การใช้ระดับ NT-proBNP เพื่อทำนายการเกิดภาวะความดันหลอดเลือดแดงในปอดสูงในผู้ป่วย secundum atrial septal defect ที่ได้รับการปิดผ่านทางสายสวนหัวใจ

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Abstract: Use of Plasma NT-proBNP Level to Predict Persistent Pulmonary Arterial Hypertension in Patients with Secundum Atrial Septal Defect after Transcatheter Closure

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Background: Persistent pulmonary arterial hypertension (PPAH) after transcatheter ASD closure (TCA) in patients with secundum atrial septal defect (ASDII) is associated with high morbidity and mortality. There were few reports of biomarkers as predictors of pulmonary arterial hypertension (PAH) after TCA. **Objective:** To determine whether plasma NT-proBNP level can predict PPAH in ASDII patients after TCA. **Method:** A prospective cohort study was conducted among ASDII patients who underwent TCA in Central Chest Institute of Thailand between January 2016 and June 2016. Demographic data, body mass index, underlying diseases and echocardiographic data were assessed. The outcome in this study was the proportion of PPAH after TCA for six months in those with normal and high NT-proBNP levels. The outcome between two groups were compared with unpaired t-tests. Receiver operator characteristic (ROC) curve were used to illustrate the capacity of NT-proBNP prognostic predictor of PPAH in ASDII patients after TCA. **Result:** A total of thirty patients were prospectively recruited. Of these, twenty patients had normal baseline NT-proBNP, and ten patients had high baseline NT-proBNP. The patients with high baseline NT-proBNP had more decreased NT-proBNP than those with normal baseline NT-proBNP with statistical significance (p-value = 0.01). The proportion of patients with high baseline NT-proBNP had more PPAH than those with normal baseline NT-proBNP with statistical significance (p-value = 0.008). The ROC curve showed that baseline NT-proBNP ≥ 240 picograms/milliliter (pg/ml) had a sensitivity of 100%, a specificity of 88.5%, a positive predictive value of 57% and a negative predictive value of 100%). **Conclusion:** ASDII patients with high baseline NT-proBNP had significant PPAH after TCA compared with those with normal baseline NT-proBNP. Baseline NT-proBNP level ≥ 240 pg/ml may be used for predicting PPAH in these patients. The further larger studies will be needed for confirmation of these findings.

Keywords: secundum ASD, ASDII, transcatheter closure, pulmonary arterial hypertension, NT-proBNP

