Biventricular systolic function in young lambs subject to chronic systemic right ventricular pressure overload

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Leeuwenburgh, Boudeijn P. J., Willem A. Helbing, Paul Steendijk, Paul H. Schoof, and Jan Baan. Biventricular systolic function in young lambs subject to chronic systemic right ventricular pressure overload. Am J Physiol Heart Circ Physiol 281: H2697–H2704, 2001.—In various clinical situations of congenital heart disease, the right ventricle (RV) is subject to a chronic systemic pressure overload which affects biventricular function and may progress to the development of RV failure. Young lambs (2–3 wk old) underwent adjustable pulmonary artery banding (PAB) at systemic (aortic) level for 8 wk. Biventricular function was determined by using load-independent indexes of global ventricular contractile performance by the end-systolic pressure-volume relationship (ESPVR) using the conductance catheter at baseline and during dobutamine infusion. PAB resulted in a significant fivefold increase in RV end-systolic pressure (12–64 mmHg) and a doubling of the RV-to-left ventricular (LV) wall thickness ratio (P < 0.01). RV global contractile performance increased significantly, as indicated by an increased slope of the ESPVR. Compared with age-matched control lambs, cardiac output decreased from 2.6 to 1.6 l/min (P < 0.05) whereas heart rates were equal. In contrast with RV volume, LV volume decreased significantly after PAB (P < 0.01), whereas the LV-ESPVR slope was unchanged. In the PAB group, the RV, but not the LV, showed a reduced response to dobutamine. We concluded that chronic RV pressure overload for 8 wk results in diminished pump function despite compensatory increased RV global contractile performance.

contractile performance; hypertrophy; pressure-volume loops; ventricular function

IN PATIENTS WITH VARIOUS TYPES of congenital heart disease, the right ventricle (RV) may be subject to abnormal loading conditions, including lifetime pressure overload at systemic (aortic) levels. Several reports (22, 33, 44) on late cardiac failure in patients with untreated severe pulmonary valve stenosis and the occurrence of RV failure in patients with systemic RV pressure overloads, have raised doubt regarding the ability of the RV to function with afterload at systemic levels. Initially, the RV develops compensatory hypertrophy but sustained pressure overload may eventually progress to RV failure (34, 44). On the other hand, chronic RV pressure overload at systemic levels may be tolerated for decades in patients whose RV functions as a systemic ventricle before failure becomes clinically manifest (33). These clinical situations underline the need for improved knowledge of RV and left ventricle (LV) remodeling with prolonged high RV afterload.

For the LV, pressure-volume (PV) loop analysis has been demonstrated to be a useful technique to assess ventricular function with load-independent indexes (26, 42). Assessment of PV loops in the RV requires measurement of RV volume along with pressure. The conductance catheter can be used to measure RV volume continuously, irrespective of ventricular geometry, which allows online assessment of PV loops in the RV (8, 9, 13, 16, 32). As an initial step toward the analysis of the process of initiation of dysfunction, we designed a study to quantify the remodeling of both ventricles during an 8-wk period of chronic RV pressure overload at the level of systemic pressure. To mimic the situation of such a systemic RV pressure overload, resembling the situation as seen in several types of congenital heart disease, a pulmonary artery (PA) banding (PAB) model in young lambs has been developed, in which the degree of PA constriction can be monitored and adjusted over a wide range for a prolonged period.

Glossary

\[ E_{ES} \] End-systolic elastance
\[ \text{ESPVR} \] End-systolic pressure-volume relationship
\[ \text{PAB} \] Pulmonary artery banding
\[ \text{PRSW} \] Preload recruitable stroke work; relation between stroke work and end-diastolic volume
\[ \text{PV loop} \] Pressure-volume loop
\[ V_n \] Volume intercept of the ESPVR at a ventricular pressure of \( n \) millimeters of mercury

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METHODS

Thirteen lambs were enrolled in the study. The treatment of the animals followed the guidelines in the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, Revised 1996). The protocol was approved by the animal research committee of the Leiden University Medical Center. Two animals died during the PAB operation. One animal, in which PAB adjustment failed, died 33 days after PAB with clinical signs of heart failure. Complete hemodynamic studies were performed in 10 animals. The first group consisted of five lambs that were 2-3 wk old (mean body mass 6.4 ± 1.7 kg) at the time of PAB. After at least 8 wk of PA constriction (mean 64 ± 8 days), they were studied during a second operation (mean body mass at time of hemodynamic studies 16.6 ± 3.7 kg). A second group consisted of five control lambs (mean body mass 20.4 ± 3.0 kg) that were age matched with the PAB group.

