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Original Article

Heart size, heart function, and plasma B-type natriuretic peptide levels after transcatheter closure of patent ductus arteriosus

Mulyadi M. Djer, Sudigdo Sastroasmoro, Bambang Madiyono

Abstract

Background Patent ductus arteriosus (PDA) is a common congenital heart disease causing some blood in the aorta to flow into the pulmonary artery (PA), resulting in dilatation of the left atrium (LA) and left ventricle (LV), increased B-type natriuretic peptide (BNP) level, and the development of heart failure.

Objectives To evaluate the clinical course, changes in heart size and function, and BNP level after transcatheter closure of PDA using the *Amplatzer*® duct occluder (ADO).

Methods This quasi-experimental study used a one-group, pretest-posttest design, and was done on PDA patients who underwent transcatheter closure using ADO. The outcomes measurements were performed four times, namely, before the procedure and at one, three, and six months after the procedure. Results were compared using a serial time analysis. Outcomes measured were heart failure scores, chest x-ray (CXR) and echocardiography findings, and plasma BNP level.

Results There were 23 PDA patients enrolled, of which 12 were females. Subjects' median body weight was 11 (range 6.6 to 55) kg. Prior to PDA closure, 12 subjects had mild heart failure (class II) and 7 had moderate heart failure (class III). On follow-up at one month after the procedure, all subjects had improved heart failure scores ($P<0.0001$), and no heart failure was found on further follow up. Likewise, there was a decreased mean cardiothoracic ratio (CTR) from 58 to 55% at 1-month ($P=0.001$), and also from 55 to 52% at 3-month follow up ($P<0.0001$), but no further decrease was found afterwards ($P=0.798$). The left atrium/aorta (LA/Ao) ratio measured by echocardiography also showed a statistically significant decrease from 1.6 prior to the procedure to 1.3 ($P<0.0001$) in the first month, but it remained stable afterwards. Diastolic function, represented by peak E and A waves also significantly decreased from 127 and 91 cm/sec, before the procedure, to 90 and 68 cm/sec, respectively, at 1 month follow-up ($P<0.0001$ and $P<0.0001$, respectively). However, there were no statistically significant changes in E/A ratio, ejection fraction and fractional shortening. Plasma BNP level significantly decreased from 58 pg/mL before the procedure to 28 pg/mL at 1 month follow-up ($P=0.001$), but no further significant decrease was observed afterwards.

Conclusion After PDA closure with ADO, we observe significant improvements in heart failure scores, heart size, diastolic function, and BNP level of our subjects especially in the first month after the procedure. **[Paediatr Indones. 2013;53:181-6.]**

Keywords: *heart failure score, heart size, heart function, B-type natriuretic peptide, patent ductus arteriosus, Amplatzer® duct occluder*

Patent ductus arteriosus (PDA) is a common congenital heart disease (CHD) with an incidence of about 10% of all CHD cases.[1] In Indonesia, with a population of 235 million, an estimated 4,000 infants with PDA are born yearly.[2]

From the Department of Child Health, University of Indonesia Medical School/Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Reprint requests to: Mulyadi M. Djer, Pediatric Cardiology Division, Department of Child Health, University of Indonesia Medical School/ Cipto Mangunkusumo Hospital, Jl. Diponegoro 71 Jakarta. E-mail: *muldjer@yahoo.com*.

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PDA causes some blood to flow from the aorta to the pulmonary artery, leading to excessive blood flow in the pulmonary circulation. Excess blood in the pulmonary circulation drains into the left atrium and left ventricle, resulting in chamber dilatation and eventual left heart failure.[1,3] In response to left atrial and left ventricular dilatation, myocyte cells release B-type natriuretic peptide (BNP) hormone.[4-9]

Transcatheter PDA closure using the *Amplatzer*® ductal occluder (ADO) has been routinely performed in the last ten years and is currently the treatment of choice for PDA closure. This procedure was approved by the US Food and Drug Administration (FDA).[10-13] To date, there have been a limited number of studies examining the clinical course, changes in heart size and function, as well as plasma BNP level of PDA patients after transcatheter closure with ADO. We aimed to assess the improvements in clinical heart failure scores, cardiac size and function, as well as plasma BNP level of patients who underwent PDA closure, in order to more precisely determine when to discontinue heart failure drugs after defect closure.

