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Original Article

NT-proBNP level and left ventricle diameters before and after transcatheter closure of PDA and VSD

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Abstract

Background Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) levels before and after transcatheter closure may correlate with changes in left ventricular internal diameter end diastole (LVIDd) and end systole (LVIDs). Patent ductus arteriosus (PDA) and ventricular septal defect (VSD) are structural abnormalities which effects cardiac hypertrophy. Cardiac muscle stretching decreases after closure, followed by reduced left ventricle diameters and decreased NT-proBNP levels.

Objective To analyze for possible correlations between NT-proBNP levels and left ventricle diameters before and after transcatheter closure.

Methods Subjects were PDA and VSD patients who underwent transcatheter closure in the Pediatrics Department of dr. Moh Hoesin Hospital, Palembang, South Sumatera, from May 2016 to March 2017. Measurement of NT-proBNP levels and echocardiography were performed before closure, as well as one and three months after closure.

Results There were 34 subjects (15 girls) with median age of 91.5 months. Median NT-proBNP levels were significantly reduced after closure: before closure 111.7pg/mL, one month after closure 62pg/mL, and three months after closure 39 pg/mL ($P<0.05$). Median LVIDd and LVIDs were also significantly reduced after closure [LVIDd: 39.5mm before, 34.5mm one mo after, and 32.5mm 3 mo after ($P<0.05$); LVIDs: 23.9mm before, 20.5mm 1 mo after, and 20.0mm 3 mo after ($P<0.05$)]. At one month after closure, there was a moderate positive correlation between NT-proBNP levels and LVIDd ($r=0.432$; $P=0.011$), but no correlation with LVIDs ($r=0.287$; $P=0.100$). At three months after closure, there was a significant moderate positive correlation between changes of NT-proBNP levels and changes of LVIDd ($r=0.459$; $P=0.006$), as well as LVIDs ($r=0.563$; $P=0.001$).

Conclusion In pediatric PDA and VSD patients, NT-proBNP levels have a significant positive correlation with diastolic and systolic left ventricle diameters at three months after closure. Decreased NT-proBNP levels may be considered as a marker of closure effectiveness. **[Paediatr Indones. 2018;58:205-12; doi: http://dx.doi.org/10.14238/pi58.5.2018.205-12]**.

Keywords: *left ventricular internal diameter end diastole; left ventricular internal diameter end systole; NT-proBNP; PDA closure; VSD closure*

Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) is the primary heart hormone secreted by myocytes in the right and left ventricles. This biomarker plays an important role in diagnosis, monitoring, management, and prognosis of heart disease. The NT-proBNP production is a result of fission of greater natriuretic molecules. It has several biological effects such as diuresis, vasodilatation, inhibition of renin and aldosterone production, as well as inhibition of myocyte growth in the heart and blood vessels.[1-4] The NT-proBNP levels elevate in response to increased

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volume load and excessive pressure on the heart muscle that causes left ventricular hypertrophy, with divergent patterns. Excessive pressure usually leads to concentric hypertrophy, whereas increased volume load causes eccentric hypertrophy. Heart muscle stress, such as ventricular stretching or increased filling pressure, stimulates NT-proBNP synthesis and secretion. This biomarker is directly proportional to the degree of ventricular stretching, with greater ventricular stretch causing higher NT-proBNP levels. The NT-proBNP levels are also affected by conditions such as anemia, bronchopneumonia, sepsis, heart failure, kidney failure, puberty, and increased intracranial pressure.[1-5]

Ventricular septal defect (VSD) and persistent ductus arteriosus (PDA) are structural abnormalities of the heart that can cause alteration in the heart muscle. PDA and VSD are different structural abnormalities, but with similar effects of left atrial and left ventricle hypertrophy, caused by an excessive volume load increase. The size of the defect affects the stretching of the heart muscle that stimulates NT-proBNP production by myocyte in the heart muscle. Transcatheter closure is a therapy using a special device to close the VSD and/or the PDA to reduce left ventricular volume load, thus reducing left ventricular muscle stretching followed by decreasing NT-pro BNP levels.[6-7]

