Enhanced systolic function of the right ventricle during respiratory distress syndrome in newborn lambs

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WITH THE GROWING KNOWLEDGE of neonatal care, the number of premature and extremely premature infants has expanded enormously in the past decade. Premature infants born before 32 wk of gestational age are often incapable of producing sufficient amounts of surfactant, a surface tension-lowering substance in the alveolar epithelium. Despite substantial medical developments, this surfactant deficiency causing respiratory distress syndrome (RDS) is often fatal for the premature infant. Besides ventilatory problems, RDS induces pulmonary hypertension with a raised afterload for the right ventricle (RV). It has been suggested that this increased afterload might lead to cardiac dysfunction. Matthay and Berger (19) demonstrated RV dysfunction in patients with chronic obstructive pulmonary diseases. Abnormal elevations of RV end-systolic pressure and mean pulmonary arterial pressure (Ppa) were noted in these patients during exercise, to which the RV responded with a decreased cardiac output (CO). Sibbald et al. (26) examined RV function in patients with pulmonary hypertension and found a negative correlation between CO and Ppa. In a previous study, we investigated the effects of an increased RV afterload induced by partial balloon occlusion of the pulmonary artery in newborn lambs (7). The results of this study demonstrated that in the newborn heart the RV is able to maintain CO by improving its systolic function. However, the clinical picture of pulmonary hypertension, as seen in RDS, is much more complex than this simplified pure hemodynamic model of increased afterload. Furthermore, the effects of an increased RV afterload on cardiac performance have not been investigated for the left ventricle (LV) and RV simultaneously.

Therefore, the purpose of the present study was to determine how the newborn heart responds to pulmonary hypertension in an experimental model of RDS. With the use of combined pressure-conductance catheters, RV and LV function were measured simultaneously in 12 newborn lambs by end-systolic pressure-volume (P-V) relations (ESPVR). RDS was induced by lung lavages in seven lambs, while five other lambs served as controls. Cardiac function was quantified by indexes derived from end-systolic pressure-volume relations obtained by pressure-conductance catheters. After lung lavages, a twofold increase of mean pulmonary arterial pressure (from 15 to 34 mmHg) was obtained and lasted for the full 4-h study period. Stroke volume was maintained (5.2 ± 0.6 ml at baseline and 6.1 ± 1.4 ml at 4 h of RDS), while RV end-diastolic volume showed only a slight increase (from 6.5 ± 2.3 ml at baseline to 7.7 ± 1.3 ml at 4 h RDS). RV systolic function improved significantly, as indicated by a leftward shift and increased slope of the end-systolic pressure-volume relation. Left ventricular systolic function showed no changes. In control animals, pulmonary arterial pressure did not increase and right and left ventricular systolic function remained unaffected. In the face of increased RV afterload, the newborn heart is able to maintain cardiac output, primarily by improving systolic RV function through homeometric autoregulation.

MATERIALS AND METHODS

The surgical and experimental procedures were reviewed and approved by the Animal Research Committee of the
Leiden University Medical Center. The investigations conformed to the Guide for the Care and Use of Laboratory Animals [DHHS Publ. No. (NIH) 85-23, Revised 1986, Office of Science and Health Reports, Bethesda, MD 20892].

Animal preparation. Twelve newborn lambs (7 RDS and 5 control), 8.6 ± 1.2 days of age and 4.6 ± 1.0 kg body wt, were studied. Between the two groups there were no statistical differences in age or weight. After premedication with ketamine hydrochloride (1–3 mg/kg body wt iv), general anesthesia was maintained using a continuous infusion of ketamine hydrochloride (8–30 mg·kg⁻¹·h⁻¹ iv) supplemented with xylazine (3 mg/kg im). In addition, local anesthesia was applied with 1% lidocaine hydrochloride injected subcutaneously. During the study, the wounds were sprayed with lidocaine at regular intervals. The lambs were intubated and ventilated with an oxygen-air mixture with the use of a pressure-controlled ventilator (Babylog 8000, Dräger, Lübeck, Germany). Ventilation was adjusted to maintain PO₂ and PCO₂ within normal ranges throughout the study. On ventilation, pancuronium (0.2 mg/kg) was administered to achieve adequate muscle relaxation. An intravenous infusion of 5% dextrose in 0.5 N NaCl solution (15–20 ml·kg⁻¹·h⁻¹) was continued throughout the study, occasionally supplemented with NaHCO₃ as needed to maintain a normal base deficit (≤5 mmol/l).