PAB operation. Anesthesia was initiated with the use of propofol (4-6 mg/kg). After intubation, the animals were mechanically ventilated with the use of a volume-controlled respirator (Servo 900B, Siemens-Elema) with 0.5–1.5% isoflurane in a gas mixture consisting of 80–100% oxygen supplemented with room air. General anesthesia/analgesia was maintained with isoflurane, propofol (6–18 mg·kg⁻¹·h⁻¹ iv), and ramifenazon and fenylbutazon (Tomanol; 0.03 ml/kg iv).

Two small reservoirs, covered on top by a silicone membrane (0.25 ml, UNO; Zevenaar, The Netherlands) with pressure lines attached (2.1 mm outer diameter), were placed subcutaneously in the neck (43). The distal end of one pressure line was inserted into the right carotid artery and fixed in place. A median thoracotomy was performed and the heart was exposed in a pericardial cradle. The second pressure line was subcutaneously tunneled toward the thorax, where it passed under the sternal notch. The distal end of the line was introduced into the RV through a minor stab wound in the free wall and was then fixed in place. An inflatable cuff with a noninflated lumen diameter of 12 mm (UNO) was loosely placed around the PA. A line attached to the cuff was exteriorized through the lateral thoracic wall and connected to a third subcutaneous reservoir, which was fixed onto the underlying muscles of the back of the animal. The pericardium was approximated for two-thirds, and the thorax was closed in layers.

Pressure monitoring and PAB adjustment. Approximately 7 days after the operation, when full recovery had occurred, RV pressure overload was initiated by stepwise inflation of the PA cuff via saline injection into the third reservoir on the back according to the following protocol: RV and aortic pressure was monitored twice a week by connecting the subcutaneous neck reservoirs under local (skin) anesthesia to pressure transducers (model 56S, Hewlett-Packard; Andover, MA), while the animal was quietly resting in a canvas sling. RV peak systolic pressure was matched with peak systolic aortic pressure by adjusting the PA cuff diameter. This high PA pressure level will further be referred to as systemic RV pressure overload. After the measurements, the pressure lines were filled with heparin solution (500 IE/ml) to prevent clotting. The pressure transducers were disconnected, and the animal was returned to its cage.

Protocol for hemodynamic studies. After at least 8 wk of chronic RV pressure overload, hemodynamic measurements were performed. The interventions during this procedure were the same for both groups. Anesthesia was initiated with thiopental sodium (10 mg/kg iv). Ventilation and monitoring of the animals during the experiment were identical to those during the PAB operation. Before the chest was opened, pancuronium bromide (0.1 mg/kg) was given. A 7-Fr Swan-Ganz catheter was advanced into the PA from the right jugular vein and used for calibration of the conductance catheters in both ventricles in terms of absolute volume. A 7-Fr sheath was introduced into the left jugular vein for intravenous dobutamine administration. A midsternal thoracotomy was performed, and the heart was exposed in a pericardial cradle. For preload reduction, required to obtain systolic PV relations, a string was placed around the inferior vena cava. Two 5-Fr pig-tailed combined pressure-conductance catheters (Millar Instruments; Houston, TX) were positioned in both ventricles for continuous and simultaneous measurement of pressures and volumes (8). The LV catheter was introduced via a minor stab wound in the LV apex and positioned along its long axis. The RV catheter was inserted via a small stab wound just below the pulmonary valve and positioned towards the apex (9). The catheters were connected to two signal processors (model Sigma-5 DF, cd Leycom; Zoetermeer, The Netherlands) in one of which the excitation frequency was modified from 20 kHz to 15 kHz to avoid electrical interference between the two systems and enable simultaneous biventricular volume measurements. Calibrations were performed as previously described using cardiac output (CO) from thermodilution and venous hypertonic saline injections (4, 13). LV parallel conductance was determined from the same hypertonic saline injection as used for RV parallel conductance by analyzing the LV signal during the subsequent passage of the bolus through the LV (41). These calibrations were performed at baseline and during dobutamine infusion. After instrumentation, a 10-min stabilization period was allowed before baseline measurements. Data were acquired before and during preload reduction as described previously (13). After completion of baseline measurements, dobutamine was infused at a dose of 2 µg·kg⁻¹·min⁻¹ to determine biventricular responses to stress conditions. This dose has been shown to be adequate for β-adrenergic stimulation in sheep (24, 36). After 10 min, when a new steady state was reached, the calibrations and hemodynamic measurements were repeated. At the end of the experiment, the animals were euthanized by an intravenous injection of 20 ml KCl, and the heart was then excised. The ventricles were cut open along the interventricular septum, and RV and LV free wall thickness was measured at midventricular level. Postmortem examination ruled out the presence of a patent foramen oval.