In general, NT-proBNP levels decrease if the strain to the heart muscle is reduced, due to decreasing afterload and preload. Left ventricular muscle strain can be assessed through echocardiography by measuring systolic and diastolic left ventricular diameter, as well as left ventricular posterior wall thickness, which some studies found to be proportional to NT-proBNP hormone levels.[8-12]

The NT-proBNP assessment has become routine practice for the diagnosis of heart disease, as this hormone levels correlated with clinical signs of heart failure.[13] In addition, a study found a positive correlation between NT-proBNP levels and left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), and size of defects in children with VSD.10 Studies of NT-proBNP levels associated with current cardiac prognosis are still rare, especially with regard to catheterization. But one such study which assessed the effectiveness of percutaneous closure on left ventricular function by measuring NT-proBNP levels and left ventricular dimension, found that median diastolic volume and NT-proBNP levels decreased 6 months after closure.[11]

Examination of hormone levels is a tool used to assess the effectiveness of transcatheter closure in patients with congenital heart disease.[2] To assess the response of the treatment, hormone levels should be checked serially. The benefits of NT-proBNP examination are enormous, but in Indonesia, the research on NT-proBNP levels after transcatheter closure has been limited, especially in pediatrics, and, to our knowledge, has never been done at our institution.

Methods

This time series study with a correlation test design was done to assess for possible patterns and correlations between NT-proBNP levels and left ventricular diameters before and after transcatheter closure. The study subjects were children with PDA or VSD disease who underwent transcatheter closure between May 2016 and August 2017 at Dr. Mohammad Hoesin Hospital, Palembang, South Sumatera.

All subjects who met the criteria underwent echocardiographic examinations for diastolic and systolic left ventricular diameters as well as NT-proBNP measurements, before, one month, and three months after transcatheter closure. We analyzed the correlation coefficient in left ventricle diameter and NT-proBNP levels between before closure,1 month and 3 months after transcatheter closure, with Spearman's test.

Descriptive data were presented as median with range; normality test (Shapiro-Wilk) was performed on the data. Wilcoxon signed-rank test was used to compare changes of NT-proBNP levels and left ventricle diameters before and after closure. Box-and-whisker plots were used to illustrate the distribution of NT-proBNP levels. We analyzed all data with *SPSS 18* software. The Health Research Review Committee of Mohammad Hoesin Hospital approved the study protocol.

Results

Of 34 subjects who met the criteria, boys out numbered girls, and PDA patients outnumbered VSD patients

(24 *vs.* 10 subjects, respectively). The characteristics of study subjects are shown in **Table 1**. Echocardiographic examinations revealed that LVIDd and LVIDs sizes were wider before the transcatheter closure, and began to decrease gradually after one month and three months of closure. The NT-proBNP levels were higher before transcatheter closure than at one month and three months after transcatheter closure. Median NT-proBNP levels and left ventricular diameters before closure, and 1 month and 3 months after closure are shown in **Figure 1**. Median NT-proBNP levels were significantly decreased 3 months after closure. Also, subjects had significant weight gain at 3 months after closure, with a mean value of body weight was 22.75 (SD 11.23) kg. Distributions of NT-proBNP levels, LVIDd, and LVIDs are listed in **Table 2**.

The median NT-proBNP levels in PDA patients was higher than in VSD patients at all time points (Table 2) [PDA: 214 (range 30-2805) pg/mL before closure, 73.37 (range 15-323) pg/mL 1 month after, and 50.5 (range 5-369) pg/mL 3 months after PDA closure; VSD: 88.83 (range 12-226) pg/mL before closure, 54.5 (range 23-162) pg/mL 1 month after, and 28 (range 6-74) pg/mL 3 months after VSD closure].