บทคัดย่อ

ภูมิหลัง: การที่ความดันหลอดเลือดแดงในปอดยังคงสูงในผู้ป่วย secundum ASD (ASDII) ที่ได้รับการปิดผ่านทางสายสวนหัวใจ (TCA) แล้ว นำไปสู่การเจ็บป่วยและอัตราตายที่เพิ่มสูงขึ้น มีรายงานพบว่า biomarkers สามารถใช้ทำนายการมีความดันหลอดเลือดแดงในปอดสูงหลังปิด ASDII ได้ **วัตถุประสงค์:** เพื่อศึกษาระดับค่า NT-proBNP ว่าสามารถนำมาใช้ในการทำนายความดันหลอดเลือดแดงในปอดสูงในผู้ป่วย ASDII ที่ได้รับการทำ TCA ได้หรือไม่ **วิธีการ:** เป็นการศึกษาวิจัยแบบติดตามไปข้างหน้าในผู้ป่วย ASDII ทุกรายที่ได้รับการทำ TCA ที่สถาบันโรคทรวงอก ตั้งแต่เดือนมกราคมถึงมิถุนายน พ.ศ.2559 โดยเก็บข้อมูลพื้นฐานทางคลินิก, ดัชนีมวลกาย, โรคประจำตัวและผลการตรวจคลื่นเสียงสะท้อนหัวใจ ผลการศึกษานี้จะดูสัดส่วนผู้ป่วยที่มีความดันหลอดเลือดแดงในปอดสูงหลังการทำ TCA 6 เดือนเปรียบเทียบระหว่างกลุ่มที่มีระดับ NT-proBNP พื้นฐานปกติและกลุ่มที่มีระดับ NT-proBNP พื้นฐานสูง โดยใช้ unpaired t-test, receiver operator characteristic (ROC) curve ได้รับการนำมาใช้เพื่อแสดงความสามารถในการทำนายความดันหลอดเลือดแดงในปอดสูงในผู้ป่วย ASDII หลัง TCA **ผล:** มีผู้เข้าร่วมการศึกษาติดตามไปข้างหน้าทั้งหมด 30 คน โดย 20 คนอยู่ในกลุ่มที่มีระดับ NT-proBNP พื้นฐานปกติ และ 10 คนอยู่ในกลุ่มที่มีระดับ NT-proBNP พื้นฐานสูง ผู้ป่วยในกลุ่มที่มีระดับ NT-proBNP พื้นฐานสูงมีระดับ NT-proBNP ลดลงมากกว่ากลุ่มที่มีระดับ NT-proBNP พื้นฐานปกติอย่างมีนัยสำคัญทางสถิติ (p-value = 0.01) ผู้ป่วยที่มีระดับ NT-proBNP พื้นฐานสูง มีภาวะความดันหลอดเลือดแดงในปอดสูงมากกว่าในกลุ่มประชากรที่มีระดับ NT-proBNP พื้นฐานปรกติอย่างมีนัยสำคัญทางสถิติ (p-value = 0.008) ROC curve แสดงให้เห็นว่าระดับ proBNP พื้นฐาน ≥ 240 พิโคกรัมต่อมิลลิลิตร มีความไว 100%, ความจำเพาะ 88.5%, ค่าทำนายเมื่อผลเป็นบวก 57%, ค่าทำนายเมื่อผลเป็นลบ 100% **สรุป:** ผู้ป่วย ASDII ที่มีระดับ NT-proBNP พื้นฐานสูง มีภาวะความดันหลอดเลือดแดงในปอดสูงหลังการทำ TCA มากกว่ากลุ่มที่มีระดับ NT-proBNP พื้นฐานปกติอย่างมีนัยสำคัญทางสถิติ ระดับ NT-proBNP พื้นฐาน ≥ 240 พิโคกรัมต่อมิลลิลิตร อาจนำมาใช้ทำนายการมีภาวะความดันหลอดเลือดแดงในปอดสูงหลังการทำ TCA ได้ การศึกษาขนาดใหญ่อาจจำเป็นเพื่อยืนยันผลการศึกษานี้ต่อไป

คำสำคัญ: ผนังกั้นหัวใจห้องบนรั่ว, ASDII, การปิดโดยใช้สายสวน, ความดันหลอดเลือดแดงปอดสูง, NT-proBNP

Introduction

The prevalence of secundum atrial septal defect (ASDII) is about 30-40 % of adult congenital heart disease[1]. The treatment of choice of ASDII with favorable anatomy is transcatheter ASD closure (TCA)[2,3]. Long-term outcome in patients with chronic right ventricular (RV) volume overload leads to dilatation of the right atrium and RV. Additionally, in some cases, pulmonary arterial hypertension (PAH) and right heart failure may develop[4-8]. Pulmonary vascular histopathologic changes in those with PAH include medial hypertrophy, intimal proliferation fibrosis, plexiform lesions, and necrotizing arteritis in more severe forms[9-10].

Prevalence of moderate to severe PAH in ASDII was 10-21%[11] and associated with increased morbidity and mortality[12-14]. However, persistent PAH (PPAH) after TCA was still approximately more than half of patients with baseline moderate to severe PAH. Some patients had irreversible changes of PAH[15]. Despite the high prevalence of PAH in patients with ASDII, there were few predictors for PPAH after TCA.

To our knowledge, N-terminal pro-brain natriuretic peptide (NT-proBNP) is a pro-hormone, secreted by the myocardium in response to various stimuli including mechanical stretch, hypoxia. The increase in the severity of RV dysfunction in several disorders associated with RV pressure overload or structural abnormalities in the RV. There are several reports suggested that NT-proBNP correlated with RV dilatation, PAH in ASDII patients[16].

This study was conducted to determine whether plasma NT-proBNP level can predict PPAH in ASDII patients after TCA.

Materials and Methods

Study populations

A prospective cohort study was conducted among ASDII patients who underwent TCA at Central Chest Institute of Thailand between January 2016 and June 2016. The Ethical Review Committee of the Central Chest Institute of Thailand reviewed and approved this study protocol.

