Changes in Myocardial Function and Hemodynamics after Ligation of the Ductus Arteriosus in Preterm Infants

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Objective To characterize the changes in systemic hemodynamics and systolic, diastolic, and global myocardial performance after patent ductus arteriosus (PDA) ligation in very-low-birth-weight infants.

Study design Echocardiograms were performed on 23 neonates (mean gestational age, 26.2 ± 2.2 weeks) at 2.3 ± 2.0 hours before PDA ligation (n = 23) and at 2.0 ± 1.4 hours (n = 23) and 23.5 ± 2.5 hours after (n = 11) PDA ligation.

Results Mean blood pressure, heart rate, load-independent contractility, shortening fraction, left ventricular (LV) afterload, and diastolic function did not change. Preload (early and atrial mitral inflow velocities) decreased immediately after ligation but remained unchanged thereafter. LV output decreased and systemic vascular resistance increased after surgery. The LV myocardial performance index (MPI), a measure of global myocardial performance, deteriorated acutely after ligation but improved by 23.5 hours after surgery. Changes in LV MPI were most closely correlated with changes in LV output.

Conclusions After PDA ligation, LV output and MPI decrease, due primarily to a decrease in LV preload, although LV contractility and diastolic function do not change. However, the changes in LV MPI after ligation also reflect an acute deterioration followed by an improvement in global cardiac function, because LV loading conditions remained unchanged after surgery and thus cannot explain the improvement in MPI by 24 hours after ligation. (J Pediatr 2007;150:597-602)
atrically studied to date. Consequently, we sought to characterize the changes in myocardial function and systemic hemodynamics in VLBW infants undergoing PDA ligation.

METHODS

In this observational study, data were collected both retrospectively and prospectively. All VLBW infants admitted to the Center for Newborn and Infant Critical Care (CNICC) at Childrens Hospital Los Angeles for PDA ligation between March 2004 and November 2005 were eligible for the study. Between March 2004 and January 2005, the subjects were enrolled retrospectively; between February 2005 and November 2005, they were enrolled prospectively.

Neonates were enrolled if they were VLBW infants and presented with an echocardiographically confirmed PDA requiring surgical ligation according to the attending neonotologist and the consulting pediatric cardiologist. The decision to perform ligation was based primarily on the presence of cardiovascular dysfunction and/or on the size of the PDA. Cardiovascular dysfunction was defined by the presence of systemic hypotension not responding to low- to medium-dose vasopressor/inotrope treatment and the presence of oliguria and/or metabolic acidosis. A PDA > 2 mm in size also was considered hemodynamically significant.

All but 1 neonate was receiving mechanical ventilation during the entire study period and had received at least 1 course of indomethacin treatment. Patients were excluded from this study if they had evidence of a hypertrophic or dilated cardiomyopathy or had congenital heart defects other than a PDA or a patent foramen ovale.

The Childrens Hospital Los Angeles Institutional Review Board approved the study. Informed consents were waived by the Institutional Review Board for the retrospective phase of the study and were obtained for all patients enrolled prospectively. In the CNICC at Childrens Hospital Los Angeles, echocardiograms are performed routinely before and shortly after PDA ligation. During the retrospective phase of the study, subjects were included only if a complete echocardiographic assessment of cardiac function and systemic hemodynamics was available within 9 hours before and 6 hours after PDA ligation. A complete set of retrospective echocardiographic data was available for 11 subjects.

During the prospective phase, complete echocardiograms were performed in 12 patients within 6 hours preligation and postligation and in 11 patients at 23.5 ± 2.5 hours postligation. Thus, this study presents hemodynamic data at 2.3 ± 2.0 hours before and 2.0 ± 1.4 hours postligation on all 23 patients enrolled, and the findings of the third echocardiogram performed at 23.5 ± 2.5 hours postligation represent the findings of the prospectively enrolled preterm neonates (Table).

All echocardiograms were performed and analyzed by 1 of the authors (S.N.), who is trained and certified in pediatric echocardiography, using a SONOS 5500 echocardiography machine (Philips) equipped with 8- and 12-MHz transducers. On each echocardiogram, systolic, diastolic, and global cardiac function and hemodynamic features were evaluated. Systolic function was assessed by 2 load-dependent measures of contractility—shortening fraction (SF) and heart rate–corrected velocity of circumferential fiber shortening (VCFc)—measured by M-mode and a load-independent measure of contractility known as stress-velocity index (the relation of VCFc to wall stress [WS]). The latter was calculated as a z score based on published normative data. The advantage of using the stress-velocity index is that it assesses myocardial contractility independent of influences from altered preload and afterload. Therefore, while a load-dependent measure of contractility assesses cardiac performance, the stress-velocity index evaluates cardiac performance potential.