Calculations. For both conditions, steady-state data were recorded during 10 s to determine the hemodynamic parameters listed in Table 1. Data recorded during preload reductions were used to construct the following PV relationships: the end-systolic pressure-volume relationship (ESPVR) (42), maximal first derivative of pressure versus time (dP/dt max)-end-diastolic volume (V0ED) relationship (30), and preload-recruitable stroke work (SW vs. V0ED relationship or PRSW) (21). A close correspondence exists in the LV between the ESPVR and force-length relationships of isolated myocyte or papillary muscle fibers (10). Because the maximal force developed by a myocyte at a given length is representative for its contractile performance, it is generally accepted that the ESPVR is the closest reflection of mechanical contractile performance of the myocardium one may expect to obtain in the intact circulation (5). The volume intercept and slope of the ESPVR, as well as the slopes of the dP/dt max-V0ED and PRSW relationships, were used as load-independent indexes of global ventricular contractile performance for both ventricles (8, 9, 13, 16, 21, 30, 32, 42). Because PAB increased RV pressure considerably, the pressure level of the volume-
A regression implementation of repeated-measures analysis of parameters between the control group and the PAB group was significant. Linear regressions, whereas the age-matched control group (16.6 ± 3.7 vs. 20.4 ± 3.0 kg, P = NS) resulted in a significant increase in RV/LV wall thickness ratio (from 0.43 ± 0.04 to 0.94 ± 0.15, P < 0.01). RV and LV hemodynamic parameters at baseline and during dobutamine infusion are listed in Table 1. Table 2 gives an overview of the biventricular indexes of contractile performance, derived from the PV relations. Typical examples of RV and LV PV loops during preload reduction are given in Fig. 2. Figure 3, A and B, illustrates the average effects of banding and dobutamine on PV loops and ESPVRs in both ventricles.

**Hemodynamic effects of banding in baseline condition.** PAB resulted in a significant increase in RV systolic pressure. CO was significantly lower in the PAB group than in the control group, related to a significantly lower stroke volume (SV) in the banding group, whereas heart rate (HR) was the same in both groups. For the RV, ejection fraction (EF) also tended to be lower in the PAB group. The difference in CO was partly related to the difference in body mass, but cardiac index still tended to be lower in the banding group (0.10 ± 0.03 vs. 0.14 ± 0.06 l·min⁻¹·kg⁻¹, P = 0.27). In the RV, the slopes of the ESPVR (EESP), PRSW, and dP/dtmax-VED relations (henceforth called the three PV relations) were all steeper in the banding group (Table 2 and Fig. 3A) although the latter increased only marginally significantly (P = 0.07). The decrease of SV in the RV after PAB was the net result from an increase in end-systolic volume (VESP) and a decrease in VED. End-diastolic pressure (PED) in the RV tended to increase but only marginally significantly.

In Table 2, data were presented as means ± SD. Differences in baseline hemodynamic parameters between the control and PAB group were analyzed by unpaired Student’s t-test. Effects of dobutamine infusion on hemodynamic parameters were analyzed for each group separately using a multiple linear regression implementation of repeated-measures analysis of variance (20). A P value < 0.05 was considered statistically significant.