Instrumentation. To facilitate the insertion of catheters, 6-Fr sheaths were placed in the right and left femoral vein, right and left femoral artery, right jugular vein, and right carotid artery. To measure biventricular pressures and volumes, two 5-Fr combined pressure-conductance catheters with 5-mm spacing, 10 electrodes each (Millar Instruments, Houston, TX), were introduced through the right jugular vein and through the left femoral artery into the right (RV) and left (LV), respectively. The conductance catheters were connected to Leycom Sigma-5 signal-conditioner processors with different carrier frequencies (21 and 16 kHz, respectively; CD Leycom, Zoetermeer, The Netherlands) to measure instantaneous ventricular volume signals. A 5-Fr thermodilution catheter (Ohmeda, Madison, WI) was placed in the pulmonary artery through the right femoral vein to measure CO. This catheter was also used to measure PAw through the distal opening in the pulmonary artery, and the proximal lumen was used for hypertonic saline injections in the inferior vena cava to determine RV and LV parallel conductances (see Conductance catheter).

To assess P-V relations during venacaval occlusion, a 5-Fr, 2-ml latex balloon catheter (Fogarty true-lumen, Baxter Healthcare, Irvine, CA) was placed through the left femoral vein in the inferior vena cava (see Measurements). All catheters were positioned under fluoroscopic guidance. Figure 1 shows a chest X-ray of one of the animals after completion of the instrumentation to illustrate how the catheters were positioned. Aortic pressure was measured from the fluid-filled side port of the sheath through the carotid artery in the aortic arch. Blood samples for measurement of arterial blood gases and pH were drawn from the sheath in the right femoral artery.

Study protocol. To determine the effects of RDS on the systolic function of both ventricles, we examined hemodynamics and systolic function in an experimental model of RDS (7 newborn lambs) and in a group of control animals (5 newborn lambs). After completion of the instrumentation, a 15-min period was allowed for the lambs to obtain hemodynamic stability. When hemodynamic stability was reached, baseline measurements were performed in all lambs. Subsequently, RDS was induced in seven animals by 9–11 lung lavages with 50–60 ml/kg warm saline over a 30- to 45-min period to wash out the surfactant (11). After every lavage, the lambs were reconnected to the ventilator for 3–5 min to recover from breath holding during the lavage. After the last lavage, a 15-min period was allowed for hemodynamic stabilization and adjustment of ventilatory settings. After 15 min of stabilization, the onset of RDS was defined as “start RDS.” Measurements were performed at start RDS and at 15 min, 30 min, 1 h, 2 h, 3 h, and 4 h of RDS. At each time point, a set of measurements was performed to calibrate the conductance catheter method and to assess hemodynamics and systolic function. This measurement set consisted of assessing blood resistivity, injecting 0.6 ml of 10% NaCl intravenously to measure RV and LV parallel conductances, measuring CO with the thermodilution method, and acquiring P-V loops during venacaval occlusion. Calibration assessments were repeated twice to three times at every time point and averaged for calculation of absolute volume. Vena caval occlusion and saline injections were performed at end expiration with the ventilator turned off. From the measurements the following variables were determined: systolic function, quantified by the slope and horizontal intercept of the ESPVR, the slope and vertical intercept of the preload recruitable stroke work (PRSW) (13), stroke volume (SV), end-diastolic volume (VED), and end-diastolic pressure (PED). In addition, standard hemodynamic variables were determined: heart rate (HR), CO, mean aortic pressure (PAM), PAP, central venous pressure (CVP), and arterial blood gases (PACO₂ and PACO₃) and pH. Ventilatory settings such as oxygen fraction (FIO₂), positive inspiratory pressure (PIP), and positive end-expiratory pressure (PEEP) were also registered with every measurement.

