Left Ventricular Contractile State of Early Human Neonates with Patent Ductus Arteriosus

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During the transition from fetal to neonatal circulation, the left-to-right ductus arteriosus shunting acts as a preload to the left ventricle (LV). In animal research on newborn lambs, some investigators demonstrated the less capacity of LV response to an increased preload (Klopfenstein and Rudolph 1978; Romero and Friedman 1979; Baylen et al. 1985), whereas, others demonstrated the capa-
bility of LV to handle the increased volume load through the ductus arteriosus shunting (Baylen et al. 1986; Clyman et al. 1987). In human neonates, the LV contractile state during a patency of the ductus arteriosus has not been fully evaluated.

Although the ejection fraction and fractional shortening are commonly used to estimate LV systolic function, these load-dependent indices are unreliable in the unstable loading condition shortly after birth. We investigated the neonatal LV systolic function using the relationship between the heart rate-corrected velocity of circumferential fiber shortening (mVcfc) and the end-systolic meridional wall stress (ESS). This index, first described by Colan et al. (1984), has been used clinically for ill neonates as a sensitive and relatively load-independent index (Karr et al. 1991; Kimball et al. 1991). The purpose of this study was to estimate the changes of LV afterload and to investigate the LV contractile state of early human neonates with PDA adapting the relationship between mVcfc and ESS.

**METHODS**

Informed consent was obtained from the parents of each neonate.

**Cases.** We studied 32 full-term infants (19 male, 13 female). All cases had a history of normal pregnancy, labor, and delivery, and had normal physical findings and no symptoms or signs of cardiovascular diseases. They were confirmed to have no congenital heart disease and no severe distortion of LV shape by 2-dimensional echocardiography. The first echocardiographic examination was performed within 24 hr after birth, and the second was performed on day 5, which was served as a control. The former were divided into 2 groups based on the timing of the examinations; group 1 (n = 17), < 3 hr after birth; group 2 (n = 15), > 3 and < 24 hr after birth. These groupings were made in order to investigate the LV response to the changes of preload more precisely. There were no significant differences between groups in birth weight and its change after birth. These characteristics of each group are summarized in Table 1.

**Echocardiography.** Echocardiography was performed utilizing various methods; M-mode, two-dimensional, pulsed Doppler, and two-dimensional Doppler echocardiography. An Aloka SSD-870 ultrasound imaging system equipped with a 5.0 MHz transducer was used. All the neonates were in a non-sedated resting state during examinations. Patency of the ductus arteriosus was checked in each case by the two-dimensional and pulsed Doppler echocardiography. When it was open, the inner diameter of the ductal lumen was

| Table 1. Patient characteristics |
|-------------------------------|-----------------|-----------------|-----------------|
|                               | Group 1         | Group 2         | Control         |
|                               | <3 hr           | >3, <24 hr      | >91, <192 hr    |
| n                             | 17              | 15              | 32              |
| Timing of examination (hr)    | 1.8             | 13.0            | 135             |
| Body weight at birth (g)      | 3111            | 3176            | 3142            |
| day 5 (g)                     | 3054            | 3099            | 3074            |

Data are expressed as mean.
The M-mode echocardiograms were recorded at a paper speed of 100 mm/sec. Phonocardiograms, electrocardiograms, and axillary pulse tracings were recorded simultaneously, and peak systolic and diastolic blood pressures were obtained by a Dinamap 8100 Vital Sign Monitor (Criticon, Inc., Tampa, FL, USA). The M-mode measurements were performed according to the recommendations of the American Society of Echocardiography (Sahn et al. 1978), and the following variables were obtained: LV end-diastolic diameter, LV end-systolic diameter, posterior wall thickness at end-systole, left atrial diameter, aortic root diameter, and heart rate. End-systole was defined as the point of the first component of the second heart sound. Left ventricular ejection time was derived from the pulse trace and was rate-corrected by dividing by the square root of the R-R interval. The end-systolic pressure was measured by assigning the systolic blood pressure to the peak and the diastolic pressure to the nadir of the trace with a subsequent linear interpolation to the level of the dicrotic notch (Borow and Newburger 1982). From these data, we calculated mVcfc and ESS by the method of Grossman et al. (1975) and obtained the left atrial to aortic ratio.

All the echocardiographic measurements were performed by two (Y.T, K.H) of the authors who were unaware of patient status, and the averaged data of 3-5 cardiac cycles were used for analysis.

