The Influence of Percutaneous Closure of Patent Ductus Arteriosus on Left Ventricular Size and Function
A Prospective Study Using Two- and Three-Dimensional Echocardiography and Measurements of Serum Natriuretic Peptides

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OBJECTIVES
We aimed to evaluate the effect of percutaneous closure of patent ductus arteriosus (PDA) on left ventricular (LV) hemodynamics.

BACKGROUND
Today, most PDAs are closed percutaneously. Little is known, however, about hemodynamic changes after the procedure.

METHODS
Of 37 children (ages 0.6 to 10.6 years) taken to the catheterization laboratory for percutaneous PDA closure, the PDA was closed in 33. Left ventricular diastolic and systolic dimensions, volumes, and function were examined by two-dimensional (2D) and three-dimensional (3D) echocardiography and serum concentrations of natriuretic peptides measured before PDA closure, on the following day, and 6 months thereafter. Control subjects comprised 36 healthy children of comparable ages.

RESULTS
At baseline, LV diastolic diameter measured >+2 SD in 5 of 33 patients. In 3D echocardiography, a median LV diastolic volume measured 54.0 ml/m² in the control subjects and 58.4 ml/m² (p < 0.05) in the PDA group before closure and 57.2 ml/m² (p = NS) 6 months after closure. A median N-terminal brain natriuretic peptide (pro-BNP) concentration measured 72 ng/l in the control group and 141 ng/l (p < 0.001) and 78.5 ng/l (p = NS) 6 months after closure. Patients differed from control subjects in indices of LV systolic and diastolic function at baseline. By the end of follow-up, all these differences had disappeared. Even in the subgroup of patients with normal-sized LV at baseline, the LV diastolic volume decreased significantly during follow-up.

CONCLUSIONS
Changes in LV volume and function caused by PDA disappear by 6 months after percutaneous closure. Even the children with normal-sized LV benefit from the procedure. (J Am Coll Cardiol 2006;47:1060–6) © 2006 by the American College of Cardiology Foundation

Patent ductus arteriosus (PDA) causes volume overload of the left side of the heart and predisposes the patient to endarteritis. Transcatheter closure of the PDA has evolved over the last 30 years; today, most PDAs are closed in the catheterization laboratory. Little is known, however, of the degree and timing of changes in left ventricular (LV) size and systolic and diastolic function after percutaneous PDA closure.

Echocardiography is the most common tool for evaluation of LV systolic and diastolic performance. The measures of systolic function generally used are ejection fraction (EF) and fractional shortening. These measures of contractility correlate with the results of cardiac catheterization and radionuclide angiography (1–3). Doppler echocardiography allows assessment of LV inflow velocity at the level of the mitral valve (4–10). Under steady-state conditions, diastolic velocity measurements correlate well with data from other methods, cardiac catheterization (8,11), radionuclide angiography (12), and magnetic resonance imaging (13). Three-dimensional (3D) echocardiography is a new, non-invasive method to assess the LV systolic and diastolic function, its major advantage being independence of LV geometry. Its results correlate closely with those of cardiac catheterization (14), radionuclide angiography (15), and magnetic resonance imaging (16,17). Concentrations of plasma natriuretic peptides correlate with clinical signs and symptoms of congestive heart failure as well as with hemodynamic measurements in children with congenital heart disease (18,19). In adult patients, natriuretic peptides decrease in response to successful treatment of heart failure (20,21). To our knowledge, no reports have yet appeared on the effect of medication or of intervention on levels of natriuretic peptides in children with congenital heart disease.

The purpose of the present study was to evaluate the LV size and systolic and diastolic function in children...
patients were asymptomatic. One child was diagnosed with Mulibrey nanism.

The children treated with percutaneous PDA closure (n = 33) were examined on the day after the procedure and 6 months thereafter. The control children were examined once. All patients and control subjects underwent clinical cardiovascular examination and blood test sampling for measurement of natriuretic peptides at the time of the echocardiographic examinations. Chest X-ray was obtained and cardiothoracic ratio calculated from all PDA patients at baseline and 6 months after closure.

