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European Journal of Heart Failure 9 (2007) 660–666

The European Journal of Heart Failure

www.elsevier.com/locate/ejheart

NT-proBNP correlates with right heart haemodynamic parameters and volumes in patients with atrial septal defects

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Received 11 July 2006; received in revised form 16 November 2006; accepted 31 January 2007
Available online 7 March 2007

Abstract

Background: To investigate the role of N-terminal pro-BNP (NT-proBNP) for the estimation of right heart failure and pulmonary pressure in patients with atrial septal defects (ASD) before and after percutaneous defect closure.
Methods: We performed correlation analysis for NT-proBNP and right ventricular systolic pressure (RVSP) as well as right ventricular enddiastolic and endsystolic volume (RVEDV, RVESV) determined by cardiac magnetic resonance imaging (MRI) before and up to one year following ASD closure. Additionally NT-proBNP concentrations were correlated with right atrial (RA) and RV enddiastolic pressure (RVEDP), ASD size and interatrial left-to-right shunt.
Results: Baseline RVSP was 33±8 mmHg, which decreased significantly during follow-up. Initially, NT-proBNP levels were 240±93 pg/ml. After closure, a reduction to 116±62 pg/ml was obvious ($p<0.01$). Baseline MRI showed enlarged RV volumes in all individuals. At six and twelve months follow-up a significant reduction of RVEDV and RVESV was apparent. A positive correlation was noted between RV volumes and NT-proBNP ($r=0.65$, $p<0.05$). Furthermore RA pressure, RVEDP, RVSP and left-to-right shunt significantly correlated to peptide levels. No correlation was seen between ASD size and NT-proBNP.
Conclusion: NT-proBNP correlates to right ventricular dilatation, pulmonary pressure and left-to-right shunt in volume load of the right heart caused by an underlying ASD.

Keywords: Atrial septal defect; Percutaneous closure; Right heart failure; Pulmonary hypertension; NT-proBNP

1. Introduction

In left heart failure, high brain natriuretic peptide (BNP) levels are associated with impaired exercise capacity [1] and a poor prognosis [2–6]. In right heart failure, limited data are available showing an involvement of the natriuretic peptide system [7–9]. In particular, there are no data relating serum BNP levels to the severity of RV failure and pulmonary pressure in patients with atrial septal defects (ASDs). ASDs are among the most common congenital heart lesions found in adult life [10]. Long-term exposure to chronic right heart volume overload leads to dilatation of the right atrium (RA) and ventricle (RV) and in certain cases, due to an increased pulmonary flow, to deleterious effects such as pulmonary hypertension and right heart failure [11]. Patients may present with fatigue, dyspnoea, recurrent lower respiratory tract infection, palpitations and thromboembolic events. Closure of the interatrial defect has been accepted as the treatment of choice for an ASD with significant pulmonary to systemic flow ratio, especially if RV volume overload is present, even if the patient has few or no symptoms [10,12]. However, in some patients, especially in those with a small interatrial defect, little left-to-right shunt and no significant volume load of the RV, there is controversy about whether these ASDs should be closed [13].

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doi:10.1016/j.ejheart.2007.01.014

The aim of this study was to investigate the role of N-terminal pro-brain natriuretic peptide (NT-proBNP) for the estimation of right heart failure and pulmonary pressure in patients with ASD, before and in the long-term follow-up after percutaneous defect closure. For that purpose we performed correlation analysis for NT-proBNP levels and right ventricular systolic pressure (RVSP), which was measured by echocardiography as well as right ventricular enddiastolic and endsystolic volume (RVEDV, RVESV) determined by cardiac magnetic resonance imaging (MRI) before and up to one year following percutaneous ASD closure. Additionally, NT-proBNP concentrations were correlated with New York Heart Association functional class (NYHA), RA and RV enddiastolic pressure (RVEDP), the size of the ASD and the amount of interatrial left-to-right shunt.