Methods

This quasi-experimental study used a one-group, pretest-posttest design and was performed on PDA patients before and after transcatheter closure of PDA using ADO. The outcomes measurements were performed four times, namely, before the procedure and at one, three, and six months after PDA closure. We compared post-procedure results to pre-procedure findings. The minimum number of required subjects was 23 patients, as calculated based on the formula for two paired groups of numerical variables. Patients with PDA and body weight of greater than 6 kg were included. Patients with complex congenital heart disease, duct-dependent lesion or who already had Eisenmenger's syndrome were excluded from this study.

The ADO device was used to close the PDA in our subjects. *Amplatzer*® ductal occluders were constructed from a frame of *Nitinol* mesh (a mixture of nickel and titanium) and shaped like a mushroom. A polyester *Dacron* is placed inside the frame to stimulate thrombosis in order to completely close the PDA. This device is self-expandable after being released from the delivery catheter. It may also be retracted into the catheter, in case the device needs to be replaced by another one of more appropriate size.[13]

The PDA closure with ADO was performed using fluoroscopy guidance by the first author in the catheterization laboratory on patients under general anesthesia. Before PDA closure, pressure measurements were taken from each heart chamber and the degree of shunt was calculated. If pulmonary hypertension was observed, an oxygen test was done to ascertain whether pulmonary hypertension was reversible or irreversible (Eisenmenger's syndrome). To place an ADO in the PDA, we used the following equipment: a *Mullin* delivery sheath, a delivery cable, and a loading catheter. After the ADO was attached by screw to the tip of the delivery cable, it was inserted through the femoral vein under the *Mullin* sheath in order to place the device in the PDA. After the operator ascertained that the ADO was positioned correctly and no residual shunt was seen through the PDA on angiography, the device was released from the delivery cable.

We used the *New York Heart Association* classification to establish the clinical diagnosis of heart failure in adolescents.[3] This classification categorizes heart failure into four classes: (1) class I, if there are no limitations in performing usual activities; (2) class II, symptoms occur when doing usual activities; (3) class III, symptoms occur when doing light activity and (4) class IV, symptoms occur at rest.

In infants, the degree of heart failure was assessed using the 1992 classification recommended by Ross *et al.*[14] The criteria used were as follows: (1) amount of milk consumed in each feeding; (2) time required for each feeding; (3) respiratory rate; (4) peripheral perfusion; (5) diastolic murmur or 3rd heart sound; and (6) hepatomegaly. Each criteria was scored as 0, 1, or 2, according to the degree of abnormality. The degree of heart failure was defined as follows: (1) no heart failure / class I, if the total score was 0-2; (2) mild heart failure / class II, if the total score was 3-6; (3) moderate heart failure / class III, if the total score was 7-9; and (4) severe heart failure / class IV, if the total score was 10-12. In older children, we used the *Pediatric Clinical Heart Failure Score*,[15] a modified version of the *Ross* classification. Criteria used in the scoring system were: (1) history of sweating; (2) existence of tachypnea; (3) rate of

breathing; (4) heart rate; and (5) presence or absence of hepatomegaly. The total scores and classifications of heart failure were calculated in the same manner as the *Ross* criteria.

To determine the heart size, we calculated the cardio-thoracic ratio (CTR) on chest x-ray using the anterior-posterior projection.[3] Left atrium to aorta (LA/Ao) ratios were measured by echocardiography examinations as described .[16-18]

Heart function examination was performed by 2-D, Doppler, and M-Mode echocardiography using a *Philips Sonos* 4500 machine. Left ventricular diastolic function was determined by measuring the peak E, peak A, and the E/A ratio. The E wave represents the rapid flow of blood from the left atrium into the left ventricle in the early diastolic phase, while the A wave represents the period of left ventricular filling by atrial contraction in the late diastolic phase. Left ventricular systolic function was determined by measuring the fractional shortening (FS) and ejection fraction (EF).[16-18]

Plasma BNP level examinations were conducted at the Prodia Laboratory Clinic, Jakarta. Frozen blood specimens were examined with *AxSYM BNP* reagent, a microparticle enzyme immunoassay (MEIA), developed from conventional ELISA tests, but using microparticles as the reaction media.