Table 1. Characteristics of the study population

Characteristics	N=34
Mean age (SD), months	94.52 (55.9)
Sex, n (%)	
Male	19 (55.9)
Female	15 (44.1)
Congenital heart disease, n (%)	
PDA	24 (70.6)
VSD	10 (29.4)
Mean defect size (SD), mm	4.6 (1.4)
Mean body weight (SD), kg	
Before closure	20.07 (10.84)
1 month after closure	20.83 (10.73)
3 months after closure	31.86 (43.89)

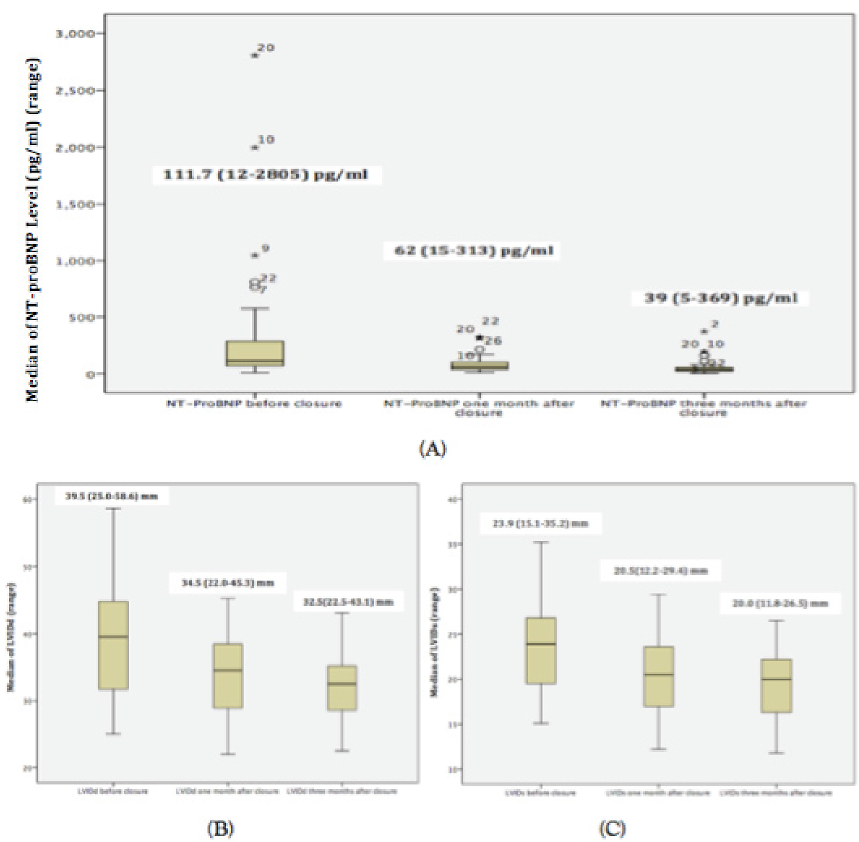


Figure 1. Distribution of NT-proBNP levels (A), diastolic (B) and systolic (C) end of left ventricle diameters

The median diastolic and systolic left ventricle diameters in PDA and VSD subjects before closure was wider than at 1 month and 3 months after closure that statistically significant, as shown in **Figure 2**. The median LVIDd and LVIDs based on type of congenital heart disease are shown in **Table 2**. In PDA subjects, median LVIDd values were 41.1 (range 25.0-58.6) mm before closure, 32.6 (22.0-45.3) mm 1 month after, and 30.9 (range 22.5-43.1) mm 3 months after closure, while median LVIDs values were 24.4 (range 15.1-35.2) mm before closure, 20.9 (range 12.2-29.4) mm 1 month after, and 19.5 (range 11.8-26.5) mm 3 months after closure. In the VSD subjects, median LVIDd values were 36.7 (range 30.8-45.6) mm before closure, 35.6 (range 28.9-45.0) mm 1 month after, and 33.7 (range 26.5-37.2) mm 3 months after closure, while median LVIDs values were 22.8 (range 18.4-27.5) mm before closure, 20.5 (range 15.3-23.6) mm 1 month after, and 20.0 (range 15.4-24.5) mm 3 months after closure.