2. Methods

2.1. Study population

Twenty consecutive patients referred for transcatheter closure of a secundum type ASD were included in this study. Closure of the interatrial defect was performed in patients with significant pulmonary to systemic flow ratio (Qp/Qs ratio of > 1.5:1) in the presence of RV volume overload and/or pulmonary hypertension and/or impairment of right ventricular function and/or functional impairment (NYHA ≥ II). Before undergoing MRI, all patients gave written informed consent in accordance with the ethical guidelines followed in our institution. To be eligible, patients had to be aged 18 years or older, with echocardiographic evidence of a dilated RV diameter, and no additional coronary artery disease, valvular heart disease or pulmonary disease. Baseline characteristics are shown in Table 1. All patients underwent clinical assessment, evaluation of functional class criteria, TTE, TEE and MRI examinations before, and six and twelve months after, transcatheter ASD closure. Patients also had a complete hemodynamic evaluation via cardiac catheterization just before closure of the defect.

Table 1
Baseline clinical and haemodynamic data

Number of patients	20
Age at closure (years)	43±13
Female gender	12 (60%)
NYHA functional class I	12 (60%)
NYHA functional class >I	8 (40%)
Stretched balloon size (mm)	24±6
Qp/Qs ratio ≥2:1	9 (45%)
Qp/Qs ratio <2:1	11 (55%)
Median Amplatzer device size (mm)	26±6
Median Cardia PFO/ASD device size (mm)	22±5
RVSP at TTE (mmHg)	33±8
Patients with RVSP >37 mmHg	7 (35%)
RVEDD at TTE (mm)	36±4
RVEDV at MRI (ml/m2 body surface area)	127±17
RVESV at MRI (ml/m2 body surface area)	81±18
RVEF at MRI (%)	37±9

Abbreviations ASD: atrial septal defect, NT-proBNP: N-terminal pro-BNP, RVSP: right ventricular systolic pressure, RVEDD: right ventricular end-diastolic diameter, RVEDV: right ventricular end-diastolic volume, RVESV: right ventricular endsystolic volume, RVEF: right ventricular ejection fraction, RA: right atrial, MRI: magnetic resonance imaging, TTE: transthoracic echocardiography, TEE: transoesophageal echocardiography, NYHA: New York Heart Association.

2.2. NT-pro BNP analysis

In all patients blood was drawn from the antecubital vein before and six and twelve months after defect closure. Serum NT-proBNP concentrations were measured on the Elecsys™ 2010 system (Roche Diagnostics) [14]. This assay is an electrochemiluminescent sandwich immunoassay using two polyclonal antibodies directed at the NT-proBNP molecule. Intra-assay and inter-assay variabilities are 1.2–1.5% and 4.4–5.0%, respectively [14].

2.3. Transthoracic echocardiography

Two-dimensional colour Doppler TTE was performed before, and six and twelve months after ASD closure, using a Sonos 5500 ultrasound system (Agilent Technologies). The examination focused on the measurement of RV end-diastolic diameter (RVEDD) and right ventricular systolic pressure (RVSP). Two measurements of the RV were made in the apical four-chamber view: maximal RV long-axis dimension, defined as the distance between the RV apex and the mid-point of the tricuspid valve and RV short-axis dimension, defined as the maximal dimension from the right septal surface to the free wall perpendicular to the long-axis. RVSP was estimated using the maximum velocity of the tricuspid regurgitant jet, the systolic pressure gradient between the RV and RA was calculated by the modified Bernoulli equation. RA pressure was estimated by examination of the jugular venous pulse as described previously [15,16]. Adding the transtricuspid gradient to the RA pressure (10±5 mmHg) gave predictions of the RVSP [17]. All patients were in sinus rhythm at the time of examination.