<table>
<thead>
<tr>
<th>Hemodynamic parameters</th>
<th>Control</th>
<th>Banding</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Dobutamine</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>117 ± 29</td>
<td>180 ± 10</td>
</tr>
<tr>
<td>CO, ml/min</td>
<td>2,649 ± 786</td>
<td>3,574 ± 1,344</td>
</tr>
<tr>
<td>SV, ml</td>
<td>23.3 ± 8.5</td>
<td>20.1 ± 8.1</td>
</tr>
<tr>
<td>Right ventricular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VESP, mmHg</td>
<td>15.2 ± 5.5</td>
<td>7.7 ± 6.4</td>
</tr>
<tr>
<td>VEDP, mmHg</td>
<td>37.7 ± 6.7</td>
<td>26.9 ± 9.8</td>
</tr>
<tr>
<td>EF, %</td>
<td>61 ± 14</td>
<td>75 ± 15</td>
</tr>
<tr>
<td>PED, mmHg</td>
<td>12 ± 3</td>
<td>29 ± 25</td>
</tr>
<tr>
<td>PED, mmHg</td>
<td>4 ± 3</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>SW, mmHg/ml</td>
<td>335 ± 98</td>
<td>559 ± 100</td>
</tr>
<tr>
<td>dP/dtmax, mmHg/ml</td>
<td>436 ± 115</td>
<td>1,417 ± 621</td>
</tr>
<tr>
<td>Left ventricular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VESP, mmHg</td>
<td>29.0 ± 8.2</td>
<td>22.0 ± 8.4</td>
</tr>
<tr>
<td>VEDP, mmHg</td>
<td>51.1 ± 14.4</td>
<td>40.8 ± 14.5</td>
</tr>
<tr>
<td>EF, %</td>
<td>45 ± 8</td>
<td>49 ± 10</td>
</tr>
<tr>
<td>PED, mmHg</td>
<td>78 ± 15</td>
<td>78 ± 8</td>
</tr>
<tr>
<td>SW, mmHg/ml</td>
<td>1,672 ± 463</td>
<td>1,800 ± 745</td>
</tr>
<tr>
<td>dP/dtmax, mmHg/ml</td>
<td>1,893 ± 601</td>
<td>3,906 ± 415</td>
</tr>
</tbody>
</table>

Values are means ± SD; numbers in parentheses are percentages. DOB, dobutamine; CO, cardiac output; dP/dtmax, first derivative of pressure vs. time; EF, ejection fraction; HR, heart rate; VESP, end-diastolic pressure; PED, end-systolic pressure; SV, stroke volume; SW, stroke work; VESP, end-diastolic volume; VESP, end-systolic volume. Results are shown for right and left ventricular hemodynamics of the control and pulmonary artery banding groups. “DOB effect” gives the absolute and % (in parentheses) change after dobutamine (DOB) administration in the DOB group compared with the baseline group. “Banding effect” gives the absolute and % change between the control and pulmonary artery banding group during baseline conditions compared with the control group. P value of the “DOB effect” was calculated using multiple linear regressions, whereas the P value of the banding effect was calculated by using an unpaired t-test. P < 0.05 was considered statistically significant.
**Effects of dobutamine.** In the control group, dobutamine increased CO. This increase was due to a significant HR increase, whereas SV decreased significantly. All systolic hemodynamic parameters except SV, LV $P_{ES}$, and LV SW were consistent with a substantial increase in systolic function (Table 1). The RV PV loop increased in height and shifted to the left (Fig. 3A) as indicated by an increase in $P_{ES}$ and decreases in $V_{ES}$ and $V_{ED}$ (Table 1). The slopes of all PV relations in the RV increased whereas the volume intercept of the ESPVR ($V_{15}$) decreased. All of these phenomena reflect a strong positive effect of dobutamine on RV global contractile performance.

In the PAB group, similar directional changes in CO and HR as in control were seen with dobutamine infusion but the effects were less pronounced. For the RV, the changes in slopes and volume intercepts of the three PV relations were directionally similar to those in control but tended to be much smaller as indicated by the percent changes (Table 2), suggesting a blunted positive inotropic response to dobutamine in the banding group compared with control.

Unlike the RV findings, in the LV neither $P_{ES}$ nor SW changed substantially in the control group. All other systolic parameters, including the parameters of global ventricular contractile performance, increased as expected (Table 2). In the control group, LV $E_{ES}$ did not increase significantly whereas in the banding group it did. Also, in the banding group, SW and $P_{ES}$ increased significantly after dobutamine infusion. Thus, in contrast to the RV, which showed a blunted response, the LV in the PAB group showed a similar or even enhanced positive inotropic response to dobutamine compared with control.