Conductance catheter. The application of the conductance catheter for measuring ventricular volume has been described and validated extensively for the LV (2, 3). More recently, the same method has been shown to be applicable for measuring RV volume as well (1, 7, 10, 28, 29). Briefly, electrical conductance was measured in both ventricles, and to obtain absolute volume, the conductance signals [G(t)] were converted to volume signals [V(t)] as follows: V(t) = (1/α)·[L²·G(t) − Vc], where α is a dimensionless slope.
factor, $L$ is the distance between the sensing electrodes, $ρ$ is the resistivity of the blood, and $V_e$ is the correction volume to account for the conductance of surrounding tissue (commonly referred to as parallel conductance volume). Parallel conductances for the RV and LV were determined from the same intravenous hypertonic saline injections by separately analyzing the signals during the passage of the hypertonic saline bolus through the RV and subsequently the LV (3). The slope factors $α$ for both ventricles were assessed by comparing the uncalibrated conductance catheter CO values of the RV and LV, respectively, with CO values obtained by the thermodilution method.

**Measurements.** To obtain P-V relations of RV and LV, pressure and volume signals were recorded during transient occlusion of the inferior vena cava to reduce inflow to the heart. For each beat during this vena cava occlusion, end systole was defined as the point in the cardiac cycle of maximal elastance. Elastance is defined as $P(t)/V(t)$, where $P(t)$ is the instantaneous ventricular pressure, $V(t)$ is instantaneous ventricular volume, and $V_e$ is the theoretical ventricular volume at zero pressure (30). $V_o$ was determined by an iterative algorithm, as described by Kono et al. (17). The ESPVR of both ventricles was determined by fitting a straight line through the end-systolic P-V points (20, 30). Even if these points showed some nonlinearity (see Fig. 4), the ESPVR was calculated by linear regression. To avoid the problem of linear extrapolation to zero pressure, we used volume intercepts at a fixed pressure within the pressure range encountered [$V_{Pes} = 25$ for the RV and $V_{Pes} = 100$ for the LV, where $V_{Pes} = 25$ and $V_{Pes} = 100$ represent volume intercepts of the RV ESPVR at 25 and 100 mmHg end-systolic pressure] to quantify the position of both ESPVRs (32). An increased slope of the ESPVR ($E_{sw}$) (16, 20, 30), a leftward shift indicated by a decreased volume intercept ($V_{Pes} = 25$ and $V_{Pes} = 100$), (4, 15), or both (16) represent an improved systolic function. Independent of the varying preload conditions, the PRSW determines SW at a given $V_{es}$. An increased slope of the PRSW ($S_{prsw}$) or an upward shift indicated by an increased vertical intercept at a fixed volume ($SW_{es} = 1$ for the RV and $SW_{es} = 15$ for the LV) represents an improved cardiac performance (13, 16, 18).

General hemodynamic indexes (CO, SV, and $V_{es}$) were determined from the steady-state beats just before each vena cava occlusion. All calculations were performed using custom-made software. HR, $P_{ao}$, $P_{pa}$, and CVP were measured continuously using a Hewlett-Packard monitoring system, and these signals were recorded simultaneously with the conductance catheter acquisitions.

**Statistical analysis.** The effects of RDS (or non-RDS in the control animals) on systolic function of the RV and LV were analyzed using a multiple linear regression implementation of repeated-measures ANOVA (12). In this model, dummy variables were used to code the different time points ($T_1$, $T_2$, baseline, start (non-)RDS, 15 min, 30 min, 1 h, 2 h, 3 h, and 4 h (non-)RDS) and animals ($L_1$, and $L_4$, RDS lambs 1–7 and control lambs 1–5). The regression equation was:

$$ y = a_0 + \sum a_i^1 \cdot L_i + \sum a_i^2 \cdot T_i $$

where $y$ represents the dependent variable of interest (HR, CO, SV, $V_{es}$, $P_{pa}$, $P_{ao}$, $V_{Pes} = 25$, $V_{Pes} = 100$, $S_{prsw}$, $SW_{es} = 7$, $SW_{es} = 10$, $P_{es}$, $P_{ao}$, $P_{CO2}$, and pH). For the animals, effects coding was used; for the time points, reference coding was used (12). Consequently, the intercept of the regression equation ($a_0$) yields the mean value of the dependent variable at baseline, and each coefficient ($a_i^1$) represents the difference between the dependent variable at that time point and baseline. The coefficient $a_i^2$ represents for each animal the difference from the overall mean.