2.4. Magnetic resonance imaging

MRI was performed for determination of RV volumes and function. From ventricular apex to base ECG-triggered, breath-hold, segmented *k*-space cine gradient echo sequences (1.5 T, Somatom Vision, Siemens) were obtained in the short-axis view. Parameters were as follows: echo time: 3.8 ms, repeat time=RR interval, slice thickness: 10 mm, field of view: 35×35 cm, read matrix: 256, phase matrix: 128, frames: 16 (typical temporal resolution of 50 ms), flip angle: 40°, phase encode grouping: 6 to 10, 8 to 12 short-axis slices were needed to encompass the entire right ventricle. Manual tracing of endocardial borders of contiguous short-axis slices at end-diastole (first cine phase of the *R*-wave triggered acquisition) and end-systole (image phase with smallest cavity area), allowed for calculation of

RVEDV and RVESV, from which RVEF could be derived. Analysis of the scans was done with the investigator blinded to the previous results. In all individuals MRI was performed in the morning, after an overnight fast. Volumes were normalized to body surface area. We used the following as normal values: RVEDV: 48.0–107.5 ml/m2, RVESV: 13.1–47.2 ml/m2, RVEF: 49.1–74.1% [18–20].

2.5. Haemodynamic study

Haemodynamic study and percutaneous closure were performed under sedation and local anaesthesia. The size, location, and relationship of the ASD to the surrounding structures were assessed by continuous TEE. A margin of more than 4 mm between these structures and the ASD had to be present for the procedure to be initiated. Patients underwent a complete hemodynamic evaluation via cardiac catheterization just before closure of the defect. Pulmonary to systemic flow ratio (Qp/Qs) was calculated by oximetry using the Fick principle. Right heart failure in patients with underlying ASD (Qp/Qs >1.5:1) was in the context of this study defined as one of the following: (a) functional impairment (NYHA ≥ II), (b) a poorly contracting right ventricle (RV ejection fraction ≤ 49%) determined by MRI, (c) a dilated right ventricle (RV end-diastolic volume ≥ 108 ml/m2) determined by MRI.

2.6. ASD closure and follow-up

The Amplatzer septal occluder (AGA Corp.) or the Cardia PFO/ASD Device (Cardia Inc.) were used for ASD closure as previously described [21,22]. Balloon sizing of the ASD was performed to determine the stretched diameter; the device size chosen was 10% greater than the stretched diameter size. All patients were anticoagulated at the time of the procedure with 10,000 IE heparin and received 1.2 g amoxycillin iv and 0.5–1.0 mg atropine iv to prevent endocarditis and catheter-induced coronary spasm. Post-interventional treatment included oral aspirin (100 mg/day) for 12 months, clopidogrel (75 mg/day) for 6 weeks and low dose heparin for the first 3 days (2×5000 IE s.c.) after intervention. Prophylaxis of bacterial endocarditis was recommended for 6 months according to the guidelines of the American Heart Association.

2.7. Statistical analysis

Correlation coefficients were calculated between NT-proBNP concentrations and haemodynamic, echocardiographic or MRI variables. Data are presented as mean value ± standard deviation.

3. Results

Closure of the ASD was achieved in 14 patients with an Amplatzer device (median device size 26±6 mm) and in 6 patients with a Cardia-Star device (median device size 22±5 mm). At TTE and TEE performed periinterventionally and after six and twelve months, no residual shunt was noted in the entire study group. No major complications occured. The mean age of the 20 patients (12 female, 8 male) was 43±13 years (range 19–65). No patient was lost to clinical follow-up. Patients' characteristics are shown in Table 1, along with baseline TTE, TEE and MRI findings.

Six and twelve months after ASD closure all patients underwent blood sampling for NT-proBNP analysis, NYHA assessment, TTE for RVSP quantification, TEE to evaluate ASD closure and MRI evaluation of RV volume and function. The mean interval from the transcatheter closure procedure to the six month follow-up was 6.4 months (5.6–9.2) and to the twelve month follow-up was 12.8 months (11.2–14.8). TEE revealed sufficient closure of ASDs in all patients.

3.1. Functional status

Before ASD closure, 12 patients were in NYHA I, 5 patients in NYHA II and 3 patients in NYHA III. Patients improved during follow-up, leading to a better functional class in 5 of the 8 symptomatic individuals.

3.2. Echocardiography

Before ASD closure, all patients had dilated RVEDD (36±4 mm), measured in 2-dimensional TTE (inclusion criterion). Baseline RVSP was 33±8 mmHg, which decreased significantly after 6 months to 27±7 mmHg and after 12 months to 24±6 mmHg ($p < 0.001$).