Statistical analysis. Interobserver and intraobserver variabilities were assessed for all the parameters measuring 5 cardiac cycles in 5 subjects. The coefficients of variation for inter- and intraobserver variability were 0.3–7.6% and 0.2–6.1%, respectively. We confirmed the normality of the distribution of each parameter. For comparison of the data, an unpaired t-test was performed, and a p-value of 0.05 or less was considered statistically significant. A simple linear regression test was used to determine the significance of the correlation between mVcfc and ESS in each group, and an analysis of covariance was used to determine significance of the distribution difference between the 2 groups and the control.

RESULTS

Echocardiographic data and changes of HR and BP. The data are summarized in Table 2. There were no significant differences between the 2 group and the control in the LV end-diastolic diameter, end-systolic diameter, posterior wall thickness, or heart rate. The left atrial to aortic root ratio was highest in group 1, and significantly decreased in group 2. The systolic blood pressure, diastolic blood pressure, and end-systolic pressure were significantly lower in both groups than in the control. Additionally, ESS was significantly lower in group 1 than in the control. No significant change was found in mVcfc.

The relationship between mVcfc and ESS. The relationships are shown in Fig 1. The top figure presents the data of both groups 1 and 2 with 95% confidence interval of the control. The 15 cases of group 1 (88%) and 11 cases of group 2 (73%) were within the control range. No significant difference was found in the distribution between the 2 groups and the control by the analysis of covariance. The bottom figure presents the regression lines of the two groups and the control. There were inverse linear correlations between mVcfc and ESS: group 1, mVcfc = −0.007 (ESS) + 1.29, correlation coefficient (r) = 0.55; group 2, mVcfc = −0.009 (ESS) + 1.37, r = 0.41; control, mVcfc = −0.006 (ESS) + 1.35, r = 0.56. There were no significant differences in the slopes of the regression lines or the Y-intercepts between either group and the control.
Ductus arteriosus. The ductus arteriosus was open in all cases in group 1. It was still open in 83% of the cases of group 2, but the inner diameter of the ductus arteriosus was significantly decreased in group 2 (Table 2). The ductus arteriosus was closed in all cases of the control.

**Discussion**

This study has demonstrated that the LV afterload shortly after birth is significantly lower than that on day 5, and that the neonatal LV successfully adapts to the increased preload due to the left-to-right ductus arteriosus shunting.

Similar to the other Doppler studies (Drayton and Skidmore 1987; Agata et al. 1991), we previously demonstrated that the left-to-right ductal shunt increased at 2 hr of age and decreased rapidly by 12 hr of age (Harada et al. 1994). In the present study, the left atrial to aortic root ratio and the inner diameter of the ductus arteriosus significantly increased in group 1 (mean age = 1.8 hr after birth) compared with group 2 (mean age = 13.0 hr after birth), thus the LV preload was suggested to be higher in group 1 than group 2. Several recent studies have shown that LV of human neonates have the ability to handle these increased preload imposed by PDA (Winberg et al. 1989; Agata et al. 1991), but the mechanism has not been clearly elucidated.
As to the relationship between mVcfc and ESS, there was no significant difference between the 2 groups and the control in the slopes of the regression lines (Fig. 1), which indicated that the sensitivity to afterload did not change before or after the closure of the ductus arteriosus. In addition, our data indicated that the afterload, represented as ESS, was significantly lower within 3 hr after birth than on day 5, the control. We suggest that the neonatal LV is capable of generating adequate contraction under the lower afterload condition during the patency of the ductus arteriosus. Clyman et al. (1987) hypothesized that an associated reduction in the LV afterload played a significant role in the increase of stroke volume in newborn lambs with a patent ductus arteriosus after birth, and our present results seems to support his hypothesis. Blood pressure is thought to be lowest at birth and increase gradually by the first 2 weeks of life (Kitterman et al. 1969; Earley et al. 1980), and these findings are consistent with our result. Thus, we suggest that the low blood pressure and low end-systolic pressure result in the lower afterload during the transitional period from fetal to neonatal circulation.
It is also interesting to speculate on the mechanisms supporting the LV contraction during the transition from fetal to neonatal circulation. One mechanism can be attributable to the presence of neuroendocrines, especially catecholamines which increase markedly in the circulation at birth (Eliot et al. 1980; Padbury et al. 1981, 1985), along with the supersensitivity of newborn myocardium to circulating catecholamines (Friedman 1972). In addition, we suggest that the low afterload condition may be one mechanism supporting the LV adaptation to various loading changes shortly after birth. We conclude that the low afterload plays an important role for LV adaptation under the high preload condition due to the left-to-right ductus arteriosus shunting in early human neonates. We consider this study provides basic data concerning the left ventricular contractile state during the transition from fetal to neonatal circulation.

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References