In addition, mean values at baseline in RDS animals were compared with mean values at baseline in control animals with the use of an unpaired Student’s $t$-test. $P < 0.05$ was considered statistically significant. Values are means ± SD.

**RESULTS**

With lung lavages, a twofold increase of $P_{pa}$ was induced that lasted throughout the 4 h of RDS (Fig. 2), whereas in control animals $P_{pa}$ remained unchanged (Table 2). During the 4 h of RDS, CO did not decrease in response to the increased RV afterload but was maintained stable during the first 2 h of RDS and even showed a significant increase toward the end of the study. This increase toward the end of the study was largely due to an increase in HR (Table 1), while SV remained constant during 4 h of RDS (Fig. 2). In response to the increased RV afterload, RV $V_{es}$ showed a weak tendency to increase, which, however, was only significant at 3 h of RDS (Fig. 3). LV $V_{es}$ did not show this tendency and remained unchanged during 4 h of RDS. RV systolic function improved significantly, as illustrated by a leftward shift of the ESPVR (Fig. 3A). The volume intercept ($V_{Pes} = 25$) of the RV ESPVR decreased significantly (ranging from 62% of baseline at the onset of RDS to 83% after 4 h of RDS),
resulting in a substantial leftward shift of the ESPVR. In addition, the slope ($E_{sa}$) of the RV ESPVR tended to increase compared with baseline, although this increase was only statistically significant at start, 30 min, 1 h, and 2 h of RDS. Figure 4A shows a typical example of RV P-V loops during vena caval occlusion at baseline and during RDS in one of seven RDS animals. It illustrates how the ESPVR becomes somewhat steeper, and the volume intercept decreases substantially in response to pulmonary hypertension. Furthermore, the $P_{\text{ed}}$ increased during RDS at almost unchanged $V_{\text{ed}}$, indicating an increased diastolic stiffness of the RV. As shown in Fig. 3A, RV $P_{\text{ed}}$ did increase significantly at all time points during RDS, and consistent with this finding, CVP also showed a significant increase during RDS (Table 1). Figure 5 shows schematically the average RV P-V loops at baseline and at 30 min of RDS for the RV. It illustrates how the RV is able to maintain its SV against an increased afterload, with only a slight increase in $V_{\text{ed}}$. The dashed P-V loop in Fig. 5 shows how the RV would have behaved in the theoretical case that SV had been maintained purely by the Frank-Starling mechanism, i.e., without a change in systolic performance. Also shown by Fig. 5, the increased P-V loop area, which represents SW, indicates an enhanced systolic function of the RV against the increased afterload (13). As demonstrated by higher PRSW, the RV stroke work (SW) at matched $V_{\text{ed}}$ ($SW_{V_{\text{ed}}} = \gamma$) is significantly increased during RDS (Fig. 3A). Even more clearly, the $S_{\text{mean}}$ increased significantly for the RV at practically all time points during RDS. This behavior of the PRSW indicates an improved contractile performance of the RV, independent of variations in preload (13).

LV systolic function showed no significant changes as shown by the various indexes of contractile performance in Fig. 3B. Figure 4B shows a typical example of LV P-V loops during vena caval occlusion in one of the RDS animals. As shown in this example, LV P-V loops show no major changes, and the LV ESPVR remains largely unaffected during RDS. Table 1 shows the results for general hemodynamics, arterial blood gases, and ventilatory settings at all time points in the RDS animals. As mentioned earlier, HR showed an increase over time that was significant at 2, 3, and 4 h of RDS. In control animals the same tendency to increase was seen, although in this group the increase was only significant at the 3- and 4-h time points (Table 2). Systemic pressure showed a slight decrease during the experiment in both groups, but this was not significant. The decrease in pH values in response to RDS remained significantly below baseline values up to 2 h of RDS, and $P_{\text{CO}_2}$ showed a significant increase during the same period. $F_{\text{O}_2}$ was decreased significantly at the start of RDS but was essentially within normal ranges throughout the study. To maintain arterial blood gases within the normal range, adjustments of ventilatory settings were necessary, illustrated by the significantly increased PIP, PEEP, and $F_{\text{O}_2}$ at all time points during RDS.

