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Relationship between Heart Rate, Left Ventricular Output, and Stroke Volume in Preterm Infants during Fluctuations in Heart Rate

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ABSTRACT. The relationship between changes in heart rate, left ventricular output, and left ventricular stroke volume was studied in 18 preterm infants, with mean gestational age 29 wk (range 26–33 wk) and mean postnatal age 10 d (range 1–21 d). To yield left ventricular output, the blood flow velocity in the ascending aorta was measured by range-gated Doppler technique and multiplied by the aortic cross-sectional area measured by cross-sectional and M-mode echocardiography. Stroke volume was calculated by dividing left ventricular output by heart rate. The individual mean left ventricular output correlated poorly with heart rate ($r^2 = 0.17$), and, accordingly, there was a closer relationship between stroke volume and left ventricular output. In only four of the 18 infants was a significant correlation between heart rate changes and left ventricular output found. Substantial changes in stroke volume were seen in most infants, and in 13 of the 18 infants the changes exceeded 25%. These variations in stroke volume were closely related to left ventricular output. In 15 of the 18 infants, the maximum heart rate change was associated with a stroke volume change in the opposite direction. The group average of the maximum heart rate increase in each individual, 24 bpm (18%), corresponded to a decrease in stroke volume of 0.15 $mL \cdot kg^{-1}$ (9%) ($p < 0.05$) and an increase in left ventricular output of 22.7 $mL \cdot min^{-1} \cdot kg^{-1}$ (9%) ($p < 0.05$). A reciprocal relationship was seen between afterload and left ventricular output. The findings indicate that the preterm infant has a substantial ability to alter stroke volume and that stroke volume is an important determinant of neonatal left ventricular output. During beat-to-beat fluctuations in heart rate, the stroke volume changes appear to reduce the effect of the heart rate changes on output. (*Pediatr Res* 31: 117–120, 1992)

Abbreviations

HR, heart rate
LVO, left ventricular output
SV, stroke volume
SVR, systemic vascular resistance
BP, blood pressure
PDA, patent ductus arteriosus

Studies of the fetal and neonatal heart have provided basic information about the myocardial immaturity on the cellular and subcellular levels. The immature myocardium has been shown to contain more water, less contractile elements per unit weight, and less sarcoplasmic reticulum (1, 2). Furthermore, the cardiac sympathetic innervation is not fully developed at birth (3, 4). In *in vitro* experiments these differences correspond to reduced compliance and reduced contractile force (1) compared with the mature myocardium. However, the hemodynamic consequences of the myocardial immaturity on the intact circulatory system are, despite extensive investigations, still not clearly delineated. It has been claimed that the fetal heart performs at or near its peak capacity even during normal conditions and has a very limited ability to change (SV) (5, 6). Accordingly, fetal and neonatal cardiac output should be almost entirely dependent on HR. This, however, has been questioned in other fetal and neonatal lamb studies (7–10), as well as in human fetal and neonatal studies (11–14). In an earlier study using the ultrasound Doppler technique, we found that changes in LVO during the postnatal circulatory transition in healthy term infants seemed to be mainly effected by changes in SV and not HR (14). The same relationship between LVO, SV, and HR has recently been reported for the preterm infant undergoing ligation of the ductus arteriosus (13). The aim of this study was to investigate this relationship during short time fluctuations in HR.

MATERIALS AND METHODS

Eighteen preterm infants with gestational age less than 34 wk were studied. Infants with asphyxia, malformations, or septicemia were not included. The infants were nursed in closed incubators, and their fluid intake was 120 mL/kg/24 h. At the time of the study, all infants had normal blood gases and no drugs, except minerals and vitamins, were used.

LVO was measured using the ultrasound Doppler technique first described in infants by Alverson *et al.* (15). The blood flow velocity in the ascending aorta was measured using a range-gated Doppler velocimeter (ALFRED, Vingmed A/S, Oslo, Norway). A 5-MHz transducer, with an 8-mm diameter tip, was positioned in the suprasternal notch and directed toward the ascending aorta. The echoes from the aortic valve were identified, and the sample volume, with a length of about 4 mm, was located 5–10 mm above the valves. By making small changes in the probe angle, the investigator searched for the highest velocity. A 400-Hz high-pass filter was used to reduce noise from vessel wall motions. The space average velocity (the average velocity over the cross-section of the aorta) and the mean flow velocity (the temporal mean of the space average velocity) signals were recorded on an oscillograph (Mingograph, Siemens Elema, Stockholm, Sweden). The Doppler recordings were continued for 20–30 min in each infant to allow for HR changes. The portions of the tracings with low quality, mostly caused by noise and artifacts

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from infant movement, were rejected. The portions of high quality were selected for analysis, and, in these parts, the mean flow velocity was calculated using the internal calibration signal of the instrument. The simultaneous HR was calculated over five heart beats from the space average velocity curve.