Spearman's test revealed a moderate positive correlation between NT-proBNP levels and LVIDd ($r=0.432$; $P=0.011$), but no correlation with LVIDs at one month after closure ($r=0.287$; $P=0.100$). In addition, there were positive moderate correlations between changes of NT-proBNP levels and LVIDd ($r=0.459$; $P=0.006$) and LVIDs at three months after closure ($r=0.563$; $P=0.001$). Scatterplot charts of the correlations between NTproBNP levels and left ventricle diameters after one and three months of closure are shown in **Figure 3** and **Figure 4**.

Discussion

The PDA and VSD are two types of congenital heart disease that cause stretching of the left atrial and left ventricular heart muscle due to excessive volume load. The current choice of management for PDA and VSD, besides a surgical procedure, is transcatheter closure. The success rate of transcatheter closure is quite high, and it has become a feasible, effective, and safe procedure with good long-term outcomes based on previous studies.[14-23]

Atrial and ventricular hypertrophy are risk factors for all cardiovascular complications. Echocardiography is the gold standard examination to diagnose left ventricular hypertrophy, but it is impractical because it requires trained experts. This study was done to assess the use of NT-proBNP level to detect left ventricular hypertrophy. The NT-proBNP is a cardiac hormone produced by the ventricle, in response to volume load or pressure load. This hormone is a sensitive and specific indicator of ventricular function.[24,25] In our study, natriuretic peptide level was significantly higher before closure than after closure. At one month after closure, NT-proBNP level had declined and further decreased at three months after closure, due to decreased volume load after closure. High levels of NT-proBNP are reflective of excess left ventricular volume in asymptomatic cases with normal left ventricular diameter. The median left ventricular diameter during diastole and systole was wider before than after closure. The left ventricle diameter began

Table 2. Median NT-proBNP levels and median left ventricle systolic and diastolic diameters in PDA and VSD

Congenital heart disease	Median NT-proBNP level and left ventricle diameters (range)			P value
	Before closure	1 month after closure	3 month after closure	
PDA				
NT-proBNP, pg/mL	214 (30-2805)	73.37 (15-323)*	50.5 (5-369)**	0.000
LVIDd, mm	41.1(25.0-58.6)	32.6 (22.0-45.3)*	30.9(22.5-43.1)**	0.000
LVIDs, mm	24.4(15.1-35.2)	20.9 (12.2-29.4)*	19.5(11.8-26.5)**	0.000
VSD				
NT-proBNP, pg/mL	88.83(12-226)	54.5 (23-162)*	28 (6-74)**	0.000
LVIDd, mm	36.7(30.8-45.6)	35.6 (28.9-45.0)*	33.7(26.5-37.2)**	0.000
LVIDs, mm	22.8(18.4-27.5)	20.5 (15.3-23.6)*	20.0(15.4-24.5)**	0.000

Wilcoxon signed rank test
*NT-proBNP level significantly decreased one month after closure compared to before closure (P<0.05)
**NT-proBNP level significantly decreased three months after closure compared to before closure (P<0.05)