**DISCUSSION**

In this study we demonstrated that chronic increase of RV pressure, at systemic level (after PAB), resulted in a decreased CO while contractile performance of the RV (as assessed from the slopes and/or intercept of the PV relations) was significantly increased. LV volume was considerably reduced after PAB despite unchanged LV pressure development. In accordance with

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**Table 2. Right and left ventricular pressure-volume loops-derived parameters**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dobutamine</th>
<th>DOB effect</th>
<th>$P$</th>
<th>Banding</th>
<th>Dobutamine</th>
<th>DOB effect</th>
<th>$P$</th>
</tr>
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<tbody>
<tr>
<td><strong>Right ventricular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$E_{ES}$</td>
<td>1.1±0.4</td>
<td>5.7±5.6</td>
<td>+4.6(418)</td>
<td>&lt;0.01</td>
<td>4.2±1.3</td>
<td>6.9±2.2</td>
<td>+2.7(64)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$V_{15}$</td>
<td>18.1±4.0</td>
<td>5.6±6.9</td>
<td>-12.5(69)</td>
<td>&lt;0.01</td>
<td>19.8±11.3</td>
<td>15.9±6.8</td>
<td>-3.9(20)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Slope PRSW</td>
<td>13±3</td>
<td>34±9</td>
<td>+21(162)</td>
<td>&lt;0.01</td>
<td>38±23</td>
<td>50±9</td>
<td>+12(32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Slope dP/dt$_{max}$</td>
<td>8±3</td>
<td>66±67</td>
<td>+58(725)</td>
<td>&lt;0.01</td>
<td>21±14</td>
<td>63±43</td>
<td>+42(200)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Left ventricular</strong></td>
<td></td>
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<tr>
<td>$E_{ES}$</td>
<td>6.3±3.7</td>
<td>6.8±6.0</td>
<td>+0.5(8)</td>
<td>0.84</td>
<td>6.1±2.2</td>
<td>9.4±7.2</td>
<td>+3.3(54)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$V_{70}$</td>
<td>26.7±10.4</td>
<td>20.2±8.9</td>
<td>-6.5(24)</td>
<td>&lt;0.01</td>
<td>13.1±4.2</td>
<td>8.9±4.2</td>
<td>-4.2(32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Slope PRSW</td>
<td>67±11</td>
<td>92±40</td>
<td>+25(37)</td>
<td>&lt;0.01</td>
<td>65±20</td>
<td>84±36</td>
<td>+21(33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Slope dP/dt$_{max}$</td>
<td>39±25</td>
<td>148±64</td>
<td>+109(280)</td>
<td>&lt;0.01</td>
<td>66±30</td>
<td>175±91</td>
<td>+107(162)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are means ± SD; numbers in parentheses are percentages. $E_{ES}$, end-systolic elastance; $V_{15}$, $V_{55}$, and $V_{70}$, pressure level at volume intercept at 15, 55, and 70 mmHg, respectively; PRSW, preload-recruitable stroke work.
earlier reports (37), the RV PV loop after PAB showed close resemblance to the LV PV loop (Fig. 3). This may be expected in view of the significantly increased RV systolic pressure and wall thickness. β-Adrenergic stimulation with dobutamine in the PAB group resulted in a blunted RV inotropic response whereas the LV response was largely unchanged. Our findings of normal RV volumes, a tendency towards reduced RV-EF, increased RV wall mass, reduced LV volumes, and normal LV EF are in full agreement with the findings in patients subjected to systemic RV pressure overload (33).