Cross-sectional and M-mode echocardiography was used to determine the end-systolic internal diameter of the ascending aorta 5 mm above the aortic valve. The calculated aortic cross-sectional area was multiplied by the mean flow velocity and divided by body weight to give LVO in $mL \cdot min^{-1} \cdot kg^{-1}$. SV was calculated by dividing LVO by HR. Arterial BP was measured in the right upper arm using the oscillometric technique (Omega 1400, In vivo Research Lab, Inc., Broken Arrow, OK). The mean value of three BP measurements was used. SVR was calculated by dividing mean BP by LVO.

Of all determinations of LVO, SV, and HR in each infant, a selection was made to obtain one LVO and SV value for every HR. When there were several LVO determinations for a given HR, the highest LVO was chosen. Thus, five to 14 HR, LVO, and SV determinations in each infant were obtained. The number of determinations in each infant depended on how much the HR fluctuated.

Color Doppler echocardiography was also used to assess ductal shunting. Based on disturbances of flow in the pulmonary artery, left atrial size, and presence of reversed diastolic flow in the descending aorta, the infants were classified as having *1)* no or minimal ductal shunt (no ductal flow detected or color flow mapping showing only minimal flow disturbance in the pulmonary artery close to the ductus); *2)* moderate shunt (flow disturbance in a larger part of the pulmonary artery; left atrium to aortic ratio < 1.25 and no diastolic reversal of flow in the descending aorta); or *3)* large shunt (left atrium to aortic ratio > 1.25; diastolic reversal of flow in the descending aorta).

The study was approved by the local committee of ethics, and informed consent from the parents was obtained before the investigation.

The statistical evaluation was made by the Mann-Whitney two-sample test, *t* test, and linear regression. Linear regression, however, was only used to analyze the relationship between HR and LVO, because these were the only variables that were measured independently of each other. SV was directly derived from LVO, and regression may accordingly not be used to analyze the LVO-SV relationship.

RESULTS

The clinical data for the study group are shown in Table 1. The group mean LVO was 257 $mL \cdot min^{-1} \cdot kg^{-1}$ (range 125–496 $mL \cdot min^{-1} \cdot kg^{-1}$). No infant had echocardiographic signs of a large ductus shunt, and none was considered for surgical or pharmacologic closure of the ductus. Four infants had a moderate ductus shunt and showed a higher LVO (388 $mL \cdot min^{-1} \cdot kg^{-1}$) than those without ductus shunt (216 $mL \cdot min^{-1} \cdot kg^{-1}$) ($p < 0.01$). This was mostly related to higher SV in infants with a moderate ductus shunt than in those without ductus shunt (2.51 and 1.57 $mL \cdot kg^{-1}$, respectively) ($p < 0.01$), but was also related to higher HR (156 and 139 bpm, respectively) ($p < 0.05$).

Table 1. *Clinical data in 18 preterm infants**

	Mean	Range	*n*
Gestational age (wk)	29.6	(26–33)	
Birth weight (g)	1363	(696–2200)	
Age at study (d)	10.3	(1–21)	
Weight at study (g)	1317	(675–2154)	
BPm (mm Hg)	46	(36–61)	
5-min Apgar score	8.6	(7–10)	
Hematocrit	55	(41–64)	
Moderate PDA			4
Ventilator			3
CPAP			4

* BPm, mean arterial pressure; CPAP, continuous positive airway pressure.

A poor correlation was found between mean HR and mean LVO for each infant ($r^2 = 0.17$) (Fig. 1). Accordingly, a stronger association was found between mean SV and mean LVO (Fig. 2).