The study enrolled all consecutive ASDII patients aged 15 years or more with significant left to right shunt underwent TCA. The patients with recent (< 4 weeks) hospitalization for heart failure, chronic kidney disease (eGFR < 60 ml/min/1.73 m^2), severe chronic lung disease,

severe valvular dysfunction and body mass index (BMI) ≥ 30 kg/m^2 were excluded.

Clinical findings at baseline including demographic data, underlying diseases, BMI and echocardiographic data were assessed. Blood sampling for plasma NT-proBNP was collected before and after TCA for 2 days and 6 months. Transthoracic echocardiography (TTE) was performed before and 6 months after TCA.

Previous study showed the average NT-proBNP levels before ASD closure in patients with New York Heart Association (NYHA) I and III group were 142±72 and 285±101 picograms/milliter (pg/ml), respectively [17]. The NT-proBNP level in this study was averaged between upper and lower boundary between both groups of those trials and showed the NT-proBNP of 200 pg/ml was used to classify our patients to two groups.

Patients were categorized into two groups as normal baseline NT-proBNP < 200 pg/ml and high baseline NT-proBNP ≥ 200 pg/ml. PPAH was defined as mean pulmonary artery pressure (mPAP) by Abbas after TCA ≥ 25 mm Hg as shown in Figure 1.

Study outcome

The outcome in this study was the proportion of PPAH (mPAP by Abbas ≥ 25 mm Hg) after TCA for six months in those with normal and high NT-proBNP levels.

Statistical analyses

Continuous data were presented as the median and interquartile range and categorical data were shown as frequency and percentage.

Quantitative data were compared with Student t-test or Mann-Whitney U test. The proportion of patients with PPAH between two groups were compared with unpaired t-tests. A p-value < 0.05 was considered as statistical significance.

Correlation between plasma NT-proBNP level and mPAP by Abbas and correlation between percentage change of NT-proBNP and mPAP by Abbas were analyzed by bivariate correlations (Pearson correlation coefficients). Receiver operator characteristic (ROC) curve were used to illustrate the capacity of NT-proBNP as a prognostic predictor of PPAH in ASDII patients after TCA.