To test the stability of the preparation and to exclude the possibility that the effect observed in the RDS group could be attributed to a factor other than the induced RDS and subsequent afterload increase, the same measurements were performed in control animals without RDS. Comparison of the groups at baseline showed no statistically significant differences in any of the measured indexes between the RDS and the control group. During the experiments the control animals showed no significant changes in any of the above-described indexes of the cardiac performance for RV and LV, except an unexplained decreased $V_{\text{ed}}$ at the 2-h time point for the RV and at the 3-h time point for the LV and a simultaneously increased slope of the RV and LV ESPVR at the end of the experiments (Table 2). Systemic pressure and CVP showed no significant changes during the experiments in control animals. Furthermore, pH and blood gases remained within the normal range, while no significant adjustments in $F_{\text{O}_2}$ were required.

Unlike LV volume measurements, the application of the conductance method for the RV is fairly new. Table 3 shows the calibration factors ($\alpha$) and parallel conductance ($V_{\text{c}}$) for the RV. During the course of the experiments, there were no significant changes in the RDS or control animals.

**DISCUSSION**

The present study shows that in the newborn heart the RV enhances its systolic function in response to RDS. The increased slope and, even more pronounced,
the decreased volume intercept of the ESPVR reflect the improved contractile state in response to the increased $P_{pa}$, as previously shown for an isolated pure hemodynamic RV afterload increase induced by partial balloon occlusion of the pulmonary artery (7). Apparently, in this experimental model of RDS, the newborn heart is able to maintain CO during pulmonary hypertension primarily by improving its RV systolic function. With only a slight and nonsignificant dilatation of the RV, this study demonstrates that, although intact, the Frank-Starling mechanism plays a limited role in coping with the increased RV afterload. Figure 5 illustrates the mean RV P-V loops before and during RDS. Furthermore, it shows a hypothetical example of a P-V loop during the increased afterload with an unchanged systolic function. With constant systolic function, the RV would rely solely on its Frank-Starling mechanism, and consequently the RV would have been dilated.
substantially to maintain CO. In contrast, our study demonstrates that, in a more complex model of afterload increase resembling much closer the clinical situation of RDS, the same phenomenon can be observed. Another important difference between our present study and our previous study is the nature of the afterload increase. Theoretically, the effect of the increased afterload during pulmonary hypertension on RV function might be different from the effect of isolated pulmonary artery occlusion, because the changes in arterial impedance are very different in these two models. Pulmonary artery occlusion results in a strong pressure wave reflection, which could have been the main cause of the shown HAR effect. The RDS-related pulmonary hypertension, however, is associated with an overall increase of pulmonary resistance, without the strong wave reflection. Yet it did cause a similar HAR effect in the RV.

A possible explanation for the improved RV systolic function, as seen in HAR, could be the release of endogenous catecholamines in response to an increased afterload (34). This explanation was favored by Szabo et al. (31), because they found that the HAR-like effect was abolished after brain death. However, in the present study, we did not observe any clear signs suggesting such a catecholamine release: Systemic blood pressure did not increase, and although HR did increase during RDS, the same tendency to increase was present in control animals without RDS. Even more important, LV systolic function, which is known to be sensitive to catecholamine releases (30), showed no changes during RDS. A more likely explanation for the improved RV systolic function could be a local effect induced by the increased afterload. The increased RV end-systolic pressure, even without changes in ventricular volume, causes an increased wall tension. It could be hypothesized that the signal for HAR lies in mechanical stretch-activated channels (21). Another en-

![Fig. 5. Average RV pressure-volume loops at baseline (black curve) and during the increased afterload at 30 min RDS (gray curves). Dashed line, hypothetical pressure-volume loop subjected to the same increased afterload, without an improved systolic function.](http://ajpheart.physiology.org/)
Table 2. \textit{Indexes of systolic function and other hemodynamic variables in control animals}