The range of fluctuation in HR varied markedly among the infants. In 14 of 18 infants, the HR changes were larger than 14%. A significant HR-LVO correlation was seen in only four of 18 infants. Substantial SV changes were seen in most infants, and in 13 of 18 these changes exceeded 25%. These variations in SV were closely related to LVO changes (Fig. 3). Although a direct relationship between changes in HR and changes in LVO was found, this was obvious for single observations only with larger HR changes (Fig. 4). Small LVO changes however, might not be discerned by the method, and to overcome this problem the recordings in each infant with the maximum and the minimum HR were selected and the group data were analyzed. The individual maximum HR change ranged from 9 bpm (7%) to 84 bpm (127%). The maximum HR change was inversely related to the SV change in 15 of 18 infants and directly related to the

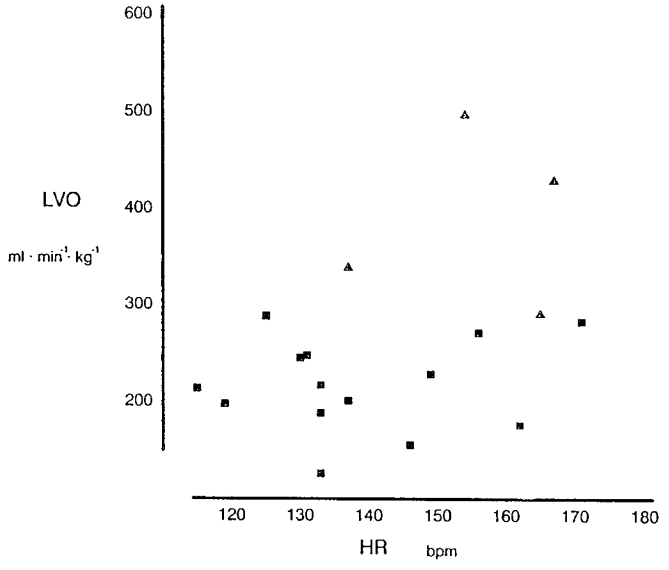

Fig. 1. Mean HR and mean LVO in 18 preterm infants with (▲) and without (■) PDA.

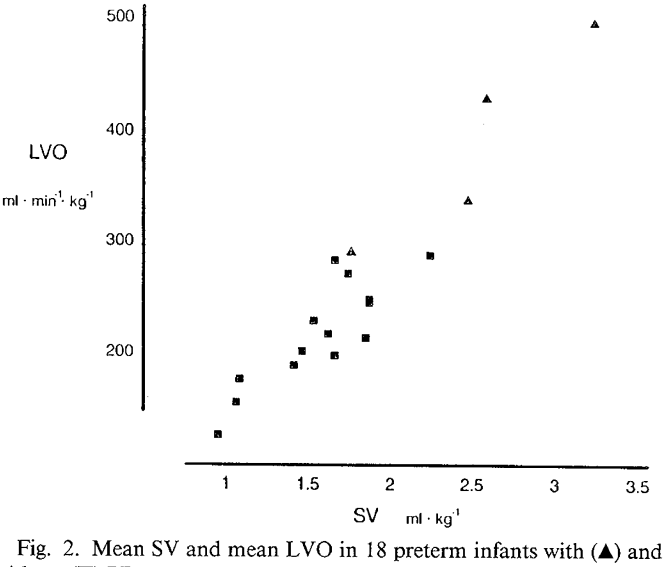

Fig. 2. Mean SV and mean LVO in 18 preterm infants with (▲) and without (■) PDA.

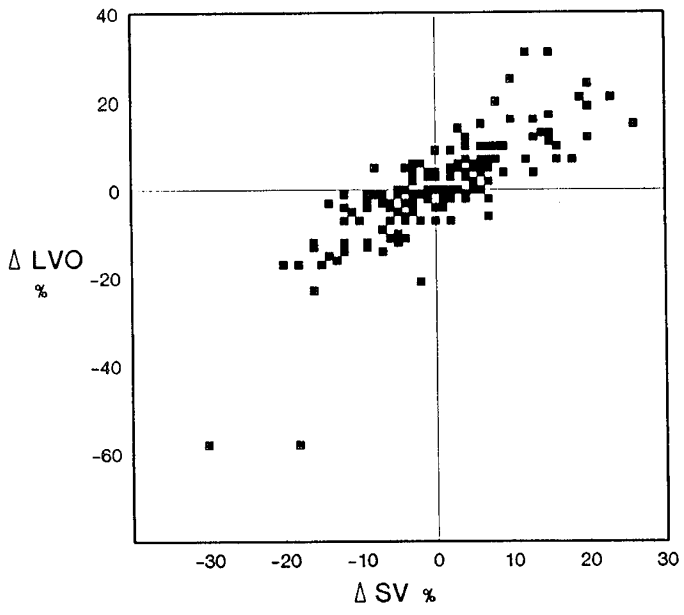

Fig. 3. Plot of the relative changes from the mean in SV and LVO in 18 preterm infants.