**Echocardiography.** The echocardiographic examination took place with the patient in the supine position or in left lateral semirecumbency. All studies were carried out by a single observer (Dr. Eerola) with the Acuson Sequoia C256 echocardiography system (Siemens, Mountain View, California). Data were saved on magneto-optic disks for later analysis. An electrocardiographic tracing was recorded simultaneously with the echocardiogram. Transducer frequency was 7 MHz or 5 MHz, either or both used for each patient, to provide optimal 2D imaging and Doppler echocardiographic recordings. Standard parasternal, apical, and subcostal views were used to detect any additional cardiac abnormalities in the PDA group and normal cardiac anatomy in the control group.

**2D echocardiography.** Left ventricular diastolic function was estimated from the mitral inflow signal obtained by Doppler echocardiography. Transmural flow velocity patterns were recorded from the apical four-chamber view, with the sample volume being positioned between the tips of the mitral valve leaflets. We measured early peak flow velocity (E) and atrial peak flow velocity (A), and calculated E/A ratio. Areas under the curves of the E and A waves were measured and the velocity integral ratio (EVTi/EAVti) was calculated. In addition, we measured the deceleration time of E velocity and deceleration rate of the early diastolic flow.

We measured peak systolic flow velocity in the LV outflow track with the apical five-chamber view and velocity in the ascending and descending aorta with the suprasternal view. The LV end-diastolic and end-systolic dimensions were measured, and LV volumes and contractility (fractional shortening and EF) were calculated by M-mode echocardiography performed from the parasternal long-axis view. The z-score of LV end-diastolic dimension was determined (23). The mean of measurements from three cardiac cycles for each participant was saved for analysis.

**3D echocardiography.** Three-dimensional echocardiography was performed with the TomTec computer software.
system. A series of cross-sectional echocardiographic images resulted from the apical view by rotating freehand scanning. Image acquisition was triggered by electrocardiogram. In free-hand scanning, a sensing device determined and registered the position and orientation of the transducer during the acquisition process. A complete cardiac cycle of images was taken on a selected image plane. Images of nine planes were collected by rotating the transducer at apical position by hand in a semicircle of 180°. Scanning of the plane took place if the heart rate was within ±20 beats/min of average. Digitized images were saved in the computer memory during acquisition. After this, the 3D dataset underwent a post-processing procedure.

The 3D datasets were analyzed with a detached computer. Manual tracing of the endocardium was performed on the white side of the black-white boundary. Papillary muscles, if discontinuous with the myocardium, were included in the ventricular volume. End-diastolic volume was calculated from the frame at the beginning of the R-wave on the electrocardiogram or from the last frame with the mitral valve still open. End-systolic volume was calculated from the frame with the smallest cavity size when the mitral valve was still closed. Time-volume curves obtained were used to determine end-diastolic and end-systolic volumes, stroke volume, and EF. From the calculated first derivatives of these curves, we measured peak filling rate and time to peak filling rate as indices of diastolic function and peak ejection rate as an index of systolic function.

**Serum natriuretic peptides.** Serum samples were frozen at −20°C. Serum concentrations of the N-terminal brain natriuretic peptide (pro-BNP) were measured by the electrochemiluminimetric method. The reagent kit was manufactured by Roche (Mannheim, Germany), and the samples were analyzed at Limbach Laboratory (Heidelberg, Germany). Serum concentrations of N-terminal proatriopeptide (ANPN) were measured by immunofluorometric assay. The reagents were manufactured by Medix Biochemica (Espoo, Finland) and the instruments by Delfia Research Fluorometer (Wallac, Turku, Finland).

**Cardiac catheterization.** Children with PDA underwent cardiac catheterization for closing the PDA with a percutaneous device. The procedure was performed under general endotracheal anesthesia, systemic heparinization, and antimicrobial prophylaxis with intravenous cefuroxime (30 mg/kg). The pressure and saturation measurements came from the LV, the aortic arch, and the main pulmonary artery before the occlusion of the PDA. Angiography was performed in the distal aortic arch before and after PDA occlusion. In addition, aortic pressure was measured after occlusion.