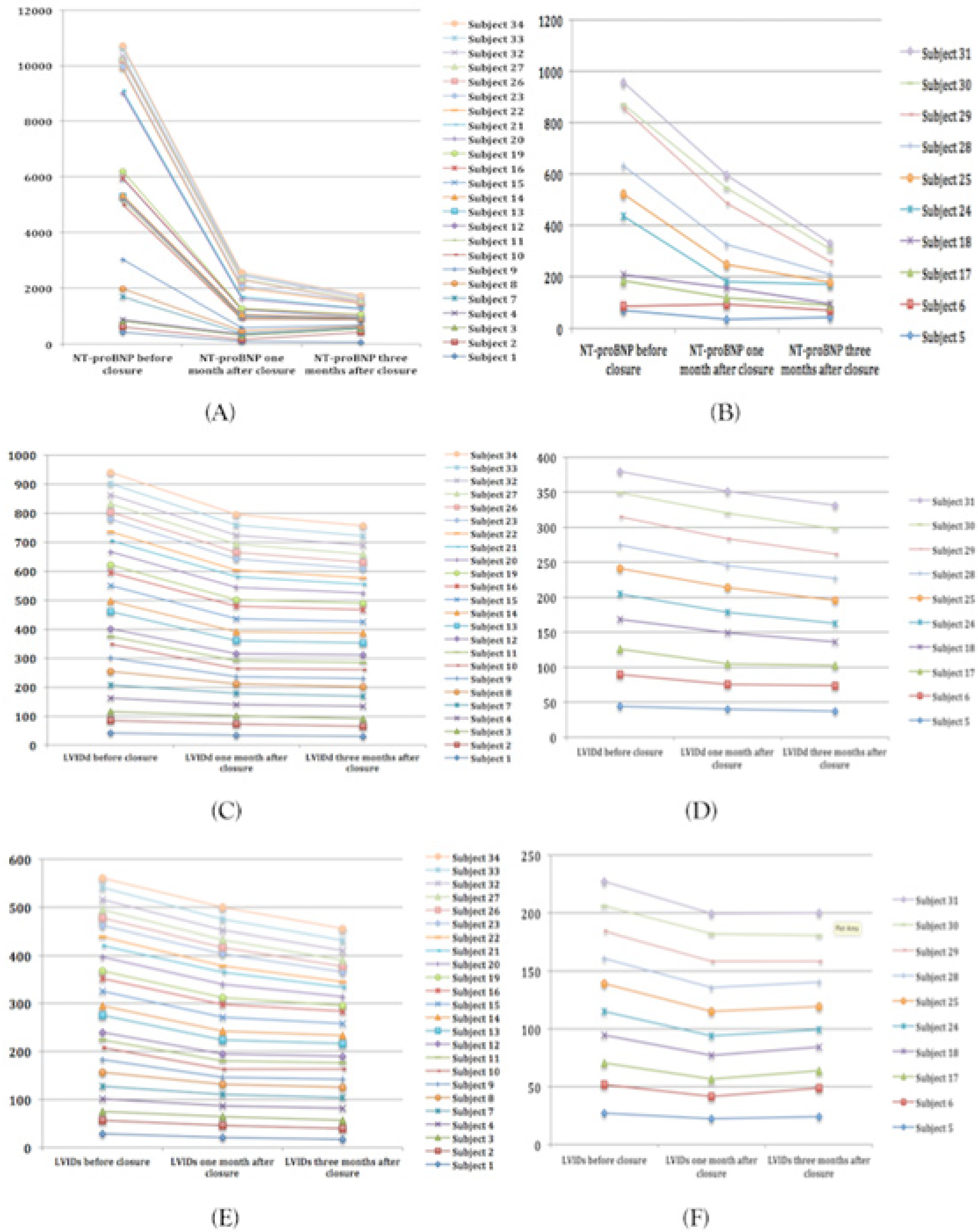
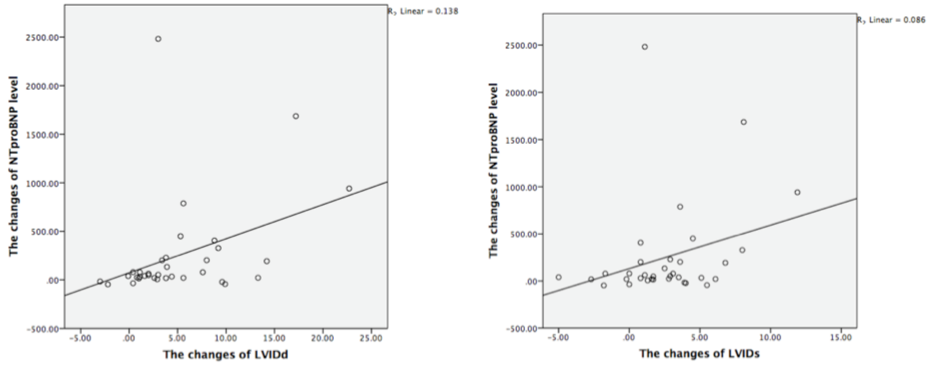
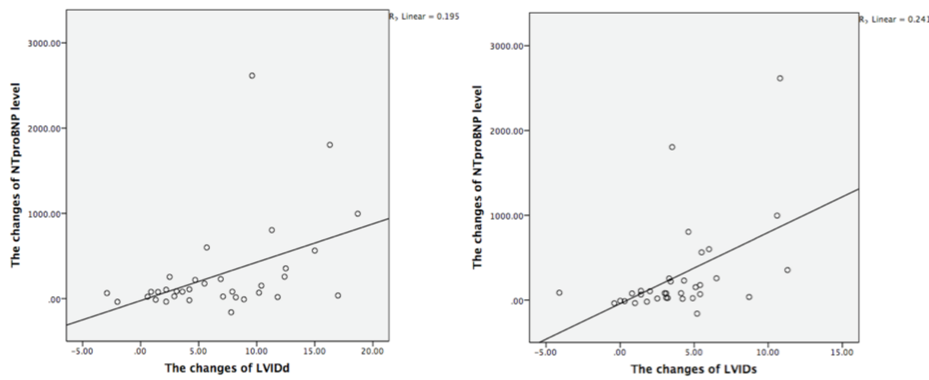