3.3. NT-pro BNP analysis

Mean peptide levels before closure were 240±93 pg/ml. At six months after closure a significant reduction to 141±54 pg/ml was observed ($p<0.01$); with a further reduction to 116±62 pg/ml after 12 months (Fig. 1).

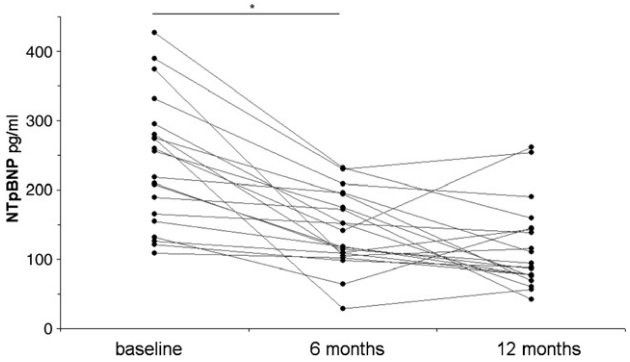

Fig. 1. Changes in NT-proBNP-levels after transcatheter closure of ASD. Asterisk indicates significant alterations ($p<0.01$).

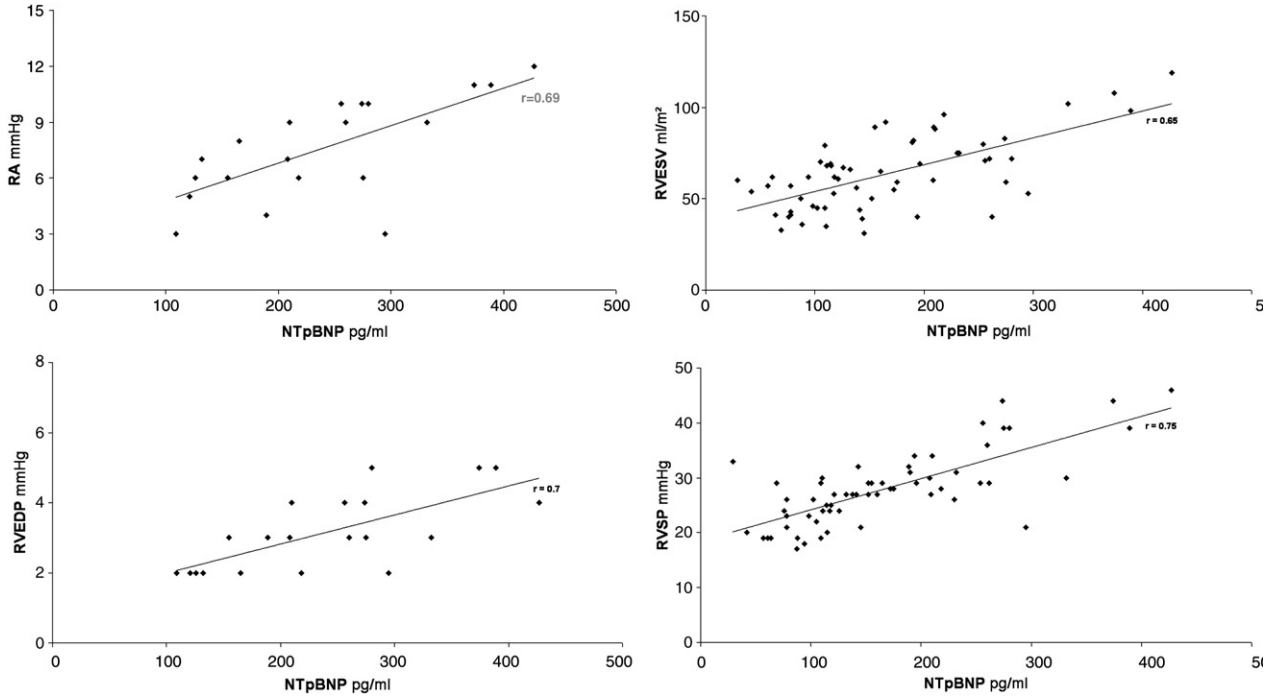

Fig. 2. A positive correlation between RA pressure, RVESV, RVEDP, RVSP and NT-proBNP levels was obvious. RA pressure and RVEDP were measured during invasive haemodynamic evaluation before defect closure only.RVESV and RVSP were determined by MRI respectively TTE before defect closure and during follow-up.