**Reproducibility.** Intraobserver variability was assessed in a randomly selected subset of 12 patients by repeating all M-mode and 3D echocardiographic measurements on separate occasion. To test the interobserver variability, all M-mode measurements of 14 randomly selected patients were performed by a second observer (Dr. Jokinen) who was blinded to the results of the initial echocardiographic examination. As indices of intraobserver and interobserver variability, coefficient variations (mean difference ± 2 SD) were calculated.
**Statistical analysis.** Analyses were performed with the Statistical Package for Social Science (SPSS Inc., Chicago, Illinois). For variables derived from echocardiograms and blood samples, mean and SD or median and range were calculated when appropriate. Distribution of parameters tested by Kolmogorov-Smirnov’s goodness-of-fit test was not normal. Therefore, the Mann-Whitney test was used for statistical analysis between groups, and the Wilcoxon signed rank test was used for the analysis within groups. Correlations between the smallest diameter of the PDA, serum concentration of pro-BNP, and LV diastolic volume were measured with Spearman’s correlation coefficient. The level of significance chosen was at \( p < 0.05 \).

**RESULTS**

Transcatheter closure of the PDA was carried out in 33 children. In 10 children, the PDA was occluded with an Amplatzer PDA occlusion device (AGA, Golden Valley, Minnesota) and, in 23 children, with a detachable coil (Cook, Bloomington, Indiana). No complications occurred in the catheterization procedures. Seven children with the Amplatzer device and 19 children with a coil completed the 6-month follow-up. During the follow-up, no residual shunts were visible in the children with PDAs closed with an Amplatzer device. Two children with PDAs occluded with a coil had minimal residual shunts at the time of the 6-month follow-up.

**Baseline.** In chest X-ray, cardiothoracic ratio measured a median 0.52 (range 0.44 to 0.71). Three patients had cardiothoracic ratios of more than 0.60.

In 2D echocardiography, LV diastolic (Fig. 1) and systolic volumes adjusted to BSA were larger in the patient group than in the control group (Table 2). The median \( z \)-score of LV diastolic diameter was 0.75 (range \(-1.25 \) to 3.75) SD in patients and \(-0.25 \) (range \(-1.75 \) to 1.25) SD in control subjects. It was abnormal (>2 SD) in five (15%) patients with PDA before PDA closure and in none in the control group. Early mitral peak flow velocity (E) was higher in the patient group (Table 2). The other indices of diastolic function (atrial peak flow velocity (A), the E/A ratio, areas under the curves of the E and A waves or Evti/Avti, or deceleration rate of early diastolic flow) did not differ from those of the control group. The LV fractional shortening and EF were lower in the patient group than among control subjects (Table 2).

In 3D echocardiography, the LV diastolic (Fig. 1) and systolic volumes adjusted to BSA were larger in the PDA group (Table 2). There were no differences in systolic and diastolic indices of LV function between the patients and the control subjects.

Concentrations of serum natriuretic peptides were higher in the patient group (Fig. 2). The ANPN measured 0.39 (range 0.21 to 1.21) nmol/l in the PDA group and 0.31 (range 0.10 to 0.77) nmol/l in the control group (\( p = 0.007 \)); the pro-BNP measured 141 (range 31 to 974) ng/l and 72 (range 27 to 321) ng/l (\( p = 0.001 \)), respectively. In the patient group, the levels of pro-BNP correlated with the \( z \)-score of LV diastolic diameter (\( r = 0.388 \), \( p = 0.025 \)) and the diastolic LV volume adjusted to BSA by 2D echocardiography (\( r = 0.404 \), \( p = 0.020 \)) but not with the smallest diameter of the PDA.