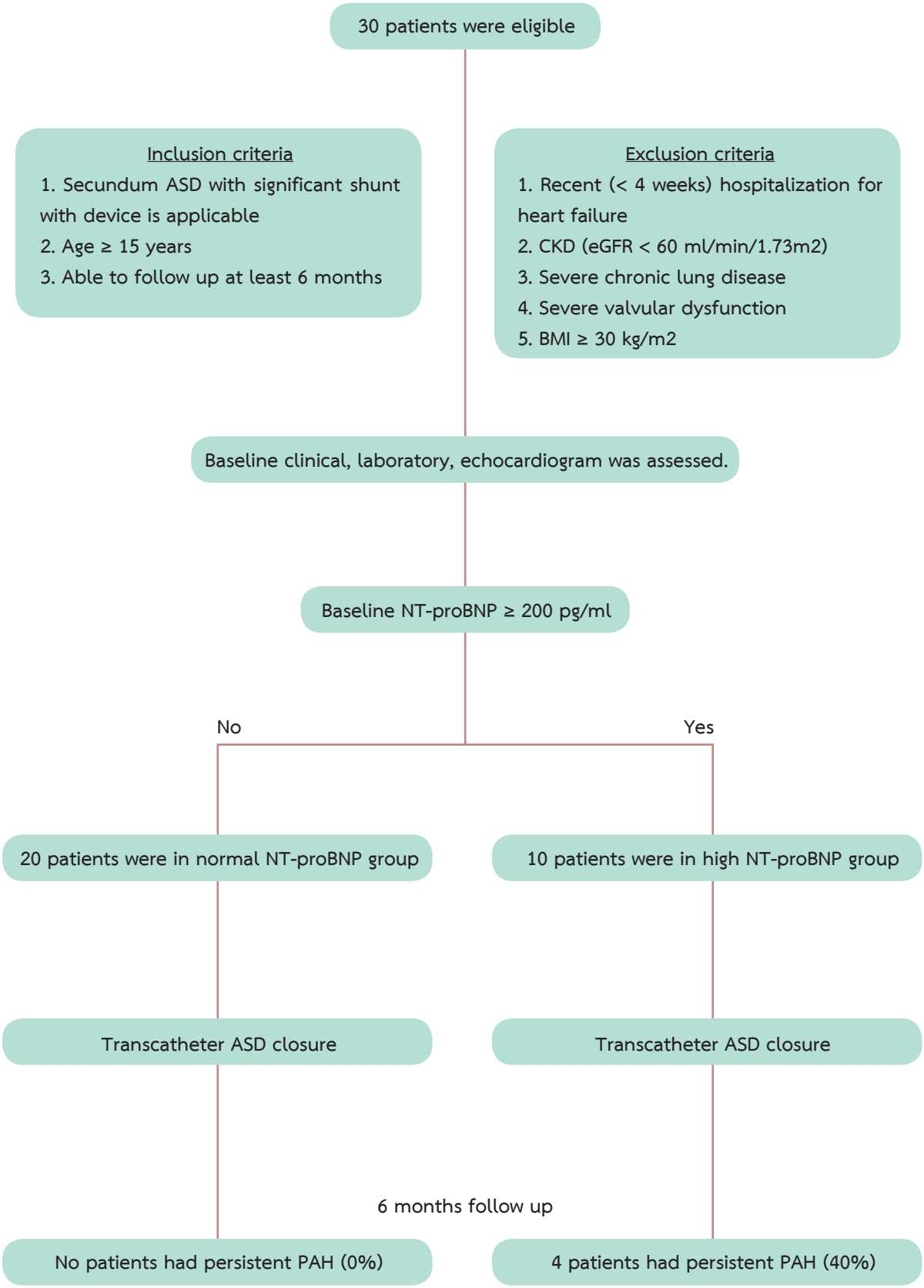

Figure 1. Study flow chart of enrollment and follow-up in ASDII patients

Results

A total of 30 patients were prospectively enrolled. Of these, 20 patients had normal baseline NT-proBNP (group 1) and 10 patients had high baseline NT-proBNP (group 2). The overall mean age was 42.07 ± 15.49 years, and 20% of patients were males. The patients with normal baseline NT-proBNP had more body mass index (BMI) than those with high baseline NT-proBNP. An average mPAP by Abbas in patients with normal and high baseline NT-proBNP was 20.35±4.53 and 26.9±10.95 mmHg, respectively. An average size of ASD in patients with normal and high baseline NT-proBNP was 22.55±7.47 and 27±5.52 millimeters, respectively. The baseline characteristics of the patients was shown in table 1.

After TCA 6 months, an average NT-proBNP was lower than baseline in both groups and the percentage changes of NT-proBNP was improved for -6.77% (95% CI-62.51% to 36.12%) and 62.07% (95%CI 72.51% to 18.38%) in patients with normal and high baseline NT-proBNP, respectively. The patients with high baseline NT-proBNP had more decreased NT-proBNP than those with normal baseline NT-proBNP with statistical significance (p-value = 0.01). Of those, 4 patients (13.33%) had PPAH. The proportion of patients with high NT-proBNP (4/10, 40%) had more PPAH than those with normal NT-proBNP (0/20, 0%) with statistical significance (p-value = 0.008).

Table 1. Baseline characteristics of the patients

Demographic data	All patients (n=30)	Normal NT-proBNP (n=20)	High NT-proBNP (n=10)	p-value
Male, n (%)	6 (20)	4 (20)	2 (20)	1.00
Age (years), mean±SD	42.07±15.49	42.45±16.59	41.3±13.84	0.85
BMI (kg/m^2), mean±SD	23.79±3.69	24.83±3.76	21.72±2.62	0.03
Comorbidity, n (%)				
Diabetes mellitus	2 (6.67)	1 (5)	1 (10)	
Hypertension	6 (20)	3 (15)	3 (30)	
Dyslipidemia	4 (13.33)	3 (15)	1 (10)	
Coronary artery disease	2 (6.67)	1 (5)	1 (10)	
Paroxysmal AF	1 (3.33)	1 (5)	0 (0)	
Valvular heart disease	1 (3.33)	0 (0)	1 (10)	
LVEF (%), mean±SD	63.53±10.16	63.82±8.73	62.94±13.09	0.83
mPAP by Abbas(mmHg), mean±SD	22.53±7.78	20.35±4.53	26.9±10.95	0.10
Creatinine, mean±SD	0.69±0.15	0.67±0.11	0.73±0.22	0.27
eGFR (ml/min/1.73 m^2, mean±SD	107.23±20.04	108.7±20.2	104.3±20.43	0.58
NT-proBNP (ng/L)	119 (72-234)	90 (49.50-119)	300 (234-250)	< 0.001
ASD size (mm), mean±SD	24.03±7.11	22.55±7.47	27±5.52	0.11

n = number, SD = standard deviation, BMI = body mass index, AF = atrial fibrillation, LVEF = left ventricular ejection fraction, mPAP = mean pulmonary artery pressure, eGFR = estimated glomerular filtration rate, ASD = atrial septal defect