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Non-RDS</th>
<th>15 min</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ppa, mmHg</td>
<td>19 ± 1</td>
<td>20 ± 2</td>
<td>20 ± 2</td>
<td>19 ± 2</td>
<td>20 ± 2</td>
<td>17 ± 2</td>
<td>16 ± 2</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>1.05 ± 0.11</td>
<td>0.97 ± 0.29</td>
<td>0.92 ± 0.28</td>
<td>0.88 ± 0.26</td>
<td>0.89 ± 0.26</td>
<td>0.78 ± 0.26</td>
<td>0.99 ± 0.26</td>
<td>1.15 ± 0.26</td>
</tr>
<tr>
<td>SV, ml</td>
<td>7.0 ± 0.5</td>
<td>6.8 ± 1.3</td>
<td>6.1 ± 1.3</td>
<td>6.5 ± 1.2</td>
<td>6.1 ± 1.2</td>
<td>5.2 ± 1.2</td>
<td>5.9 ± 1.2</td>
<td>6.5 ± 1.2</td>
</tr>
<tr>
<td>VEd, ml</td>
<td>10.3 ± 1.0</td>
<td>10.9 ± 2.7</td>
<td>8.2 ± 2.5</td>
<td>8.2 ± 2.5</td>
<td>8.8 ± 2.5</td>
<td>6.7 ± 2.5*</td>
<td>8.0 ± 2.5</td>
<td>8.4 ± 2.5</td>
</tr>
<tr>
<td>RV</td>
<td>16.5 ± 1.1</td>
<td>15.2 ± 2.8</td>
<td>15.9 ± 2.5</td>
<td>15.1 ± 2.5</td>
<td>15.2 ± 2.5</td>
<td>14.2 ± 2.5</td>
<td>13.2 ± 2.5*</td>
<td>15.4 ± 2.5</td>
</tr>
<tr>
<td>RVVpex=25 ml</td>
<td>6.3 ± 0.9</td>
<td>5.7 ± 2.3</td>
<td>5.6 ± 2.1</td>
<td>6.0 ± 2.1</td>
<td>6.4 ± 2.1</td>
<td>4.9 ± 2.1</td>
<td>5.9 ± 2.1</td>
<td>4.6 ± 2.1</td>
</tr>
<tr>
<td>RVVpex=100 ml</td>
<td>10.7 ± 1.2</td>
<td>8.0 ± 3.1</td>
<td>8.6 ± 2.8</td>
<td>7.0 ± 2.8</td>
<td>8.2 ± 2.8</td>
<td>9.2 ± 2.8</td>
<td>8.2 ± 2.8</td>
<td>10.2 ± 2.8</td>
</tr>
<tr>
<td>E*, mmHg/ml</td>
<td>3.2 ± 0.5</td>
<td>3.0 ± 1.4</td>
<td>3.1 ± 1.2</td>
<td>3.0 ± 1.2</td>
<td>3.3 ± 1.2</td>
<td>4.5 ± 1.2</td>
<td>4.9 ± 1.2*</td>
<td>3.8 ± 1.2</td>
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<tr>
<td>LV</td>
<td>8.3 ± 2.8</td>
<td>9.9 ± 7.5</td>
<td>9.7 ± 6.8</td>
<td>9.0 ± 6.8</td>
<td>10.3 ± 6.8</td>
<td>12.7 ± 6.8</td>
<td>19.3 ± 6.8*</td>
<td>17.9 ± 6.8*</td>
</tr>
<tr>
<td>RV SWVpex=7 mmHg/ml</td>
<td>108 ± 17</td>
<td>112 ± 46</td>
<td>112 ± 42</td>
<td>105 ± 42</td>
<td>86 ± 42</td>
<td>86 ± 42</td>
<td>103 ± 42</td>
<td>128 ± 42</td>
</tr>
<tr>
<td>LV SWVpex=10 mmHg/ml</td>
<td>294 ± 57</td>
<td>351 ± 150</td>
<td>337 ± 136</td>
<td>324 ± 136</td>
<td>292 ± 136</td>
<td>285 ± 136</td>
<td>398 ± 136</td>
<td>314 ± 136</td>
</tr>
<tr>
<td>S* v,m l</td>
<td>14.0 ± 0.5</td>
<td>0.97 ± 0.29</td>
<td>0.92 ± 0.28</td>
<td>0.88 ± 0.26</td>
<td>0.89 ± 0.26</td>
<td>0.78 ± 0.26</td>
<td>0.99 ± 0.26</td>
<td>1.15 ± 0.26</td>
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</table>
| Values are means ± SD. CO, cardiac output; SV, stroke volume; VEd, end-diastolic volume; RV, right ventricle; LV, left ventricle; E*, slope of end-systolic pressure-volume relation; SW, stroke work; S* v,m l, slope of preload recruitable SW; PEd, end-diastolic pressure. RVVpex=25 ml and RVVpex=100 ml, volume at 25 and 100 mmHg end-diastolic pressure; RV SWVpex=7 mmHg/ml and LV SWVpex=10 mmHg/ml at 7 and 10 ml VEd; see Table 1 footnote for definition of other abbreviations. * P < 0.05 vs. baseline.