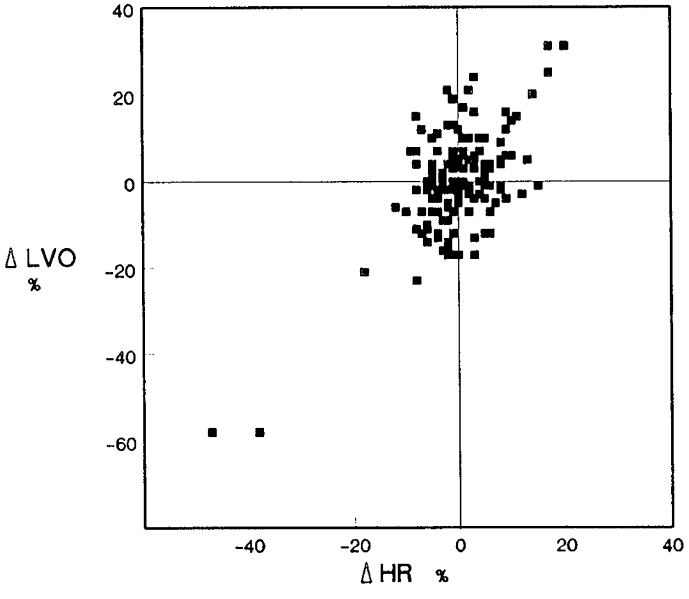

Fig. 4. Plot of the relative changes from the mean in HR and LVO in 18 preterm infants.

LVO change in 12 of 18 infants. The group average of the maximum HR increase, 24 bpm (18%), corresponded to an increase in LVO of 22.7 $mL \cdot min^{-1} \cdot kg^{-1}$ (9%) ($p < 0.05$) and a decrease in SV of 0.15 $mL \cdot kg^{-1}$ (9%) ($p < 0.05$). A reciprocal SVR-LVO relationship was found (Fig. 5). SVR was lower in infants with PDA ($p < 0.01$). Mean BP was 41.0 mm Hg in infants with PDA and 47.5 mm Hg in infants without PDA (NS).

DISCUSSION

The ultrasound Doppler technique for measurement of LVO is especially useful in neonates because it is strictly noninvasive and inflicts a minimum of stress on the infants. It also allows measurements of beat-to-beat changes. The method has been validated in several studies in newborn infants, and a good correlation with other techniques has been demonstrated (15–17). A good reproducibility has also been shown for the method (17–19). Slightly different methods for the velocity and the

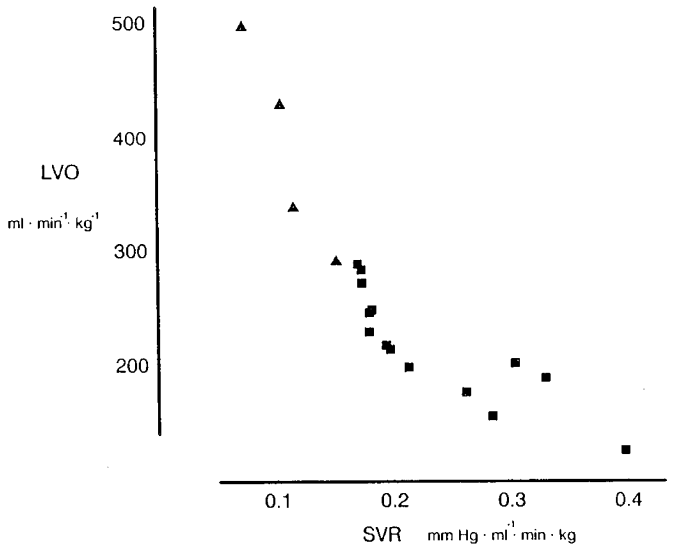

Fig. 5. Mean SVR and LVO in 18 preterm infants with (▲) and without (■) PDA.