Plasma NT-proBNP level was positively correlated with mPAP by Abbas (r = 0.452, p-value = 0.012) as shown in Figure 2. The area under the curve (AUC) for the diagnosis of PPAH in ASDII patients was 0.93 (95% CI 0.84 to 1.00%) [Figure 3]. The ROC curve revealed that the best cut-offs value is 240 pg/ml which exhibited a

sensitivity of 100%, a specificity of 88.5%, a likelihood ratio positive (LR+) of 8.67, a positive predictive value (PPV) of 57% and a negative predictive value (NPV) of 100%. The predictive value of NT-proBNP for the diagnosis of ASDII patients was shown in table 2.

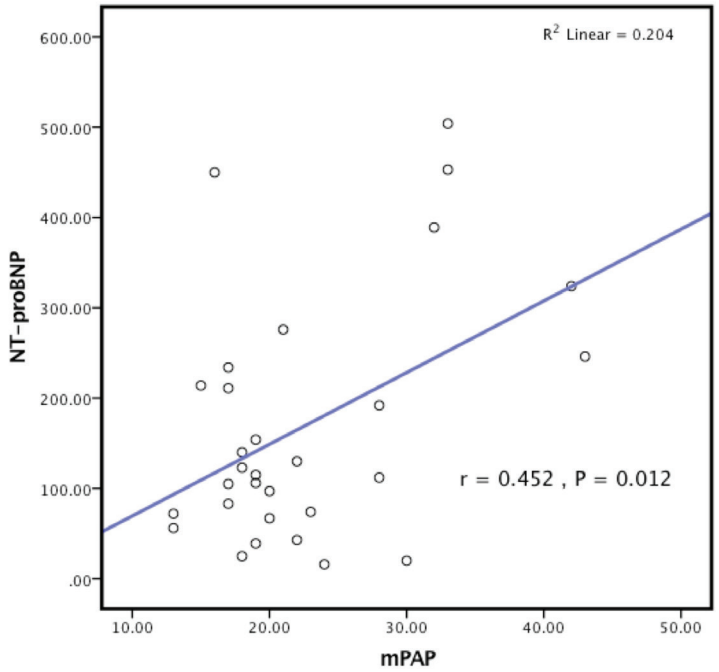

Figure 2. Correlation between NT proBNP and mPAP by Abbas

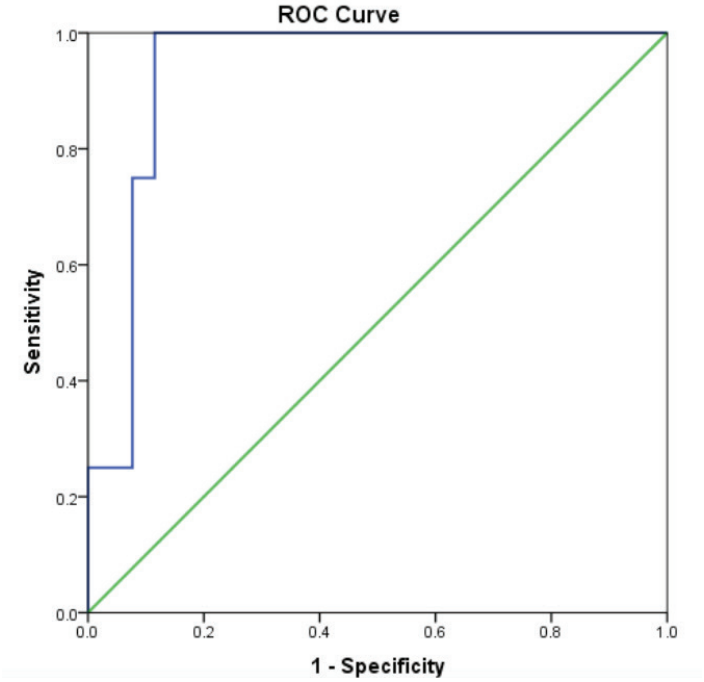

Figure 3. Receiver operating characteristic (ROC) curve showed the discrimination performance of NT-proBNP in ASDII patients with PPAH (AUC = 0.93)

Table 2. The predictive value of NT-proBNP for the diagnosis of PPAH in ASDII patients.