In cardiac catheterization, before PDA closure, the systolic, diastolic, and mean pressures in the pulmonary artery measured a median 22 (range 16 to 45) mm Hg, 10 (range 6 to 20) mm Hg, and 15 (range 11 to 25) mm Hg, respectively. The LV end-diastolic pressure measured 7 (range 3 to 18) mm Hg. Aortic pressures increased significantly after PDA closure (Fig. 3). Before closure, systolic, diastolic, and mean pressures in the aortic arch measured a median 87 (range 65 to 107) mm Hg, 48

### Table 2. Indices of LV Systolic and Diastolic Function as Measured by 2D and 3D Echocardiography in Patients With PDA Measured Before PDA Closure, 1 Day, and 6 Months After the Procedure and in Control Subjects

<table>
<thead>
<tr>
<th>Method</th>
<th>Variable</th>
<th>Control Group</th>
<th>PDA Group Before PDA Closure</th>
<th>PDA Group 1 Day After PDA Closure</th>
<th>PDA Group 6 Months After PDA Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D</td>
<td>Diastvol/BSA (ml/m²)</td>
<td>62.5 (43.9–85.7)</td>
<td>78.4 (44.7–117.1)*</td>
<td>80.6 (40.3–108.6)†</td>
<td>63.7 (37.6–89.5)‡</td>
</tr>
<tr>
<td></td>
<td>Systvol/BSA (ml/m²)</td>
<td>18.2 (9.9–30.6)</td>
<td>24.5 (12.3–45.0)*</td>
<td>23.5 (11.2–40.7)*</td>
<td>19.6 (11.9–33.3)‡</td>
</tr>
<tr>
<td></td>
<td>E (m/s)</td>
<td>0.96 (0.67–1.18)</td>
<td>1.05 (0.72–1.65)§</td>
<td>0.97 (0.64–1.42)§</td>
<td>0.97 (0.6–1.36)‡</td>
</tr>
<tr>
<td></td>
<td>A (m/s)</td>
<td>0.62 (0.29–1.08)</td>
<td>0.7 (0.31–1.18)</td>
<td>0.65 (0.33–1.07)</td>
<td>0.55 (0.35–1.07)</td>
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<tr>
<td></td>
<td>E/A</td>
<td>1.50 (0.98–3.5)</td>
<td>1.69 (0.87–3.55)</td>
<td>1.47 (0.73–3.63)</td>
<td>1.66 (0.94–3.12)</td>
</tr>
<tr>
<td></td>
<td>E dec rate (m²/s)</td>
<td>9.0 (4.0–23.2)</td>
<td>10.3 (5.0–28.1)</td>
<td>9.6 (4.1–17.4)</td>
<td>8.7 (4.8–15.4)‡</td>
</tr>
<tr>
<td></td>
<td>FS (%)</td>
<td>40.0 (32.9–49.9)</td>
<td>38.0 (28.6–50.5)</td>
<td>35.9 (28.9–47.4)‡</td>
<td>36.8 (26.9–45.3)</td>
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<td></td>
<td>EF (%)</td>
<td>72.1 (62.4–82.5)</td>
<td>69.2 (56.6–82.0)§</td>
<td>67.2 (57.7–78.9)§</td>
<td>68.2 (53.9–78.0)</td>
</tr>
<tr>
<td>3D</td>
<td>Diastvol/BSA (ml/m²)</td>
<td>54.0 (32.6–74.4)</td>
<td>58.4 (37.7–99.9)§</td>
<td>61.7 (43.9–99.9)†</td>
<td>57.2 (41.0–84.4)</td>
</tr>
<tr>
<td></td>
<td>Systvol/BSA (ml/m²)</td>
<td>27.2 (14.1–42.5)</td>
<td>30.5 (16.2–54.0)</td>
<td>29.1 (18.8–49.8)</td>
<td>27.3 (18.1–37.6)</td>
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<tr>
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<td>PFR (ml/s)</td>
<td>74.4 (20.0–166.1)</td>
<td>83.2 (22.8–165.3)</td>
<td>88.7 (44.7–187.2)</td>
<td>79.0 (38.0–151.9)</td>
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<td>TPFR (ms)</td>
<td>120.5 (10.0–272.0)</td>
<td>119.5 (10.0–314.0)</td>
<td>105.0 (10.0–584.0)</td>
<td>115.5 (12.0–408.0)</td>
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<td>PER (ml/s)</td>
<td>91.8 (24.5–176.9)</td>
<td>103.8 (53.7–211.6)</td>
<td>108.9 (51.4–274.7)§</td>
<td>94.8 (69.6–178.3)</td>
</tr>
<tr>
<td></td>
<td>EF (%)</td>
<td>49.4 (40.5–67.1)</td>
<td>51.7 (37.1–64.5)</td>
<td>52.7 (38.2–63.6)§</td>
<td>53.1 (42.0–64.8)‡</td>
</tr>
</tbody>
</table>