Figure 2. Distribution of NT-proBNP level in PDA subjects (A) and VSD subjects (B). Distribution of diastolic diameter in PDA subjects (C) and VSD subjects (D). Distribution of systolic diameter in PDA subjects (E) and VSD subjects (F).



(A) (B)

Figure 3. The correlation between NT-proBNP level and LVIDd (A) and LVID s (B) before and 1 month after closure



(A) (B)

Figure 4. The correlation between NT-proBNP level and LVIDd (A) and LVIDs (B), before and 3 months after closure

to decrease gradually at one month and continued to decrease at three months after closure.

Increasing NT-proBNP levels reflect the stretching of the heart muscle, which tends to be higher in PDA subjects than in VSD subjects. Increased stretching in PDA patients may be the results of a different pathophysiological mechanism from that of VSD. Left ventricular hypertrophy in PDA and VSD occurs due to excessive volume load. The volume load occurs in the diastolic and systolic phases in PDA, but only in the systolic phase in VSD. This study was conducted to assess for possible correlations of NT-proBNP levels and left ventricular diameter before, one month after, and three months after closure. One month after closure, there was a moderate, positive correlation between NT-proBNP levels and diastolic left ventricular diameter, but no correlation with systolic left ventricular diameter. At three months after closure, a positive moderate correlation was observed between NT-proBNP levels and systolic and diastolic left ventricular diameters. Based on this study, three months after closure is a good time to assess NT-proBNP levels. This biomarker can used to determine the success of transcatheter closure. The results of our study were similar to those done by Elsharawy *et al.* and Eerola *et al.*, but we put more emphasis on the correlation between NT-proBNP and left ventricular diameter after closure. Elsharawy et al. noted a positive correlation between NT-proBNP levels and LVEDD, LVESD, and defect size.[10] Eerola *et al.* examined NT-proBNP levels with left ventricular dimensions at 1 day and 6 months after transcatheter closure compared to a control group in PDA patients. They found an increase of NT-proBNP levels on the first day following the transcatheter closure, and decreased median diastolic volume and NT-proBNP levels after 6 months of transcermination.[11] Eerola *et al.* performed another study to investigate the association between peptide hormone levels and echocardiographic results, at 6 months and 12 months observation in ASD and coarctation of the aorta patients.[26] They reported decreased left ventricle diameters at six months after closure by about 20%, but in our study, left ventricular diameters decreased about 25% at three months after closure.

A limitation of this study was the small sample size, leading to difficulty in comparing between PDA and VSD. Also, our subjects were too heterogeneous with a wide age range as we did not exclude adolescent pubertal children. In addition, the monitoring period in this study was short, and should be continued to 12 months in order to assess for more significant reductions.

In conclusion, NT-proBNP level and left ventricular diameter are significantly correlated 3 months after closure. Decreased NT-proBNP levels are reflective of successful transcatheter closure.

Conflict of Interest

None declared.

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