic and diastolic function indices, such as the tricuspid annular plane systolic excursion, the tricuspid E/A and E/e' ratio decreased immediately after the closure. The NT-proBNP value increased in the 24 hours following closure, and after 30 days, it was still higher than the measurement recorded before the transcatheter closure. The LV structural and functional parameters were significantly correlated with the NT-proBNP value (LVEDV: $r=0.37$, $p=0.02$; LVESV: $r=0.38$, $p=0.01$; left atrium area: $r=0.46$, $p=0.002$; mitral E/e': $r=0.28$, $p=0.04$).

Conclusion: Percutaneous ASD closure can lead to both early and sustained changes in cardiac anatomy and function involving both sides of the heart. The NT-proBNP level had increased at 24 hours post procedure, and was also notably increased 30 days after the percutaneous ASD closure, which is associated with increased LV diameter and volume.

ÖZET

Amaç: Bu çalışmada sekundum tip atriyal septal defektin transkateter kapatılmasının transtorasik ekokardiyografi ile değerlendirilen atriyal ve ventriküler genişlik ile fonksiyonlar üzerine erken etkisi ve N-terminal beyin natriüretik peptid (NT-pro BNP) düzeyi ile ilişkisinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Çalışmaya perkütan olarak kapatılmak üzere yönlendirilen sekundum tip ASD tanılı 22 hasta ve kontrol grubu olarak 22 sağlıklı birey alındı. Hastalara işlem öncesinde, 24 saat sonrası ve 30 gün sonrası TTE işlemi ve biyokimya incelemesi yapıldı.

Bulgular: Kapama işlemi sonrası 24. saat ve 30. günde sağ atriyum ve sağ ventrikül alanı, sağ ventrikül diyastol sonu hacmi (DSV), sağ ventrikül sistol sonu hacmi (SSV) azalmakta, diğer tarafta sol ventriküler diyastol sonu hacmi (SVDSV), sol ventriküler sistol sonu hacmi (SVSSV) ve SV atım hacmi artmakta idi. Global sağ ventriküler sistolik ve diyastolik fonksiyon parametreleri (triküspit halkası düzlemi sistolik yer değiştirmesi - TAPSE, triküspit E/A ve E/e' oranı) işlemten hemen sonra azaldı. NT-proBNP düzeyi işlem sonrası 24. saatte yükseldi ve 30. günde işlem öncesi değere göre hala yüksek saptandı. Sol ventrikülün fonksiyonel ve yapısal parametreleri ile NT-Pro BNP seviyesi arasında anlamlı korelasyon saptandı (SVDSV: $r=0.37$, $p=0.02$; SVSSV: $r=0.38$, $p=0.01$; sol atriyum alanı: $r=0.46$, $p=0.002$; mitral E/e': $r=0.28$, $p=0.04$).

Sonuç: Perkütan ASD kapatılması, kalbin iki tarafında da erken dönemde ve devamlılık gösteren anatomik ve fonksiyonel işlevlerde değişikliklere yol açabilir. NT-pro BNP seviyesi sol ventrikül çapının ve hacminin artmasına bağlı olarak, perkütan ASD kapatılmasından sonra 24. saatte ve 30. günde artmaktadır.

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Atrial septal defect (ASD) is the most common form of congenital heart disease in adults.^[1] Transcatheter closure of ASDs has been performed for 3 decades, and today this has become the preferred method to manage the majority of cases with secundum-type ASD.^[2,3] Several devices have been designed for this purpose and have been used safely and effectively.^[4]

Patients with an ASD may become symptomatic due to chronic volume overload of the right heart chambers. Common presenting symptoms are dyspnea on exertion, fatigue, and/or palpitations. Arrhythmias may occur due to age-related chronic atrial stretch predisposing to electrophysiological remodeling and resulting in either atrial flutter or fibrillation.^[5,6] After closure of the defect, a sudden change in volume status occurs. In previous studies it has been demonstrated that closure of an ASD may lead to reduced right heart volume due to diminishing left-to-right shunting.^[7] However, there is controversy about the recovery of the performance of the right ventricle (RV) and right atrium (RA). Additionally, the effects of ASD closure on the left side of the heart have been poorly characterized. The objective of this study was to evaluate the early effects of transcatheter closure of secundum-type ASDs on both the right and left heart chambers in terms of size and function using transthoracic echocardiography (TTE) and to determine any correlation with N-terminal pro-brain natriuretic peptide (NT-pro BNP) level.