3.4. Magnetic resonance imaging

Manual tracing of endocardial borders of contiguous short-axis slices at end-diastole and end-systole allowed for calculation of RVEDV and RVESV, from which RVEF could be derived. Baseline measurements showed enlarged RV volumes in all individuals: RVEDV 127±17 ml/m2, RVESV 81±18 ml/m2, RVEF 37±9%. At six months after closure a

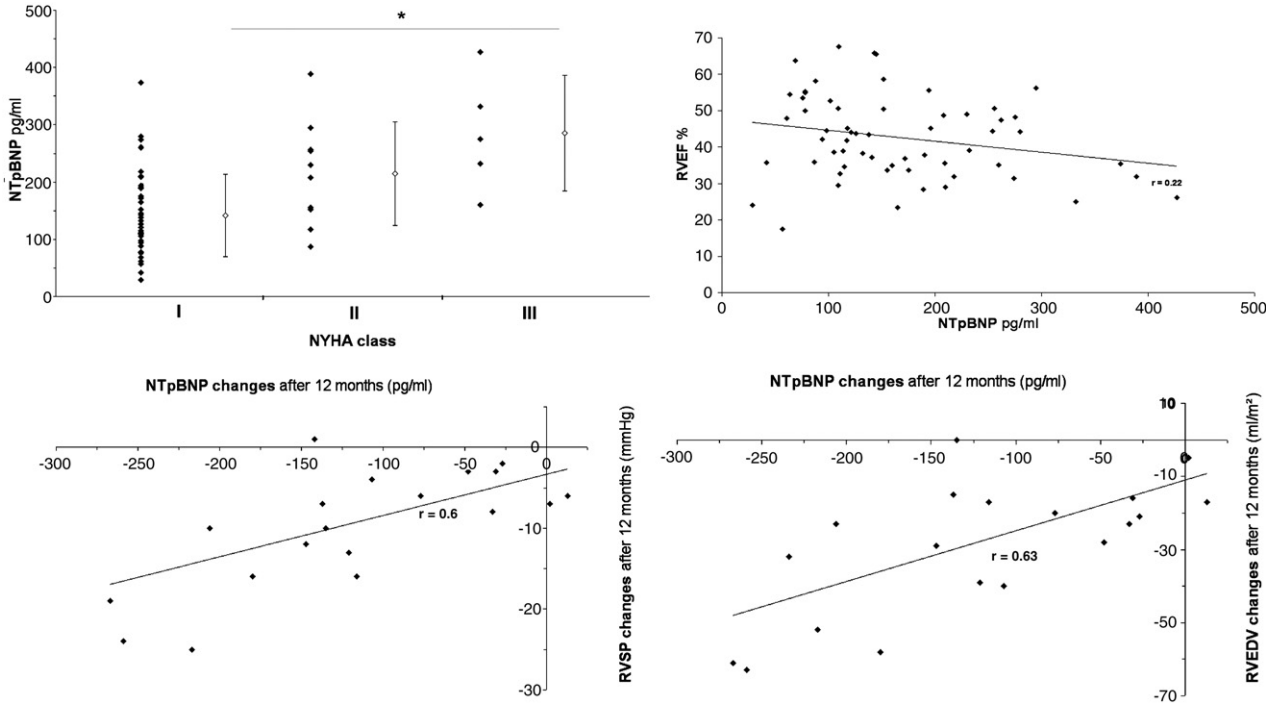

Fig. 3. Patients presenting with NYHA I at baseline and during follow-up had significantly lower NT-proBNP levels than patients in NYHA class III (*$p<0.05$). Also a positive correlation between the decrease in RVSP and changes in NT-proBNP levels was obvious. A similar coherence could be demonstrated between the decrease in RVEDV and changes in NT-proBNP during follow-up. However, RVEF did not correlate with peptide levels.

significant reduction of RVEDV to 103±20 ml/m2 and of RVESV to 57±14 ml/m2 was obvious ($p<0.001$); RVEF increased by 8% compared to baseline MRI measurements. Follow-up after 12 months showed a further reduction of RVEDV to 99±18 ml/m2 and of RVESV to 53±15 ml/m2 ($p<0.001$), RVEF improved by 9% compared to baseline measurements ($p<0.05$).