Contractility of cardiac muscle is commonly assessed by force-length or force-velocity relations measured in intact or skinned trabeculae (27). In the intact heart and circulation, such measurements are obviously impossible, which has led to the introduction of the load-independent ESPVR by Suga and Sagawa (42) as a measure of global ventricular contractile performance. A close resemblance between the ESPVR and the force-length relationship in both the normal and the ischemic LV has been shown (10). As the maximal force developed by the myocyte at a given length is representative for its contractile function (27), the maximal (end systolic) pressure at a given VED likewise reflects global ventricular contractile performance (5). Such a resemblance between the myocardial force-length relation and the ESPVR has not been established yet for the RV, but characterizing its global contractile performance has become common practice in many laboratories (1, 8, 9, 13, 14, 16, 19, 24, 25, 32, 37). Indeed, the response of the RV ESPVR to positive or negative inotropic stimuli has been shown to occur as expected, similar to our findings with dobutamine. For practical reasons, we maintained the use of the ESPVR and related parameters to characterize global contractile

Fig. 2. Typical representation of actual RV (A) and left ventricular (LV) (B) pressure-volume (PV) loops during a vena cava occlusion. Solid loops represent the control group and dotted loops represent the banding group. The black solid lines represent the end-systolic PV relationships (ESPVR) in both groups. It is clearly illustrated that in the RV, PAB resulted in a significant increase in systolic pressure generation while stroke volume is reduced. In the LV, a significant reduction in end-systolic and end-diastolic volume can be seen.

Fig. 3. Schematic representation of PV loops during baseline and dobutamine conditions in the RV (A) and LV (B) in both groups. Each end-systolic PV point represents the mean end-systolic pressure and volume. The other three points of the loop are derived from (idealized) isovolumic relaxation and contraction, using the measured average values for end-diastolic pressure and volume. ESPVRs are shown with actual average slopes. The intercept of each ESPVR with the horizontal black lines indicates the volume intercept at the corresponding pressure level (15, 55, and 70 mmHg, see text for details). These data summarize the effect of PAB on RV and LV PV loops and the parallel leftward shift of the ESPVR in both groups after dobutamine administration (B, banding group and C, control group). Solid-line loops represent the baseline condition and the dashed-line loops represent the dobutamine condition.
performance of the RV after chronic PAB. For the hypertrophic LV, this approach has been used: taking into account the increased muscle mass after aortic banding, Sasayama et al. (38) showed that, when calculated, wall stress is substituted for LV pressure, the end-systolic stress-volume relation is almost identical before and after hypertrophy. This led them to conclude that the enhanced global LV contractile state may be characterized by a “hyperdynamic” state of the systemic circulation based on the increased muscle mass. It is doubtful whether a similar conclusion can be drawn for the chronically overloaded RV. First, RV free wall thickness increased by a factor of 2, which is not sufficient to explain our finding that P\textsubscript{ES} increased by a factor of 5 at almost unchanged V\textsubscript{ES} (the slope E\textsubscript{ES} of the ESPVR increased by a factor of 4). Even if RV wall stress could be estimated (e.g., using Laplace’s law), the end-systolic stress-volume relations before and after PAB would not superimpose. Second, there is no doubt that, unlike in the LV, the shape of the RV changes considerably after PAB, because the septum has been reported to shift towards the left (28), thus making the RV cross section more circular. This might render RV performance more effective and could contribute to the observed increased global contractile state. On the other hand, by the same reasoning, the circularity of the LV should have decreased; however, its contractile performance was not diminished: if anything, it increased after PAB because the same end-systolic LV pressure is generated at a much reduced V\textsubscript{ES}. In conclusion, it is plausible that the increased global contractile state caused by acute obstruction of the PA as observed by our group earlier (13, 32) and ascribed to homeometric autoregulation, persists to some extent after chronic PAB, although the increased muscle mass undoubtedly contributes to the phenomenon as well.

Only a few reports (11, 12, 40) are available on the hemodynamic effects of a chronic RV pressure overload on RV function. In these studies, it was found that contractile state of isolated RV cat papillary muscles, as assessed from force-shortening relationships, was decreased after chronic PAB. However, comparison of the results of the study by Cooper et al. (11) with ours may not be valid. Apart from differences in animal species, the proximal PA in the above studies was banded in 7- to 8-wk-old cats, whereas in our study, the banding was performed at the age of 2–3 wk. It has been shown that there is a fundamental difference in the hypertrophic response to a pressure overload present early after birth compared with the response to one acquired later in life (i.e., hypertrophic vs. hyper-plastic response, adaptation of the coronary artery bed) (3, 17, 35). On the other hand, onset of a decrease in global contractile performance in our model if the banding had been maintained much longer cannot be excluded.

Gradual PAB has been demonstrated to produce RV pressure overload without activation of the sympathetic nervous system or systemic renin-angiotensin system (29). Combined with our finding of unchanged HRs in the PAB group, these observations make it unlikely that the increased RV contractile performance results from sympathetic nervous stimulation.