METHODS

Study population

A total of 22 patients with secundum type ASD who were referred for percutaneous closure between December 2012 and January 2014 were included in this prospective study. A control group was consisted of 22 healthy age- and sex-matched adults. ASD was diagnosed with both TTE and transesophageal echocardiography and then confirmed by cardiac catheterization. All of the patients had single-secundum type ASD. Clinical indications for the closure of the ASD and the inclusion criteria for the study were a significant left-to-right shunt (pulmonary:systemic flow ratio: >1.5-1), shunt-related symptoms, and/or echocardiographic signs of dilatation of the right heart chambers. The exclusion criteria were contraindications for percutaneous

closure of ASD (primum ASD, partial anomalous pulmonary venous drainage, pulmonary vascular resistance of >4.6 Wood units, and/or >2/3 systemic vascular resistance even after reversibility testing, right-to-left shunt with a peripheral arterial saturation of <95%), associated structural cardiac defect requiring surgery, coronary artery disease, moder-

ate-severe valvular heart disease, and left ventricular ejection fraction (LVEF) ≤55% on TTE. The study protocol was approved by the ethics committee of our institution and written consent was obtained from all of the participants. TTE and blood sampling were performed prior to the closure, and 24 hours and 30 days after the procedure.

Transcatheter closure of atrial septal defect

Percutaneous closure of the ASD was performed under general or local anesthesia with fluoroscopic and transesophageal echocardiographic guidance. Following the measurement of the native and balloon-stretched diameters of the defect, the procedure was performed using an appropriately sized Occlutech septal occluder (Occlutech GmbH, Jena, Germany).

Echocardiography

Echocardiographic examinations were performed according to American Society of Echocardiography recommendations with a Vivid 7 instrument (GE Healthcare, Inc. Chicago, IL, USA) and a 2.5 MHz transducer.^[8] Measurements were made on 3 representative beats and the results were averaged. Standard echocardiographic analysis included 2-dimensional, M-mode, and Doppler flow measurements. All of the echo-Doppler studies were carried out by the

Abbreviations:

<i>a'</i>	Peak late (atrial contraction) diastolic velocity
<i>A</i>	Mitral late diastolic filling velocity due to atrial contraction
<i>ASD</i>	Atrial septal defect
<i>DTE</i>	Deceleration time
<i>E</i>	Early diastolic mitral inflow velocity
<i>e'</i>	Annular early diastolic velocity
<i>EDV</i>	End diastolic volume
<i>ESV</i>	End systolic volume
<i>ET</i>	Ejection time
<i>LA</i>	Left atrium
<i>LV</i>	Left ventricle
<i>LVEDV</i>	Left ventricle end-diastolic volume
<i>LVEF</i>	Left ventricular ejection fraction
<i>LVESV</i>	Left ventricle stroke volume
<i>MPI</i>	Myocardial performance index
<i>NT-pro BNP</i>	N-terminal pro-brain natriuretic peptide
<i>RA</i>	Right atrium
<i>RV</i>	Right ventricle
<i>Sm</i>	Maximum systolic volume
<i>SV</i>	Stroke volume
<i>TAPSE</i>	Tricuspid annular plane systolic excursion
<i>TTE</i>	Transthoracic echocardiography

same observer who was unaware of the clinical data in order to avoid inter-reader variability. Each examination was recorded and another cardiologist blinded to the status of the patients interpreted the results off-line. Inter- and intra-observer variability was calculated using correlation analysis and the inter-observer variability was determined to be <5%.