LV and right ventricular (RV) outputs were also followed. The LV output was calculated using the aortic diameter and velocity time integral (VTI) measured at the aortic valve annulus from parasternal long-axis and apical views, respectively. The RV output was calculated using the pulmonary valve annulus diameter and VTI measured at the pulmonary valve annulus from parasternal long-axis and subcostal views, respectively. Cardiac output was assessed by mitral valve inflow Doppler and mitral annulus tissue Doppler performed at the septal and lateral mitral annulus. The ratio of early (E) to atrial (A) mitral inflow Doppler (E/A) and early mitral inflow Doppler to early (E') mitral annulus tissue Doppler (E/E') were used to evaluate diastolic function.

Global myocardial function of the LV was assessed using the myocardial performance index (MPI). A widely used measure of global myocardial function, MPI is calculated by dividing the sum of isovolumic contraction and relaxation times with the ejection time. Accordingly, the following formula was used to calculate MPI: (A − B)/B, where A is the time span between the end of one mitral flow Doppler envelope to the beginning of the next envelope and B is the ejection time. Because the MPI is inversely related to myocardial function, an increase in MPI indicates a deterioration of global myocardial function. Preload was assessed by measuring the LV internal diameter in diastole (LVIDD) and the mitral E and A velocities. SVR was calculated using the following formula: SVR = (mean blood pressure − right atrial pressure)/LV output. Right atrial pressure was estimated as 4 mm Hg in all studies. PDA size was measured as the diameter of the ductus arteriosus at its narrowest site using color flow Doppler imaging.

Blood pressure (BP) was measured directly by a transducer connected to an indwelling arterial catheter, or noninvasively using the oscillometric method. Mean arterial BP (recorded at the time of the echocardiogram) was used to calculate WS. We used mean BP because it is more representative of the entire cardiac cycle, and previous studies have shown an excellent correlation between mean arterial pressure and end-systolic pressure. Mean BP was also used to calculate SVR. As for systolic and diastolic BP, we present the
average values over 6-hour blocks (the 6 hours before and after ligation and the 6 hours from 18 to 24 hours postligation). Because this was an observational study, all aspects of patient care were directed by the attending neonatologist.

Statistics

All data are given as mean ± standard deviation unless stated otherwise. Cardiovascular features were analyzed using 1-way analysis of variance for repeated-measures and pairwise comparisons with adjustment for multiple comparisons (Scheffé’s method). Univariate and multivariate linear regression models were used as appropriate. A P value < .05 was considered to indicate statistical significance.

RESULTS

The study population comprised 23 VLBW infants, with 11 enrolled retrospectively and 12 enrolled prospectively. Mean birth weight was 845 ± 280 g, and mean gestational age was 26.2 ± 2.2 weeks. PDA ligation was done on day 20 ± 11 of postnatal life. Echocardiograms were performed 2.3 ± 2.0 hours before ligation (n = 23) and 2.0 ± 1.4 hours (n = 23) and 23.5 ± 2.5 hours (n = 11) after ligation. The average size of the PDA was 2.5 ± 0.9 mm.

Changes in cardiovascular measures and hemodynamics are given in the Table. Compared with preligation status, a significant reduction in LV output occurred both immediately postligation (P = .0001) and at 23.5 hours postligation (P = .02). Because there was no significant change in heart rate, the reduction in LV output resulted principally from a reduction in LV preload. Although the decrease in LVDD did not reach statistical significance, the drop in mitral E and A velocities (both P = .0001) indicates a reduction in preload immediately after ligation. LVDD and mitral E and A velocities remained unchanged at 23.5 hours postligation. There were no significant changes in RV output, mean airway pressure, and dopamine dose before and immediately after PDA ligation; however, in 35% of the patients (n = 8), the vasopressor dose was increased by at least 25% by 23.5 hours postligation. Systolic and mean BP did not significantly change after PDA ligation, but a modest increase in diastolic BP occurred by 23.5 hours postligation (P = .036).

As for the measures of systolic function, SF and VCFc did not change. The load-independent measure of myocardial

Table. Changes in cardiac function and hemodynamics

<table>
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<tr>
<th></th>
<th>Preligation (−2.3 hours)</th>
<th>Postligation (2 hours)</th>
<th>Postligation (23.5 hours)</th>
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ET, ejection time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; LVDD, left ventricular internal diameter at end-diastole; LVO, left ventricular output; NS, not significant; RVO, right ventricular output.

P value1 = Preligation (−2.3 hours) versus postligation (2 hours).
P value2 = Preligation (−2.3 hours) versus postligation (23.5 hours).
P value3 = Postligation (2 hours) versus postligation (23.5 hours).

*Values at the time of echocardiography.
contractility—the stress-velocity index—was unchanged and remained within 2 standard deviations below the normative mean (z score).