The most remarkable finding of our study is that the apparent increase in global contractile performance is accompanied by a decreased CO and RV EF. Interestingly, the reduced CO (38%), together with the somewhat (15%) decreased end-systolic LV pressure (Table 1) signifies that the systemic vascular resistance (approximated by P\textsubscript{ES} divided by CO) is also increased by ~36%. Whereas further studies will be needed to elucidate underlying mechanisms, it may be speculated that the inability of the heart to maintain CO against chronically increased vascular resistance is a hallmark of initial ventricular dysfunction.

The adaptive mechanisms and the process of transition towards failure as a result of chronic RV afterload are poorly understood, but timely recognition of this transition is very important (23). In general, ventricular pressure overload results in increased wall stress, displacement of the interventricular septum, and reduced myocardial perfusion, leading to increased susceptibility for ischemia. Each of these changes may contribute to reduced CO and EF. This reduced ventricular function is initially prevented by compensatory mechanisms such as the Frank-Starling effect, by stimulation of the β-adrenergic system, and by the development of ventricular concentric hypertrophy. Our results, and those of others (33), demonstrate that at least at this stage the Frank-Starling mechanism plays a minor role because no increase in RV V\textsubscript{ED} was observed in response to chronic pressure overload. Reduced RV myocardial blood flow may lead to reduced CO (7). Animal studies (2, 6) (including lambs) have shown, however, that RV coronary artery flow is not decreased by RV pressure overload if the load is applied at young age, as was the case in our study. Ischemia as a cause for reduced systolic function in our model seems therefore not likely.

Chronic RV pressure overload also affects LV geometry, exemplified particularly by the large reduction in LV volume. Two factors may account for this finding: first, the decreased RV output reduced LV filling, and second, chronic RV pressure overload abolished the pressure gradient across the interventricular septum. Consequently, the interventricular septum is displaced toward the left, thereby compromising LV volume (28). Whatever the mechanism, a large decrease in LV volume suggests remodeling of this ventricle, albeit in the opposite direction of dilatation-related remodeling commonly found in heart failure (18).

The contractile performance of both ventricles increased after β\textsubscript{1}-adrenergic stimulation with dobutamine administration in the control group, which is in accordance with studies in the LV (31), the RV (16, 19), or both ventricles (24). In the RV of the PAB group, the effects of dobutamine were blunted, but not absent. This again might be interpreted to reflect a state of partly compensated myocardial dysfunction. Derrick et al. (15) made similar observations in patients after the Mustard operation. In these patients, the RV supports
the systemic circulation, and the LV the pulmonary circulation. These investigators demonstrated that in late survivors of the Mustard operation, dobutamine administration resulted in a failure to augment RV SV, despite adequate increases in load-independent indexes of ventricular contractile performance (15). In our study, only the RV response to dobutamine was blunted in the banding group, whereas the LV response was maintained after chronic PAB.

**Study limitations.** A limitation of this study may be the absence of the pericardium, but this was the case in both groups. Pericardiotomy-related ventricular dilatation (absence of pericardial restraint) did not occur in our study because ventricular volume of both ventricles in the banding group remained fairly constant. The second limitation concerns the nature of our control group. After careful consideration, we decided not to perform a sham operation in the control group. We consider it highly unlikely that the insertion of a small incision while the effects of the operation on cardiac function are affected by the initial operation. It does not appear to be justified to subject healthy animals to a thoracotomy which makes it extremely unlikely that our findings are affected by the initial operation. It does not appear to be justified to subject healthy animals to a thoracotomy while the effects of the operation on cardiac function are not expected to occur after a period of 8 wk.

In conclusion, medium-term increase of RV afterload at the systemic level is characterized by considerable increase in RV global contractile performance. This increase in ventricular contractile performance is, however, not sufficient to prevent a decrease in CO. The RV response to dobutamine is blunted. LV volume is reduced but LV contractile performance is generally maintained. These results point out that after 8 wk of PAB, ventricular remodeling has occurred and the heart is unable to maintain its normal output in the situation of chronically increased RV afterload at a systemic level. This might be speculated to be a potential hallmark of initial ventricular dysfunction.

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