Values are median (range). \( p < 0.001 \), \( p < 0.01 \), \( p < 0.05 \), as compared with the control group; \( p < 0.05 \), as compared with the PDA group at baseline.

A = atrial peak flow velocity; BSA = body surface area; Diastvol/BSA = left ventricular diastolic volume adjusted to body surface area; E dec rate = deceleration rate of early diastolic flow; E/A = ratio; E = mitral early peak flow velocity; EF = ejection fraction; FS = fractional shortening; LV = left ventricular; PDA = patent ductus arteriosus; PER = peak ejection rate; PFR = peak filling rate; Systvol/BSA = left ventricular systolic volume adjusted to body surface area; TPFR = time to peak filling rate.
a median 1.5 (range 0.9 to 3.6) mm. In the patient subgroup with a normal-sized LV, the PDA measured 1.4 (range 0.9 to 3.6) mm. The smallest diameter of the PDA correlated with LV diastolic volume adjusted to BSA measured by 2D echocardiography ($r = 0.601$, $p < 0.001$), $z$-score of LV diastolic diameter ($r = 0.640$, $p < 0.001$), and LV diastolic volume adjusted to BSA measured by 3D echocardiography ($r = 0.382$, $p < 0.05$).

**Intraobserver and interobserver variability.** For LV diastolic and systolic diameter and LV diastolic and systolic volume measurements in M-mode echocardiography, the intraobserver variability was 2.2% (0.08 ± 2.58), 5.1% (0.49 ± 3.44), 5.3% (0.54 ± 10.98), and 12.0% (1.22 ± 7.44), respectively. For the same measurements, interobserver variability was 3.1% (0.41 ± 2.38), 3.1% (0.33 ± 1.3), 8.1% (0.58 ± 2.24), and 6.5% (−1.77 ± 7.46), respectively. For 3D diastolic and systolic LV volumes, intraobserver variability was 9.5% (−0.33 ± 6.1) and 8.8% (−0.80 ± 10.74), respectively.

**Day 1 after the procedure.** One day after the PDA occlusion, differences in diastolic (Fig. 1) and systolic volumes as well as the difference in LVEF between the PDA group and control group remained significant in 2D echocardiography (Table 2).

In 3D echocardiography, the LV diastolic volume adjusted to BSA remained larger (Fig. 1) and the peak ejection rate was higher in the PDA group than in control subjects (Table 2).

Levels of serum natriuretic peptides, on the first day after occlusion, remained higher in the PDA group than in control subjects. The serum concentration of pro-BNP had

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**Figure 2.** Serum concentrations of (A) N-terminal proatriopeptide (S-ANPN) and (B) N-terminal brain natriuretic peptide (S-proBNP) measured at baseline, 1 day, and 6 months after patent ductus arteriosus (PDA) closure in the whole PDA group and in patients with normal-sized left ventricle (LV) at baseline and in control subjects. *p < 0.05, †p < 0.01, ‡p < 0.001 as compared with control group; §p < 0.05, ¶p < 0.01 within PDA group as compared with baseline.

**Figure 3.** Aortic systolic, diastolic, and mean pressures measured in cardiac catheterization before and after patent ductus arteriosus (PDA) closure in the whole PDA group and in patients with normal-sized left ventricle (LV) at baseline. ¶p < 0.001 within the PDA group as compared with baseline.
increased to 192 (range 17 to 1,182) ng/l (Fig. 2). The ANPN concentration measured 0.41 (range 0.16 to 1.13) nmol/l (Fig. 2).