Although E and A significantly decreased immediately after PDA ligation, both the mean E/A and E/Ea ratios remained unchanged throughout the study. LV MPI deteriorated immediately after ligation ($P = .0001$); however, although LV MPI remained elevated in the postoperative period, an improvement was seen by 23.5 hours relative to the 2-hour postligation value ($P = .03$). The LV ejection time decreased, and the sum of the isovolumic contraction and relaxation times increased immediately after ligation ($P = .0001$). Although WS remained unchanged throughout the study period, SVR increased significantly immediately after ligation ($P = .0003$).

Among the determinants of LV output (ie, LVIDD [preload], stress-velocity index [contractility], WS [afterload], and heart rate) and MPI, changes in LVIDD and MPI were significantly correlated with LV output 2 hours after ligation by univariate analysis. When adjusted for all variables, however, only MPI remained significantly correlated with LV output ($R^2 = .52; P = .02$).

Because we observed a decrease in LV output and deterioration in MPI immediately after ligation, we further analyzed the data to investigate correlations between any of the preligation factors and the postligation changes in LV output and MPI. The factors examined included infant’s birth weight and gestational age, mother’s postmenstrual age, postnatal age at ligation, PDA size and preligation LV output, MPI, stress velocity index, E/A ratio, heart rate, SF, LVIDD, and pressor/inotrope level. Only preligation PDA size, LV output, and stress velocity index exhibited a significant correlation with LV output at 2 hours postligation by univariate analysis. When adjusted for all of these 3 variables, only the preligation PDA size correlated significantly with changes in LV output at 2 hours postligation ($R^2 = .58; P = .0008$). This finding indicates that the larger the PDA, the greater the reduction in LV output after ligation. As for the postligation MPI, univariate analysis revealed a significant direct correlation with preligation PDA size and an inverse correlation with preligation MPI. These correlations remained statistically significant even after adjustment for the other variable by multivariate analysis ($R^2 = .49; P = .001$). No differences were seen in the patterns of changes in cardiac function and systemic hemodynamics between the prospective and retrospective data sets (data not shown).

**DISCUSSION**

In our study, LV MPI increased in all but 1 patient after PDA ligation. Because MPI is inversely related to global myocardial function, an increase in MPI indicates a deterioration of cardiac function. However, because contractility and indices of diastolic function remained unchanged after ligation, the deterioration of LV MPI suggests that MPI may be affected by loading conditions in preterm neonates or a greater sensitivity of this index to changes in cardiac function compared with more conventional measures. Indeed, studies in animals have suggested at least some load dependence of MPI, because an acute reduction in preload is associated with an increase MPI. However, the relationship between MPI and preload also appears to be affected by cardiac function. For example, volume loading does not alter the MPI with normal LV function, even though MPI decreases with volume loading if LV dysfunction exists.

It is important to keep in mind that a PDA causes LV volume overload, with the load decreasing (and presumably normalizing) after PDA ligation. In our patients, baseline LV MPI was in the normal range (0.33 ± 0.08) but increased after ligation to an abnormally high level. By 23.5 hours postligation, however, LV MPI began to normalize even though the loading conditions remained unchanged. Therefore, although a sudden decrease in preload immediately after ligation likely contributed to the increase in LV MPI, the data suggest that transient deterioration in global cardiac function also occurred, possibly due to the acute decrease in myocyte fiber length after the sudden decrease in LV loading volume. The finding that PDA size correlates with both the postligation decrease in LV output and the deterioration in LV MPI underscores the significance of the severity of volume overloading on postligation myocardial performance. Thus, these findings indicate that the decrease in stroke volume immediately after ligation was caused by both the acute LV volume unloading and cardiac function deterioration. Global cardiac function then improved by 23.5 hours postligation, perhaps because the normalized and unchanged volume loading after surgery promoted a “resetting” of myocyte fiber length over time.

Furthermore, multivariate analysis revealed that changes in LV output after ligation correlated with changes in MPI but not with any of the determinants of LV output (preload, contractility, heart rate, and afterload). This finding further supports the notion that MPI might be a more sensitive measure of global myocardial function in preterm neonates than the conventional methods.

There is little information in the literature regarding the effect of PDA ligation on myocardial performance. Most animal studies have been limited to describing changes in cardiac function after closure of the PDA within the first 24 postnatal hours and thus do not represent the frequently encountered clinical situation in which the PDA remains open for many days or weeks before ligation. Therefore, the impact of prolonged exposure of the immature myocardium to a high preload cannot be extrapolated from these animal studies. One recent study reported the effect of PDA ligation performed on postnatal day 6 on cardiopulmonary function in a preterm baboon model. Although the findings suggest a medium-term beneficial effect of PDA ligation on myocardial function, the study did not systematically examine the changes in cardiac function in the immediate postoperative period.