LVEF was measured from the apical 4-chamber view using the biplane Simpson's method. End-diastolic areas of cardiac chambers were measured with manual planimetry in the apical 4-chamber view. Chamber quantification and other echocardiographic measurements were assessed according to the American Society of Echocardiography guidelines.^[8]

Using apical 4-chamber views and pulse wave recordings at the level of the mitral leaflet tips-annulus, diastolic function of the left ventricle (LV) was evaluated. Mitral inflow velocity during early diastolic filling (E) and late diastolic filling velocity due to atrial contraction (A) were measured, and the E/A ratio and E wave deceleration time (DTE) were also calculated. Using a 5-mm sample volume placed in the lateral mitral annulus, maximum systolic (Sm), early (e'), and late (a') diastolic velocities were measured. The E/e' ratio of the LV was also calculated.^[9] The myocardial performance index (MPI) was calculated as the sum of the isovolumic contraction time and isovolumic relaxation time divided by ejection time (ET).^[10] Standard Doppler and tissue Doppler imaging measurements were also obtained for the RV. To determine the motion and excursion of tricuspid annulus (TAPSE), an M-Mode cursor was placed at the junction of the tricuspid valve plane with the RV free wall using the apical 4-chamber view images.^[11] The pulmonary to systemic flow shunt ratio was calculated as previously described.^[12]

NT-pro BNP analysis

Blood samples were collected from the antecubital vein before the procedure, and 1 day and 1 month after transcatheter closure of the ASD. The plasma level of NT-pro BNP was measured using the Elecsys 2010 system (Roche Diagnostics GmbH, Risch-Rotkreuz, Switzerland). This is an electrochemiluminescent sandwich immunoassay using 2 polyclonal antibodies directed at the NT-pro BNP molecule.

Statistical analysis

Statistical analyses were performed using IBM SPSS

Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Comparison of categorical variables between the groups was performed using a chi-squared test. The Kolmogorov–Smirnov test was performed to evaluate the normality of distribution of all continuous variables. Analysis of variance was used to assess continuous variables. Correlations between NT-pro BNP level and echocardiographic parameters were assessed using the Pearson correlation test. A 2-tailed $p < 0.05$ was considered statistically significant.

RESULTS

A comparison of baseline demographic and clinical data of the patients with an ASD and the control group was shown in Table 1. Transcatheter closure of the ASD was successfully performed in all of the patients using an Occlutech septal occluder device without any complications. There was no residual shunt detected 30 days after the procedure.

Echocardiographic findings

The mean diameter of the native defect was 19.3 ± 7.8 mm using echocardiography and 21.6 ± 6.7 mm with a sizing balloon. The trend in the echocardiographic parameters and NT-pro BNP level before the procedure, and 24 hours and 30 days after the transcatheter closure of the ASD and comparison with the control group is provided in Table 2. Transcatheter ASD closure resulted in significant cardiac remodeling with reversal of the right-to-left volumetric imbalance.

Table 1. Demographics of patients enrolled in the study

	ASD patients (n=22)	Control Group (n=22)	p
Age (years)	39.3±12.4	39.6±9.5	0.943
Gender (male/female)	(8/14)	(11/11)	0.194
Weight (kg)	68.8±10.7	74.7±14.3	0.129
Height (cm)	164±9.6	165.2±8.7	0.671
ASD diameter (echo) (mm)	19.8±7.4		
Balloon size (mm)	21.6±6.7		
Device size (mm)	23.4±7.7		
Qp/Qs	1.97±0.24		

ASD: Atrial septal defect.

Table 2. Comparison of morphological echocardiographic parameters and NT-pro BNP level

	Before	24 hours	30 days	Control	F	p
LVEF (%)	65.1±3.4	65.9±4.4	64.7±2.9	63.7±3.1	0.72	0.543
LVDD (mm)	40.4±2.6 ¹	41.6±3	43.2±4.1	46.3±4.1 ²	5.181	0.002
LVSD (mm)	26.1±2.3*	26.1±2.2**	28±2.9***	30.3±2.3	4.808	0.004
LA (mm)	32.7±6	32.7±7.2	32.8±6	33.1±3.6	1.89	0.903
LV area (mm ²)	23.3±4.2 ^a	21.9±5.7	23.1±5.7	19.6±5.3	2.02	0.11
LA area (mm ²)	16.4±5.4 ^{aa}	15±5.4	14.9±6.5	12.6±3	1.94	0.13
RV area (mm ²)	21.4±7.6 ^{aaa}	17±5.9	15.7±5.2	11.7±2.8 ^{aaaa}	10.23	<0.001
RA area (mm ²)	17.3±6.8 ^b	12.3±2.8 ^{bb}	12±3.3	10.7±2.1	9.69	<0.001
NT-ProBNP (pg/mL)	25.3±29.2 ^e	51.6±46.1	87.7±101.7	16.2±17.7 ^{ee}	4.86	0.004
LVEDV (mL)	70.5±11.6 ^f	77.2±14.6	80.3±21.5	101.1±16.1 ^{ff}	11.52	<0.001
LVESV (mL)	23.8±6.2 ^g	26.2±6.1 ^{gg}	31.3±8.2	35.8±6.9	10.81	<0.001
LVSV (mL)	46.6±7	49.6±9.2	54.7±14.7	65.2±11.2 ^h	10	<0.001
RVEDV (mL)	38.9±36.3	22.3±25.8	24.2±11.9	12±5.4 ^{hh}	3.31	0.03
RVESV (mL)	26.3±28.3	13.1±17.7	9.9±7.2	4.3±1.9 ^{hhh}	4.09	0.01
RVSV (mL)	12.5±8.5	9.3±8	14.3±5.7	7.7±4 ^g	2.51	0.07