Numeric data with normal distribution was analyzed by repeated ANOVA / time series analysis, while non-normal distributions were analyzed by *Friedman* test. A P value of less than 0.5 was considered to be statistically significant. This study was approved by the Medical Research Ethics Committee of the University of Indonesia Medical School, Jakarta.

Results

The study was conducted from November 2006 until February 2008. During the study period, 23 patients underwent PDA closure using ADO devices at the Integrated Cardiovascular Services (ICS) of Dr. Cipto Mangunkusumo Hospital, Jakarta. All patients were included in this study, and comprised of 12 females and 11 males. The subjects' median age was 23 months (range 5 months to 14 years). Subjects' median body weight was 11 kg (range 6.6 to 55 kg), while the median height or length was 82 cm (range 65 to 162 cm). The subjects' median body surface area (BSA) was 0.47 m^2 (range 0.35 to 1.6 m^2).

To assess the functional class of heart failure, each patient was categorized into one of four groups: no heart failure (class I), mild heart failure (class II), moderate heart failure (class III) or severe heart failure (class IV). Prior to PDA closure, most subjects had mild heart failure (12 subjects), followed by moderate heart failure (7 subjects), and no heart failure (4 subjects). In this study, no patients had severe heart failure. One month after the PDA closure with ADO, subjects with mild and moderate heart failure improved into functional class I (no heart failure), and these changes were statistically significant ($P<0.0001$).

In this study, CTR was used toassess forcardiomegaly, and to evaluate the changes in heart size. **Figure 1** shows the CTRs at the various time points. There was a significant decrease in mean CTR from 58% prior to PDA closure, to 55% at one month after the procedure ($P = 0.001$). At the three-month follow-up, the CTR decreased further to 52%, a higher degree of CTR decrease ($P<0.0001$) than the decrease observed at one month post-procedure. At six months after the procedure, there was no further statistically significant change in CTR ($P=0.798$) (**Figure 1**).

Echocardiography showed a significant decrease in LA/Ao ratio from 1.6 before PDA closure, to 1.3 at one month after the procedure ($P < 0.0001$). At the 3- and 6- month post-procedure follow-up, no further statistically significant change in LA/Ao ratios was

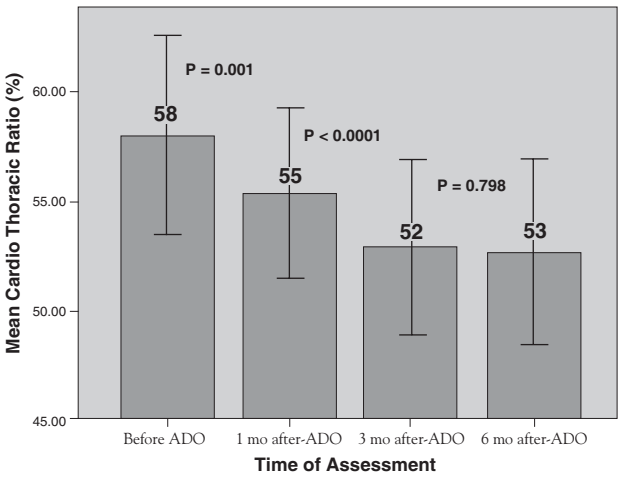

Figure 1. Mean cardiothoracic ratio before PDA closure and at 1, 3, and 6 months after the procedure

found compared to each previous level (P = 0.163 and P=0.550, respectively).

The E wave represents the rapid flow of blood from the left atrium into the left ventricle in the early diastolic phase. The subjects' mean E wave before PDA closure was 127 cm/sec, which was higher than normal values (60-68 cm/sec), showing impaired restrictive pattern. At one-month post-procedure, mean peak E wave decreased significantly to 90 cm / sec (P<0.0001). While at 3 month follow-up, mean peak E wave increased from 90 cm/sec to 102 cm/sec (P=0.002). After that it did not significantly change further at 6-month after the procedure (P=0.487).