As for human data on cardiac function after ligation, the information is equally scarce. To the best of our knowl-
edge, only 2 studies have specifically addressed this issue in preterm infants. Lindner et al. assessed cardiac function by measuring LV output, stroke volume, and heart rate 2 days after PDA ligation and compared the findings with preligation measurements. Similar to our observations, they found a significant decrease in LV output and stroke volume without a significant change in heart rate. In contrast, Kimball et al. found an increase in systemic vascular resistance and heart rate and no changes in the load-independent measures of myocardial contractility, LV output, or afterload. Interestingly, although the decrease in LV output did not reach statistical significance, the magnitude of the decrease was similar to what we found. The lack of a statistically significant decrease in LV output may be related to the small number of patients enrolled in the study.

Changes in RV output after PDA ligation have not been reported. We found no difference in RV output after PDA ligation. In addition, we found a higher RV output compared with LV output throughout our study. This finding may be explained by the observation that all of our patients had a left-to-right or a predominantly left-to-right shunt at the level of the foramen ovale. Indeed, in the presence of a patent foramen ovale, others have also found a greater RV than LV output even with concomitant ductal shunting.

During the first 24 hours after ligation, 35% of our patients required at least a 25% increase in the dose of dopamine to maintain BP in the normal range. Indeed, an increased vasopressor requirements after PDA ligation has been reported in approximately 1/3 of patients who have undergone surgical PDA ligation. Among the various cardiac function indices evaluated in our patients (including the MPI), none was found to predict an increase in the need for vasopressor support. Although this could be due to the small sample size, it is also conceivable that the increased dopamine requirement might have resulted from postoperative changes in vascular tone rather than cardiac function. Down-regulation of cardiovascular adrenergic receptors, relative adrenal insufficiency, and anesthesia could be associated with alterations in vasomotor tone, necessitating escalation of vasopressor support to maintain BP in critically ill preterm neonates undergoing surgery.

In addition to the limitations inherent to the use of functional echocardiography in the preterm neonate, another important limitation of our study is the lack of a control group. Therefore, although echocardiograms were performed before and after PDA ligation and each patient served as his or her own control, we could not control for the effects of anesthesia or the stress of surgery. There was some individual variation in the administered dopamine dose for each patient over the course of the first postoperative day. This variation might have contributed to some of the changes in the cardiac function measurements. However, for the study group as a whole, there was no significant difference in mean dopamine dose at the time of each echocardiogram.

The acute decrease in LV output documented after PDA ligation might result from both a reduction in LV preload and the deterioration of global cardiac function immediately after surgery. As the myocardium then resets to the new loading conditions, its performance improves, as documented in our study. It is unclear whether the postligation increase in vasopressor support is required due to abnormal peripheral vasoregulation, a subtle decrease in global cardiac function, or a combination of these 2 factors.

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50 Years Ago in The Journal of Pediatrics

SUICIDE IN CHILDREN AND ADOLESCENTS

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Bakwin sought to raise awareness about adolescent suicide, the relative importance of which “has increased as other causes of death, notably the infections, have diminished.” Suicide was the fifth most frequent cause of death in young adults in the United States (US) in 1957; it is now the third most common cause of death in youth ages 10 to 24 years. 50 years ago suicide accounted for 2.5% of all deaths in youth 15 to 19 years old; in 2004, it accounted for 11.7% of all deaths in those 10 to 24 years old. Then, as now, the most common method of suicide in adolescents was through firearms, although in the US during the past decade, suffocation has become the most common method in adolescents 10 to 14 years old.

During the past few decades, the suicide rate has generally increased in adolescents. A half-century ago, suicide rates varied considerably across nations, ranging from 0.6 of every 100,000 male adolescents in Ireland to 26.1 of every 100,000 male adolescents in Japan. The wide range (and male preponderance) in rates of countries still exists, but the range is higher (from 2-44 per 100,000); the greatest rates are now found in Europe. However, in the US, there has been a decline in suicide rates, falling from 6.2 to 4.6 per 100,000 population in youth ages 10 to 19 years between 1991 and 2002.

The most notable difference in suicide today compared with that 50 years ago is the enormous attention focused on the problem and the availability of preventive measures. Only 2 small paragraphs were needed to describe prevention options available at that time; hospitalization after a suicide attempt appeared to be helpful, and there was consideration of creating a society similar to Alcoholics Anonymous. Since then, hundreds of prevention programs have been developed and evaluated, with some evidence that school-based suicide prevention programs based on behavioral change and coping, those based on skill training and social support, or both can be effective. A wide range of medical and non-medical therapies have been developed, some of which have been demonstrated to be effective in specific conditions. The observational relationship between depression and subsequent suicide attempts (in 1957 and now) led to the widespread interest in identifying and treating youth who are depressed. However, the possibility of an adverse effect of some anti-depressants illustrates the complexity of the disorders that result in the final common pathway of suicide.

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