LVEF: Left ventricle ejection fraction; LVDD: Left ventricle diastolic diameter; LVSD: Left ventricle systolic diameter; LA: Left atrium; RV: Right ventricle; RA: Right atrium; LVEDV: Left ventricle end diastolic volume; LVESV: Left ventricle end systolic volume; LVSV: Left ventricle stroke volume; RVEDV: Right ventricle end diastolic volume; RVESV: Right ventricle end systolic volume; RVSV: Right ventricle stroke volume.

¹p=0.01 vs. group III; ²p<0.001 vs. group IV. ³p<0.001 vs. group II; ⁴p=0.01 vs. group III. ⁵p=0.06 vs. group II; ⁶p<0.001 vs. group IV. ⁷p=0.02 vs. group III; ⁸p<0.001 vs. group IV. ⁹p=0.01 vs. group IV. ¹⁰p=0.02 vs. group IV. ¹¹p=0.01 vs. group VI. ¹²p=0.06 vs. group II; ¹³p=0.01 vs. group III; ¹⁴p<0.001 vs. group IV. ¹⁵p=0.002 vs. group II; ¹⁶p=0.006 vs. group III. ¹⁷p=0.006 vs. group II; ¹⁸p=0.005 vs. group III; ¹⁹p=0.001 vs. group III. ²⁰p=0.04 vs. group IV. ²¹p=0.02 vs. group III. ²²p=0.01 vs. group II; ²³p=0.01 vs. group III. ²⁴p=0.01 vs. group III; ²⁵p<0.001 vs. group IV. ²⁶p<0.001 vs. group II; ²⁷p=0.01 vs. group III. ²⁸p=0.003 vs. group III; ²⁹p<0.001 vs. group IV. ³⁰p=0.03 vs. group III; ³¹p<0.001 vs. group IV. ³²p<0.001 vs. group I; ³³p<0.001 vs. group II; ³⁴p=0.02 vs. group III. ³⁵p=0.004 vs. group I; ³⁶p=0.03 vs. group III. ³⁷p=0.002 vs. group I; ³⁸p=0.04 vs. group II. ³⁹p=0.02 vs. group III. ⁴⁰p<0.05 versus before closure group. ⁴¹p<0.05 versus after 24 hours group. ⁴²p<0.05 versus after 30 days group. ⁴³p<0.05 versus control group.

The comparison of baseline measures with those of the follow-up examinations at 24 hours and 30 days after the procedure revealed a significant decrease in the area of the RA and the RV. The RA and RV areas in the study group were higher at 24 hours than those of the control group; however, after 30 days, the RA

area was similar in the 2 groups while the RV area of the patient group was still greater than that of the control group after 30 days. The end diastolic volume (EDV), end systolic volume (ESV), and stroke volume (SV) of the RV were lower following closure of the ASD. However, these parameters were still higher than those of the control group at 30 days. The area of the LA and LV was not significantly different at 24 hours or 30 days when compared with the baseline values. The EDV, ESV, and SV of the LV were greater immediately after the procedure. At 30 days, these parameters were still lower than those of the control group.