The A wave represents the period of left ventricular filling by atrial contraction during diastolic phase. Before the PDA was closed, subjects' mean peak A wave was higher than normal (91 cm/sec vs. normal values of 30-48 cm/sec), showing impaired relaxation pattern. At one-month post-PDA closure follow-up, the mean peak A wave height decreased significantly to 68 cm/sec (P<0.0001). Further follow-up at three and six months post-procedure, revealed that the mean peak A wave increased slightly, but the differences were not statistically significant.

The E/A ratio of the subjects before PDA closure was within normal range, i.e., 1.3 to 3.4. After PDA closure, the mean E/A ratio initially decreased slightly at one month after the procedure, then increased slightly at the three- and six-month follow-ups. These E/A ratio changes were not statistically significant.

The mean FS before PDA closure was 39%, which was within normal limits (normal range 28-44%, mean 36%). At the one-month follow-up, the mean FS decreased to 35% (P=0.001), followed by a sharp increase to 38% at the three-month follow-up (P<0.0001). At the end of the six-month follow-up, the FS increased again to 40%, but the incremental change was less than the previous one (P=0.045).

The mean EF before PDA closure was 70%, which was within the normal range of 64-83%, mean 74%. After PDA closure, the mean EF decreased to 65% (P=0.003) at the one-month follow-up, but then rose to 69% at the three-month follow-up (P<0.0001). After that, the EF still increased, but the increment was not as large as that of the first 3 months after PDA closure (P=0.037).

B-type natriuretic peptide is a hormone secreted by cardiac muscle cells, with levels depending on the severity of heart failure. In our subjects, before PDA closure with ADO, the mean BNP level was 58 pg/mL. One month after PDA closure, the BNP level significantly decreased to 28 pg/mL (P=0.001). At three and six months after the procedure, the mean BNP levels did not significantly further change as compared to each previous level (**Figure 2**).

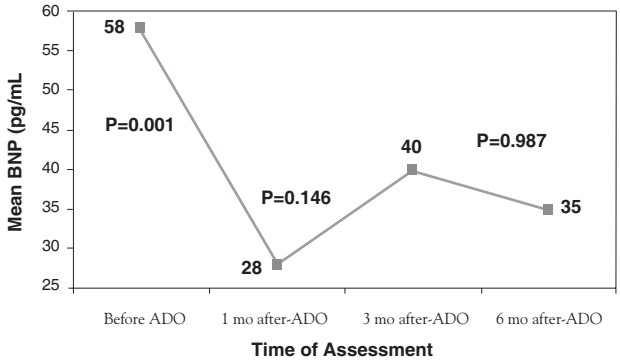

Figure 2. Mean B-type natriuretic peptide levels before PDA closure and at 1, 3, and 6 months after the procedure

Discussion

Heart failure is a complication of PDA resulting from volume overload due to a left-to-right shunt.[1,3] In this study, before PDA closure, 7 out of 23 patients had moderate heart failure and 12 of 23 had mild heart failure. We found that no patients had signs and symptoms of heart failure at one month after PDA closure. This improvement was due to the cessation of left-to-right shunt after the PDA was closed with the ADO.[1,3] Time series analysis showed a significant clinical improvement in the functional heart failure class at one-month post-PDA closure.