dogenous response leading to an adjustment of the systolic function might be the release of stimulating factors from the endocardial endothelium (5). Demer et al. (9) showed that mechanical stimulation of aortic endothelial cells resulted in increased calcium concentrations in neighboring cells. Brutsaert et al. (6) demonstrated in isolated papillary muscles that damaging the endocardial endothelium, while keeping the myocardial cells intact, resulted in a decreased contractile performance. Particularly in the RV, with its extensive trabecularization, the large endocardial endothelial surface area may play an important role in the response to an increased afterload.

RV PEd increased during RDS, while RV VEd changed only slightly. This finding indicates an increased diastolic stiffness of the RV. Consistent with this finding, CVP also showed a significant increase during RDS (Table 1). For the LV there were no significant changes in PEd. The solitary increase in RV PEd suggests an isolated rise in stiffness of the RV wall in response to a raised RV afterload. Possibly the extent of increase in RV diastolic pressure is not high enough to influence LV diastolic pressure, as might be expected by diastolic ventricular interaction (8, 27). Another explanation for the increased RV PEd and CVP with the onset of RDS might be the necessary adjustment of PEEP (23). Although it seems that the extent of PEEP increase did not compromise venous return, since CO remained unchanged (Fig. 1), it is also possible that the enhanced systolic function of the RV enabled the heart to main-

Table 3. \textit{Calibration factors of conductance-catheter volume signals for the right ventricle}

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Start RDS</th>
<th>15 min</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
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<td>RDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>α</td>
<td>0.45 ± 0.04</td>
<td>0.38 ± 0.09</td>
<td>0.38 ± 0.09</td>
<td>0.43 ± 0.09</td>
<td>0.39 ± 0.09</td>
<td>0.44 ± 0.09</td>
<td>0.45 ± 0.09</td>
<td>0.46 ± 0.09</td>
</tr>
<tr>
<td>VEd, ml</td>
<td>14.0 ± 0.9</td>
<td>14.7 ± 2.2</td>
<td>14.5 ± 2.2</td>
<td>14.8 ± 2.2</td>
<td>16.5 ± 2.2</td>
<td>16.1 ± 2.2</td>
<td>15.7 ± 2.2</td>
<td>16.1 ± 2.2</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>0.57 ± 0.04</td>
<td>0.49 ± 0.11</td>
<td>0.51 ± 0.10</td>
<td>0.54 ± 0.10</td>
<td>0.48 ± 0.10</td>
<td>0.60 ± 0.10</td>
<td>0.63 ± 0.10</td>
<td>0.67 ± 0.10</td>
</tr>
<tr>
<td>VEd, ml</td>
<td>18.8 ± 0.5</td>
<td>20.3 ± 1.3</td>
<td>19.7 ± 1.2</td>
<td>19.6 ± 1.2</td>
<td>19.1 ± 1.2</td>
<td>18.9 ± 1.2</td>
<td>18.9 ± 1.2</td>
<td>18.8 ± 1.2</td>
</tr>
</tbody>
</table>
| Values are means ± SD. α, Slope factor; VEd, parallel conductance.
tain CO in response to pulmonary hypertension and increased PEEP.