Six months after PDA closure. At 6 months after PDA closure, all patients were asymptomatic with no signs of congestive heart failure. In chest X-ray, cardiothoracic ratio measured a median 0.50 (range 0.44 to 0.73) (p < 0.01 as compared with baseline). In one patient, the cardiothoracic ratio was still more than 0.60; however, in echocardiography, the z-score of her LV end-diastolic diameter was −1.0 SD.

In 2D echocardiography, 6 months after PDA occlusion, LV diastolic (Fig. 1) and systolic volumes had decreased significantly as compared with the baseline and did not differ from those in the control group (Table 2). The z-score of LV diastolic diameter was 0.0 (range −2.0 to 1.75) SD (p = NS as compared with the control group). The difference in velocity of early mitral flow seen at baseline between groups had disappeared. The deceleration rate of the early diastolic flow was now lower than at baseline and did not differ from that in the control group (Table 2).

In 3D echocardiography, no differences appeared between groups in LV systolic and diastolic (Fig. 1) volumes adjusted to BSA (Table 2). There were no differences in diastolic indices of LV function between patients and control subjects. The EF was higher in the patient group.

At the follow-up, serum concentrations of pro-BNP and ANPN did not differ from those in the control group (Fig. 2). The pro-BNP concentration measured a median 79 (range 21 to 480) ng/l in the PDA group and 72 (range 27 to 321) ng/l in the control group (p = NS); the ANPN concentration measured a median 0.38 (range 0.14 to 0.58) nmol/l and 0.31 (range 0.10 to 0.77) nmol/l (p = NS), respectively.

Within the PDA group, significant changes appeared in both systolic and diastolic indices of LV function and in LV size by 2D echocardiography 6 months after PDA occlusion as compared with baseline (Table 2): Early mitral peak flow velocity (E), atrial peak flow velocity (A), and deceleration rate of the early diastolic flow had decreased as compared with baseline. This might reflect decreased flow through the mitral valve, decreased sympathetic activity, and normalized LV compliance.

Levels of natriuretic peptides were significantly higher before PDA closure in the PDA group than in the control group. Pro-BNP on the first day after PDA closure was higher than at baseline, probably due to anesthesia and excessive volume load caused by intravenous fluids and contrast media. Six months after the procedure, levels of natriuretic peptides showed no differences between the groups. Even in the subgroup of patients with normal-sized LVs at baseline, the decrease in the levels of natriuretic peptides was significant (Fig. 2). Elevated pro-BNP levels seem to reflect volume overload of LV even in asymptomatic patients with normal-sized LV. In the adult population, levels of BNP vary with hemodynamic state and can serve to reveal the effect of treatment (21). In pediatric patients, plasma concentrations of pro-BNP correlate well with clinical signs of heart failure (19). The plasma atrial natriuretic peptide concentrations correlate with hemodynamic measurements in children with congenital heart diseases (28). In preterm infants, the magnitude of shunting through a PDA is the main determinant of plasma levels of natriuretic peptides (29). In our study, the pro-BNP levels correlated with LV diastolic volume. To our knowledge, the effect of treatment or intervention on the levels of natriuretic peptides has not been previously studied in a pediatric population.

Harada et al. (30) have shown that the systolic and diastolic blood pressures increase after coil occlusion of PDA, leading to increased flow volume and maximum peak flow velocity in the left anterior descending coronary artery. Similarly, in our study, significantly higher aortic systolic, diastolic, and mean pressures were measured in cardiac catheterization after PDA closure than at baseline (Fig. 3).

No correlation has been found between the presence of a murmur and the size of the PDA (31). This might be owing to differences in the direction of ductal flow. The size and
the shape of an elastic PDA and the amount of shunting through it might vary and cause more significant volume overload of the LV than anticipated. All our patients had either systolic or continuous murmur. Our follow-up data suggest that even a PDA that appears small by echocardiography might cause significant LV volume overload. In the subgroup of patients with normal-sized LV, the LV size and the levels of natriuretic peptides decreased after PDA closure. Patients with small PDAs thus need to be evaluated carefully. They might need to be followed up and subsequently considered as candidates for PDA closure.

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