Subjects' chest x-rays showed the presence of cardiomegaly before PDA closure. At the first month of follow-up after PDA closure, there was a significant decrease in the mean CTR from 58% prior to the procedure to 55% post-procedure (P=0.001). The mean CTR significantly decreased further at the third month after PDA closure (55% to 52%, P<0.0001). At the next follow-up, the mean CTR did not significantly change (P=0.789). Based on time series analysis, the mean CTR progressively and significantly decreased in the first 3 months after PDA

closure (**Figure 1**). This reduction of CTR is likely due to decreased left-to-right shunt, which minimizes left ventricle volume overload.[1,3]

Heart dimension measurements using echocardiography showed similar results. At the first month after PDA closure, the LA/Ao ratio significantly decreased from 1.6 to 1.3 (P<0.0001). Follow-up at 3 and 6 months after PDA closure showed insignificant changes in the LA/Ao ratios. We observed a significant decrease in LA/Ao ratio only at the first month after PDA closure, whereas the decrease in CTR was more noticeable at 3 months after the procedure. This finding was likely because the anatomical configuration reflected by CTR required more time to change than the heart dimension, which was influenced by hemodynamic change. Eerola *et al.*[4] found similar results in their study.

We noted interesting results regarding the change in diastolic physiology. The E wave was higher than normal prior to PDA closure, showing an impaired restrictive pattern, due to volume overload and the relative decrease in left ventricle capacity to receive blood from the left atrium. After PDA closure, the mean peak E wave decreased to nearly normal values, but it increased again at 3-month follow-up after PDA closure. At the six-month follow-up after PDA closure, the mean E wave was still higher than normal, but better than that of pre-PDA closure. Prior to PDA closure, the mean peak A wave was higher than normal, showing a decreased relaxation pattern. At one month after PDA closure, we found that the A wave significantly decreased, showing an impaired relaxation pattern. It was still higher than the normal limits at 6 months after PDA closure, but it had improved compared to that of before PDA closure.

Our findings regarding diastolic physiology changes showed that there was diastolic physiological impairment in patients with PDA. Park[3] found impaired relaxation pattern in the early change of diastolic function, followed by a decrease in the restrictive pattern. In our study, some subjects had diastolic impairment with a restrictive pattern, whereas others had decreased relaxation pattern. Because our subjects were not homogenous, both diastolic impairment patterns were found in our study. The E/A ratio was relatively stable because the E and the A waves both increased. The E/A ratio was within normal limits before PDA closure. One month after PDA closure, the E/A ratio decreased, but not significantly, then increased again. The change in E/A ratio at 6 months after PDA closure compared to that prior to procedure was not statistically significant.

The systolic function did not change significantly because, according to the literature, systolic impairment typically occurs late.[3] In our study, the FS and EF of all subjects were normal. After PDA closure, the systolic function parameters decreased. According to Starling's law, myocardial contraction increases along with the gaining of myocardial strain, until at a certain point is reached, whereby adding further strain cannot further increase myocardial contraction. The latter situation may even decrease myocardial contraction. Our findings supported the theory in that systolic function decreased due to diminishing myocardial strain caused by lessening blood flow into the left heart after PDA closure. The systolic physiology returned to normal limits within 3-6 months after PDA closure.

B-type natriuretic peptide hormone has been used as a marker for heart failure and therapy evaluation.[5-9] Our subjects' mean BNP value before PDA closure was within normal limits (<100 pg/mL). However, nine of 23 subjects had high BNP levels. At one month after PDA closure, only 2 of 23 subjects still had high BNP values (P = 0.020), and only one had an abnormally high value at 3 months after PDA closure. However, at six months after PDA closure, there were 2 of 23 subjects with high BNP levels. Based on time series analysis, decreased BNP level occurred in the first month after PDA closure. In our study, after PDA closure, the mean BNP level significantly decreased from 58 to 28 pg/mL (P=0.001). Eerola *et al.*[4] found that the BNP level significantly decreased from 141 (31-974) ng/L to 79 (21-480) ng/L, 6 months after PDA closure. They also found that the BNP level of children with PDA was significantly different from that of normal children.[4,5] Thus, BNP may be used as a marker of heart dilatation due to volume overload in patients with PDA.[6-9]

In conclusion, PDA causes heart failure, heart dilatation, diastolic function impairment, and increased BNP levels. After PDA closure with ADO, we find improved heart failure scores, decreased heart size, improved diastolic function and decreased BNP levels. The improvements are found to be significant in the first month after PDA closure. For clinical practice, this pattern of changes may be used as a

guide to discontinue anti-failure drugs at one month after PDA closure.

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