Global systolic and diastolic function indices of RV, such as TAPSE, tricuspid DTE, tricuspid E/A ratio, and tricuspid E/e' ratio decreased immediately after closure. However, among these measures, only the change in TAPSE reached statistical significance. The EF and MPI of the RV were increased at 24 hours and 30 days compared with baseline values. Systolic and

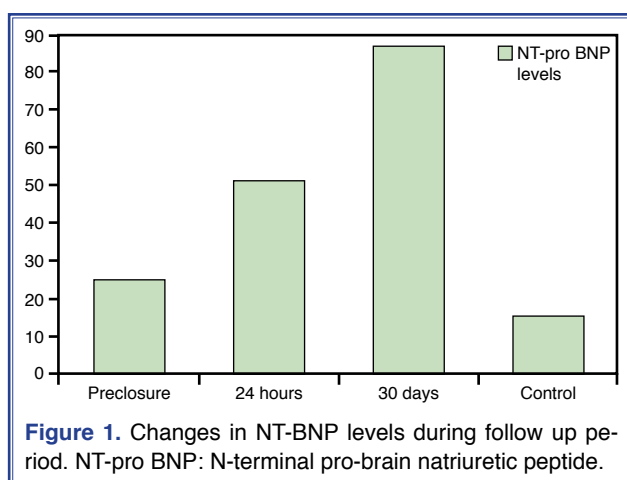


Table 3. Comparison of Doppler echocardiographic parameters

	Before	24 hours	30 days	Control	F	p
Mitral E/A	1.25±0.3	1.18±0.4	1.18±0.4	1.16±0.3	0.21	0.88
Mitral E/e'	7.36±2.5	7.86±3	7.78±3.1	6.94±3.1	0.42	0.73
Mitral Dec T (ms)	257±56	254±69	263±83	309±82 ^c	2.4	0.07
LV MPI	0.64±0.33	0.66±0.19	0.59±0.14	0.47±0.06 ^{cc}	3.78	0.01
Tricuspid E/A	1.19±0.4	1.1±0.2	1.03±0.2	1.12±0.2	0.907	0.44
Tricuspid E/e'	5.75±3.9	5.04±2.3	4.41±1.6	5.06±1.5	0.968	0.41
Tricuspid Dec T (ms)	258±69	254±46	222±62	293±57 ^{ccc}	4.86	0.004
TAPSE (mm)	21.8±4.5 ^d	18.7±4.6	17.6±4.2	18±2.3	4.9	0.003
RV MPI	0.48±0.1 ^{dd}	0.56±0.1	0.59±0.1	0.53±0.1	2.12	0.1

Mitral E: Mitral early diastolic velocity; Mitral A: Mitral late diastolic velocity; Mitral e': Mitral annular early diastolic velocity; Mitral Dec T: Mitral deceleration time; LV MPI: Left ventricle myocardial performance indices; Tricuspid Dec T: Tricuspid deceleration time; Tricuspid E: Tricuspid early diastolic velocity; Tricuspid A: Tricuspid late diastolic velocity; Tricuspid e': Tricuspid annular early diastolic velocity; TAPSE: Tricuspid annular plane systolic excursion; RV MPI: Right ventricle myocardial performance indices.

^cP=0.02 vs. group I; p=0.02 vs. group II. ^{cc}P=0.03 vs. group I; p<0.001 vs. group II; p=0.001 vs. group III. ^{ccc}P=0.02 vs. group II; p=0.001 vs. group III. ^dP=0.02 vs. group II; p=0.03 vs. group III; p=0.001 vs. group IV. ^{dd}P=0.03 vs. group III. ^aP<0.05 versus before closure group. ^bP<0.05 versus after 24 hours group. ^cP<0.05 versus after 30 days group. ^dP<0.05 versus control group.

diastolic function indices of the LV were not significantly changed after closure. The NT-pro BNP values in the ASD patients were similar to those of the control group before the transcatheter closure. Following the procedure, the NT-pro BNP value increased 24 hours after closure, and after 30 days, it was still higher than the values recorded before the transcatheter closure (Fig. 1). The correlation between NT-pro BNP value and echocardiographic measurements is demonstrated in Table 3. The structural and functional parameters of the LV were significantly correlated with the NT-pro BNP value.

DISCUSSION

Our results indicated that percutaneous closure of ASD has multiple beneficial effects on cardiac anatomy and physiology. A decrease in the right chamber size of the heart appeared as early as the first day after the procedure. However, the left side of the heart may be exposed to hemodynamic stress, depending on volume overload after the ASD closure, and LV volume was found to be increased. The levels of NT-pro BNP increased within the first day and were still elevated 30 days after the procedure, which is associated with increased LV diameters and volumes.