3.5. Correlation analysis

A positive correlation was noted between right ventricular volumes and NT-proBNP levels in patients with ASD ($r=0.65$, $p<0.05$). Furthermore, RA pressure ($r=0.69$, $p<0.05$), RVEDP ($r=0.7$, $p<0.01$), RVSP ($r=0.75$, $p<0.01$) and the amount of left-to-right shunt ($r=0.62$, $p<0.05$) significantly correlated to peptide levels. Correlation analysis between NT-proBNP and RA pressure, RVESV, RVEDP and RVSP are shown in Fig. 2. No correlation was seen between the size of the ASD and NT-proBNP concentration (data not shown).

Fig. 3 shows NT-proBNP levels in different NYHA classes in the 20 patients before ASD closure and during follow-up. NT-proBNP measurements in the NYHA I group (142±72 pg/ml) were significantly lower than NT-proBNP measurements in the NYHA III group (285±101 pg/ml, $p<0.05$). Furthermore the decrease in RVSP and in RVEDV 12 months after ASD closure significantly correlated with changes in NT-proBNP levels ($r=0.6$, $p<0.01$, $r=0.63$, $p<0.01$ respectively, Fig. 3). However, a significant correlation between RVEF and peptide levels was not detected ($r=0.22$, Fig. 3).

4. Discussion

This is the first study showing correlation analysis between NT-proBNP levels and RV hemodynamics as well as RV volumes in patients with ASD before and during follow-up after defect closure. MRI revealed significant improvement of RV volumes and function after transcatheter ASD closure in adults. Also pulmonary pressure decreased significantly over time and patients' conditions improved during follow-up, leading to a better functional class in 5 of the 8 symptomatic individuals.

The majority of data from previous studies show that plasma BNP levels and its co-released peptide NT-proBNP are linked to haemodynamic indices of left ventricular function [3,23,24]. Moreover, in chronic left heart failure elevated BNP concentrations have been associated with a poor prognosis [4,5].

Only a few reports deal with BNP levels in the context of RV dysfunction [9,25]. The role of BNP in patients with pulmonary embolism and *acute* right heart failure has been investigated previously. Among these patients, plasma BNP levels helped to differentiate between a benign versus a complicated hospital course, although the limited specificity of the BNP analysis resulted in a certain overlap [26]. In addition to BNP concentration in *acute* pressure load of the right ventricle by pulmonary embolism, the role of BNP levels in *chronic* right heart failure have been analyzed. Both in patients with cor pulmonale due to long-term respiratory failure and in patients with primary pulmonary hypertension, BNP levels increased in proportion to the extent of *chronic* right ventricular dysfunction [27,28]. The triggering factor for BNP release seems to be an increase in myocardial shear stress or pressure of the right ventricle, which precedes right ventricular failure and depends on the degree and dynamics of the underlying disease.

Whether or not *chronic volume* load of the RV in patients with ASD leads to an increase in plasma NT-proBNP, as has been demonstrated for *acute and chronic pressure* load of the RV, was up to now not known. In our study, dilatation of the RV due to an underlying ASD was demonstrated by TTE (inclusion criterion) and more precisely by MRI in all patients with ASD. A significant regression of RV dilatation was obvious within six months and further up to twelve months after transcatheter closure of the ASD. Plasma NT-proBNP concentration measured in parallel to MRI scans decreased with good correlation to the restitution of RV dilatation. Improvement of pulmonary pressure measured by TTE during follow-up was mirrored by decreasing NT-proBNP levels. Moreover, NT-proBNP concentration before closure of the defect correlated well with the amount of interatrial left-to-right shunt but not with the size of the ASD. A significant correlation between RVEF and NT-proBNP could also not be demonstrated. This missing coherence could be explained by the fact, that impairment of RVEF was only mild (37±9%) and improved by 9% to almost normal values during follow-up. Furthermore, the primary stimulus for NT-proBNP release appears to be ventricular wall stretch in response to volume or pressure overload and primarily not RVEF.