Baseline NT-proBNP level (pg/ml)	No. of all patients with PPAH	Sensitivity (%)	Specificity (%)	LR+	PPV (%)	NPV (%)
≥200	4/30	100	76.9	4.33	40	100
≥240	4/30	100	88.5	8.67	57.1	100
≥320	3/30	75	92.3	9.75	60	96

No. = number, PPAH = persistent pulmonary artery hypertension, ASDII = secundum atrial septal defect, LR+ = likelihood ratio positive, PPV = positive predictive value, NPV = negative predictive value

Discussion

Our study found that TCA certainly led to decrease the proportion of patients with high baseline NT-proBNP compared with normal baseline NT-proBNP with statistical significance. BMI in patients with normal baseline NT-proBNP was significantly higher than those with high baseline NT-proBNP (p = 0.03). Previous studies showed that obese patients tended to have lower plasma NT-proBNP[18-19], so this study excluded patients with BMI ≥ 30 kg/m^2. However, the mean BMI of patients with normal baseline NT-proBNP and those with high baseline NT-proBNP in this study was 24.83±3.76 and 21.72±2.62 kg/m^2, respectively. Nevertheless, no study demonstrated whether BMI ≥ 25 kg/m^2 affected the interpretation of the NT-proBNP level because this level of BMI was the cut off point for the diagnosis of overweight in Caucasian patients, but obese in Asian patients.

A previous study by Zhao-Feng Li and his colleagues has reported the first study to explore the expression of NT-proBNP and the relationships between it and some hemodynamic parameters in ASD patients with PAH.[20] This study suggested that NT-proBNP might be a predictor of the severity of mPAP in ASD patients. However, this study had several limitations, such as different kinds of congenital heart disease, small sample size and short-term follow-up period.

In this study, we found that the high baseline NT-proBNP group had PPAH significantly. Furthermore, baseline NT-proBNP level was positively correlated with mPAP by Abbas (r = 0.452, p = 0.012) and the proportion of patients with high NT-proBNP had more PPAH than those with normal NT-proBNP with statistical significance (p-value = 0.008). These results might indicate that NT-proBNP level was helpful to use as the predictor for the diagnosis of PPAH. Because the lowest false negative test should be used to avoid the missed diagnosis of PPAH after TCA, the best cut-offs value of 240 pg/ml from the ROC curve, which exhibited a sensitivity of 100%, a specificity of 88.5%, LR+ of 8.67, PPV of 57% and NPV of 100% led to the least false negative test.

Previous study has demonstrated that mean NT-proBNP levels before TCA were 240±93 pg/ml and reduced significantly to 141±62 pg/ml after 6 months of TCA (p-value < 0.01) and there was the positive correlation between NT-proBNP and pulmonary pressure[17]. The mean NT-proBNP levels in this study were consistent with our study showing the best cut-offs value was 240 pg/ml. Because of the very high sensitivity of this cut-offs value, the ASDII patients with baseline NT-proBNP of less than 240 pg/ml had high probability of no PPAH after 6 months of TCA.

However, there were several limitations of this study. First, this pilot study had a relatively small sample size, and a small number of patients with high baseline NT-proBNP led to significant result by chance. Nevertheless, this study was the first study in Thai patients showing the baseline NT-proBNP may be used to predict PPAH in ASDII patients after TCA. Second, the follow-up period may be short for evaluation of PAH after TCAP. However, long-term follow-up period should be assessed in the future. Finally, overweight patients may cause a lower NT-proBNP level compared with normal weight patients. The patients with normal baseline NT-proBNP had more overweight than those with high baseline NT-proBNP leading to cause the false low NT-proBNP. Effect of overweight for NT-proBNP level should be proved in the future.

Conclusion

ASDII patients with high baseline NT-proBNP had significant PPAH after TCA compared with those with normal baseline NT-proBNP. Baseline NT-proBNP level ≥ 240 pg/ml may be used for predicting PPAH in these patients. The further larger studies will be needed for confirmation of these findings.

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