Similar to our study findings, previous studies have demonstrated reductions in RA and RV dimensions after percutaneous closure of ASD.^[7,13–15] Ağaç

et al.^[16] reported that the diameters of the RV and the RA were both decreased after the early period of transcatheter closure of ASD. Following the procedure, reduction in the volume of the right heart chambers can be an expected finding as a result of the removal of the left-to-right shunt. Remodeling of the RV and the RA has been reported to occur within 24 hours and to improve over the course of the next 6 to 8 weeks following the procedure.^[17,18] In our study, the areas of the RA and the RV decreased within the first 24 hours and had continued to decrease 30 days after the closure of the ASD, and the RA area was similar to that of the control group at 30 days. However, the area of the RV was still greater than that of the control group. These results are comparable to those of previous studies.^[7,13–15]

The functional measures of RV (i.e., TAPSE and basal systolic tissue Doppler velocity) have been generally reported to decrease significantly within 24 hours of closure and to continue to decline over the succeeding 6 to 8 weeks.^[18,19] Previous studies have demonstrated that the TAPSE value decreased and the MPI of the RV increased following percutaneous closure of an ASD. In addition, Vitarelli et al.^[19] found that the global longitudinal strain of the RV was significantly greater in patients with an ASD than in a control group and it significantly decreased after closure of the defect. In our study, the TAPSE measurement decreased significantly and the MPI of the RV

increased after the procedure. These results are consistent with physiological distinctions of the RV and can be explained by lower volume in the RV after the closure, which leads the RV to pump sufficient volume with a slightly decreased functional state.

In other studies it has been reported that the diameter and volume of the LV has been larger after percutaneous closure of an ASD.^[18,20] Monfredi et al.^[18] showed a significant increase in diastolic diameter and fractional shortening of the LV following the procedure and these findings progressed until as late as 6 to 8 weeks post procedure. It has been postulated that in patients with an ASD due to volume overload of the RV, adverse ventricular interdependence occurs and the septum bulges into the LV cavity, which leads to impairment of LV filling, and consequently, LV systolic and diastolic functions worsen. This situation has been reported to be resolved following percutaneous closure of ASD.^[18,20,21] Similarly, we found that both the EDV and the SV of the LV were greater immediately after closure of the ASD and continued to increase for 30 days. LVEDV and end systolic diameter were greater after the procedure, but did not reach the level of statistical significance.

It is well known that plasma BNP and NT-pro BNP levels are hemodynamic indicators of LV function.^[22] In chronic left heart failure, an elevated BNP concentration has been associated with a poor prognosis.^[23] In previous studies, BNP levels have been reported to increase early after percutaneous ASD closure and they have decreased to pre-procedural levels after 1 to 2 months of follow-up.^[24,25] In the present study, NT-pro BNP levels were increased 24 hours after the procedure and they were still elevated after 30 days. In addition, the NT-pro BNP level was significantly correlated with the ESV and SV of the LV, the E/e' ratio of the LV, and the area of the LA. It has been speculated that the NT-pro BNP level may be significantly correlated with RV hemodynamics and volume.^[26] However, we did not find any correlation between NT-pro BNP and measurements of RV. The primary stimulus for NT-pro BNP release appears to be LV wall stretch in response to volume or pressure overload.^[22] Our results on this issue were compatible.

Limitations

The small number of participants is the main limitation of this study. Secondly, since our follow-up pe-

riod was relatively short, it is not possible to predict the long-term effects of percutaneous closure of an ASD. It may be reasonable to predict normalization of cardiac structure, functions, and NT-pro BNP level with longer follow-up periods. Thirdly, more sophisticated echocardiographic methods (speckle tracking, 3D) can be used for myocardial assessment in both cardiac chambers.

In conclusion, percutaneous closure of an ASD leads to immediate and sustained changes in cardiac anatomy and functions involving both sides of the heart. The NT-pro BNP level begins to increase within 24 hours and continue for 30 days after the procedure in relation to an increase in LV dimension and volume. These findings suggest that after transcatheter closure of an ASD with the removal of a left-to-right shunt, the LV may be subjected to hemodynamic stress, depending on volume overload.

Ethics Committee Approval: The study protocol was approved by the Katip Çelebi University Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

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