Our findings show that CO was stable during the first 2 h of RDS and even showed a significant increase toward the end of the study. This increase was largely due to an increase in HR. It is unlikely that this increase is caused by the increased afterload per se, since the same tendency of increased CO and HR was seen in the control group without RDS. In earlier studies from our group, with the same surgical and anesthetic setup in newborn lambs, the same pattern of increased HR toward the end of the experiments was seen (7). In addition to the increased HR and the concomitant increase in CO, the EFes for LV and RV showed an increase toward the end of the experiments in the control animals. This increase might be due to the increased HR through the force-frequency mechanism (staircase effect). However, since none of the other indexes of systolic function showed a similar improvement in the control animals, the solitary increase in EFes has to be interpreted with caution. In the past, it has been shown that EFes is a rather sensitive index for changes in systolic function (18, 30). Especially if the ESPVR is very steep, as is the case for the newborn heart, small differences in end-systolic volume can result in dramatic changes in the value of EFes.

A simultaneous change in the far less sensitive volume intercept of the ESPVR, or in the even more stable PRSW, would have made an actual change in systolic function much more likely.

As shown in Fig. 3, there is a difference between RV and LV Vئd at baseline. On the basis of angiographic measurements of RV volume in the past, RV volumes were assumed to be larger than LV volumes. However, more recently, several studies using various imaging techniques have demonstrated that RV volumes are similar to or even smaller than LV volumes (1, 15, 22). Thus a distinct difference in RV and LV Vئd as seen in our present study could be a physiological finding. However, since the difference in RV and LV Vئd in our study is larger than that found in most other studies, measurement artifacts cannot be excluded. Despite a wide variety of standard techniques to measure LV volume, measuring RV volume causes difficulties because of the complex geometrical shape of this ventricle. Our technique of assessing ventricular volume through electrical conductance is less hampered by this complex geometry. The accuracy of absolute volume measurement by the conductance method relies largely on calibration techniques that are independent of geometrical assumptions, since they are based on indicator dilution (thermal dilution and hypertonic saline). However, unlike LV volume measurements, the application of the conductance method for the RV is fairly new. Comparative studies validating the accuracy of absolute RV volume measurements with the conductance catheter method are not available, mainly because no true gold standard method exists. Underestimation of RV volume by the conductance catheter method could be related to the position of the catheter. Just as in other RV studies, we positioned the catheter from the tricuspid valve toward the apex. Possibly, volume in the RV outflow tract is not measured or is registered with less sensitivity than in the inflow tract. Matching RV SV with thermodilution-derived SV, as was done by using the slope factor α, will largely solve this problem. Underestimation of RV volume could be caused by an overestimation of RV parallel conductance. The assessment of parallel conductance with the hypertonic saline method has not been validated for the RV, as it has been for the LV (3). Since the hypertonic saline is injected into the inferior vena cava, mixing before entrance into the RV may not be complete. In addition, the residual hypertonic saline in the vena cava and right atrium and the rapid entrance of hypertonic saline in the pulmonary circulation, i.e., compartments that are part of the parallel conductance and are situated relatively close to the RV cavity, may cause overestimation of parallel conductance and thus lead to underestimation of absolute volume. However, the calibration factors α and parallel conductance did not change significantly during the course of the experiments in the RDS or control animals (Table 3). Therefore, if present, a possible volume underestimation will most likely be constant throughout the experiments and thus have no consequences for the conclusions regarding the P-V relationships. Moreover, our findings of the unchanged Vئd during RDS compared with baseline are valid, since the possibly existing error will be constant.

In this study we only studied the acute effects of pulmonary hypertension in an experimental model of RDS. The clinical situation of RDS generally continues for much longer than 4 h. The long-term effects of an increased RV afterload cannot directly be extrapolated from the results of our study. Furthermore, pulmonary hypertension in the clinical situation of RDS can be more severe. Possibly at some level the RV might not be able to maintain CO, leading to a reduced LV filling and a subsequent decrease in systemic pressure. Indeed, as shown by Guyton et al. (14) and more recently by Vlahakes et al. (33), a stepwise increased constriction of the pulmonary artery did not affect CO initially, but with a more severe constriction of the pulmonary artery, CO and Pئac decreased and heart failure occurred as a result of myocardial ischemia. However, the latter findings were obtained in adult hearts, whereas in the case of RDS the heart will be confronted with an increased afterload soon after birth. The RV in this newborn heart is still adjusting from a systemic thick-walled ventricle to a low-pressure thin-walled ventricle. It seems plausible, therefore, that the newborn heart is more capable of coping with pulmonary hypertension than adult hearts.

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