diameter measurements have been used. The product of the cross-sectional mean flow aortic velocity and the cross-sectional area derived from the inner aortic diameter should yield the most accurate measure of output (17). In the present study, a variation coefficient of 8% was estimated using the multiple aortic blood flow velocity determinations at the same HR in each infant. In the ultrasound Doppler technique, as in most other techniques for LVO measurements, SV is calculated directly from LVO. Thus, an over- or underestimation of LVO directly affects SV in the same direction, and the relationship between LVO and SV might accordingly be overemphasized. The close association between SV and LVO changes shown in Figure 3 must accordingly be interpreted with caution. A considerable number of the observations, however, show changes too large to be explained by methodologic errors only, and SV does seem to be of importance to LVO changes.

The group mean LVO, in both the infants with PDA (388 $mL \cdot min^{-1} \cdot kg^{-1}$) and those without PDA (216 $mL \cdot min^{-1} \cdot kg^{-1}$), are in good agreement with previous reports in preterm infants (13, 20, 21).

Reactions from the manipulation of the transducer in the suprasternal notch probably accounted for most of the HR changes. However, HR changes that were not clearly related to the interference of the transducer were also seen.

The absence of a detectable effect on LVO by smaller HR changes might suggest that SV changes compensated for the HR change and that LVO does not change until this compensatory ability is exceeded. However, the methodologic error in the LVO determination might obscure effects of smaller HR changes. To overcome this, the effect of the maximum HR change was investigated and the grouped data was analyzed. Statistically significant relationships were found. The SV changes related inversely to the HR changes, thus diminishing the effect of HR on LVO. Thus, under otherwise stable conditions, it appears that the beat-to-beat fluctuations in HR are counterbalanced by changes in SV. The finding that both SV and HR are higher in the infants with PDA suggests that when volume demand is increased, there are parallel changes in HR and SV to accomplish an elevated LVO.

In a few cases, HR and SV changed in the same direction, *e.g.* in the infant with the most marked bradycardia the decrease in HR to 66 bpm (56%) was accompanied by a 27% decrease in SV, leading to a 68% decrease in LVO. Possibly the same stimulus that caused the more substantial change in HR also affected other factors that may directly influence SV, such as afterload, diastolic filling, or myocardial contractility. For ex-

ample, a vagal response includes bradycardia, increased vascular resistance, and decreased contractility (22) and is a possible explanation for the considerable decrease in both HR and SV.

Conflicting results have been obtained regarding the relationship between HR, SV, and output in the immature heart. Rudolph and Heymann (6) found a direct relationship between HR and LVO, with very small changes in SV, whereas Kirkpatrick *et al.* (7) showed that LVO was constant over a wide range of HR, indicating a substantial ability of the immature heart to change SV. Both studies were performed in chronically instrumented fetal lambs. In a later study, Anderson *et al.* (8) reevaluated this issue and found no simple relationship between HR, SV, and LVO. Instead, HR interacted in a complex fashion with ventricular filling and contractility to modulate output. Atrial pacing showed no effect or negative effect on output. Spontaneous HR changes were mostly directly related to LVO and inversely related to SV, although in several cases HR and SV changes in the same direction. Thus, their results seem to be in agreement with those in the present study.

The vascular resistance calculated from mean BP and LVO will not only measure the resistance in the systemic circulation, but also reflect the resistance in the ductus and the pulmonary vascular bed if the ductus remains open. It is, accordingly, a measure of the total afterload resistance seen by the left ventricle, which probably explains the low SVR values in the infants with PDA. These infants are also likely to have an increased diastolic filling, which in combination with the low SVR contributes to an enhanced left ventricular performance and a further increased SV and LVO.

The reciprocal SVR-LVO relationship (Fig. 5), agrees well with most earlier studies, where fetal and neonatal LVO have been found to be sensitive to afterload changes (23, 24). In contrast, Baylen *et al.* (25) found no changes in LVO and SV in response to an acutely increased afterload in preterm sheep. Their study, however, was performed in the first hours after birth during the maximal catecholamine surge, which might have increased the contractile reserve.

This study does not support the view that SV is constant in the neonatal period and that LVO is almost totally dependent on HR. In contrast, the study indicates that the preterm infant has a substantial ability to alter SV. These SV changes are mostly inversely related to the beat-to-beat fluctuation in HR and appear to modulate the effect of HR on LVO. Thus, SV seems to be an important determinant of neonatal LVO.

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