Plasma NT-proBNP concentrations in this study were lower than NT-proBNP levels measured in acute right heart failure. This suggests that chronic volume load of the RV leads to a less intense release of NT-proBNP compared to peptide levels found in acute pressure load.

Closure of an ASD certainly leads to fundamental changes not only of the RV but also to changes of LV volumes and function. This RV–LV interdependence and LV performance before and after ASD closure was nicely described by Salehian and Giardini [29,30]. Both authors described an increase of LV stroke volumes due to better LV filling and an abolished paradoxical movement of the interventricular septum after ASD closure. Whether the described changes in RV and LV performance both contribute to BNP release is not known and cannot be drawn from these data.

The findings of the present study are in good agreement with data by Muta et al. who described elevated BNP levels in paediatric patients with ASD [31]. Additionally, Trojnarska et al. reported on increased BNP concentrations in adult patients with ASD [32]. Recently Weber et al.

postulated that NT-proBNP is not increased in patients with ASD [33]. Reconsidering the data by Weber, some crucial differences in patient characteristics are obvious. In the present observation, 20 patients had a systolic pulmonary artery pressure of 33±8 mmHg, RVEDV was 127±17 ml/m2 and RVEF 37±9% measured by MRI. By contrast, in 12 patients surveyed by Weber, mean pulmonary artery pressure was 16.3±6.3 mmHg, RVEDV 211±70 ml and RVEF 60.5 ±6.3%. Overall the Weber population had lower NT-proBNP levels but also less right ventricular dilatation, a noticeably lower mean pulmonary artery pressure and an explicitly better RVEF. These different patient characteristics may lead to different results regarding NT-proBNP levels. This hypothesis is supported, as described in the present study, by the correlation between right heart impairment and NT-proBNP as well as by Nagaya et al. who described that plasma BNP levels were elevated in proportion to the severity of pulmonary hypertension in patients with ASD [34].

In recent years, closure of the interatrial defect has been accepted as the treatment of choice for an ASD with significant pulmonary to systemic flow ratio, even if the patient has few or no symptoms [10,12]. However, in some patients, especially in those with a small interatrial defect, little left-to-right shunt and no significant volume load of the RV, there is controversy about whether these ASDs should be closed [13]. In our study, five patients (25%) had NT-proBNP levels within the upper normal range at baseline. During follow-up NT-proBNP showed no significant changes within this subgroup. Four of these patients were in NYHA functional class I and 1 patient was in class II. Regarding RVEDV, RVESV and RVSP, smaller RV volumes and lower RVSP were detectable in patients with normal NT-proBNP levels. However, the small number of patients in this subgroup did not allow for a statistical evaluation. Whether normal NT-proBNP levels are a predictor for conservative treatment of an ASD is currently not known and cannot be concluded from these data.

As suggested by the present study, elevated NT-proBNP concentrations indicate RV deterioration caused by an underlying ASD. Plasma NT-proBNP levels increase in proportion to the extent of right ventricular dilatation and right heart pressure. We speculate that NT-proBNP levels could help to differentiate between patients in whom a primary conservative approach is favourable and patients in whom the closure of the ASD should be performed. The cut-off NT-proBNP level that distinguishes between a conservative approach and an interventional treatment strategy needs to be established.

Finally, further studies are necessary to evaluate NT-proBNP as a marker of right ventricular deterioration in patients with ASD and its role in the assessment of treatment strategies. Thus far, our data show that NT-proBNP is a parameter which correlates to right ventricular dilatation, pulmonary pressure and the amount of interatrial shunting in volume load of the right heart caused by an underlying ASD.

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