Indexes of diastolic RV function: load dependence and changes after chronic RV pressure overload in lambs

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The importance of diastolic function as a major determinant of ventricular performance has long been recognized. Impaired diastolic function may precede systolic ventricular dysfunction (13, 14), and it influences the performance of the contralateral ventricle via ventricular interdependence (23, 34, 39). The gold standard for determination of right ventricular (RV) [and left ventricular (LV)] diastolic function is still considered to be cardiac catheterization with simultaneous high-fidelity pressure and volume measurements (32).

Because RV cineangiography is only sporadically performed during routine diagnostic catheterization and because complex RV geometry hampers adequate RV volume determination, few data are available about RV diastolic function. With the combined pressure-conductance catheter it has recently become possible to determine ventricular pressure and volume simultaneously and independently of ventricular geometry in the RV as well as in the LV (3, 11).

Using this method, we are able to determine parameters of diastolic function such as the end-diastolic pressure-volume relationship (EDPVR) and chamber stiffness constant (b) that are well accepted for LV diastolic analysis. Furthermore, some of the LV relaxation parameters have shown a relationship with load (systolic pressure) that may render them less reliable to characterize intrinsic diastolic properties (26, 33). The load dependence of these relaxation parameters has not been studied systematically in the RV.

One of the situations in which diastolic function may hypothetically be altered is chronic pressure overload. RV pressure overload is common in congenital and acquired heart disease and may lead eventually to RV failure or to residual abnormalities in RV function, even after relief of the pressure load (5, 7, 17). Accurate measurement of diastolic function could contribute to improved clinical management in these patients.

The purpose of this study was 1) to determine parameters of RV relaxation [minimum first derivative of pressure vs. time (dP/dt mim) and time constant of pressure decay during isovolumic relaxation (τ)] and (late) diastolic function (EDPVR) and compare them to those of the LV; 2) to determine the load dependence of the relaxation parameters in the normal RV as well as in the LV; and 3) to study the behavior of the parameters of biventricular diastolic function after chronic RV pressure overload. To generate RV pressure overload, we have developed an animal model in young lambs in which, at 2–3 wk of age, the pulmonary artery was banded for a period of 10.220.33.4 on April 18, 2017
at least 8 wk. This model offered the possibility of studying diastolic parameters at altered myocardial properties and loading conditions. Effects on systolic properties were reported earlier (24).

METHODS

Thirteen lambs were enrolled in this study and treated in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, revised 1996). The animal research committee of the Leiden University Medical Center approved the protocol. We assumed that in young animals RV functioning at systemic pressure level could be reached in a shorter period and that such a RV was better capable of withstanding a chronic pressure overload at systemic level than an adult RV (22). Complete hemodynamic studies were performed in 10 animals. The same lambs had been included in a previous study to describe the effects of chronic RV pressure overload on systolic function (24). In brief, the following procedure was used.

Protocol for hemodynamic studies. Five lambs (mean body mass 20.4 ± 3.0 kg) aged 10–12 wk were studied under control conditions. The lambs were intubated and mechanically ventilated with 0.5–1.5% isoflurane in a room air and 80–100% oxygen mixture. Anesthesia was initiated and maintained with thiopental sodium (10 mg/kg iv). Throughout the study, ventilation was adjusted to maintain normal arterial oxygen and carbon dioxide pressures. Before chest opening, pancuronium bromide (0.1 mg/kg; muscle relaxant) was given. A 7-Fr Swan-Ganz catheter was introduced into the right jugular vein and advanced into the pulmonary artery (PA) for calibration of the conductance catheters in both ventricles in terms of absolute volume (see below).

Aftermidsternal thoracotomy, the heart was exposed in a pericardial cradle. For preload manipulation, required to obtain the EDPRVR, a piece of umbilical tape was placed around the inferior vena cava. Because the preload manipulation decreased biventricular end-systolic pressure (PES), it was also used to study load dependence of several diastolic parameters (26, 33).

Pressure-conductance catheters (5-Fr; Millar Instruments, Houston, TX) were positioned in both ventricles for continuous and simultaneous measurement of LV and RV pressures and volumes (3, 11, 29). The LV catheter was introduced via a minor stab wound in the LV apex and positioned along the long axis of the LV. The RV catheter was inserted via a small stab wound just below the pulmonary valve and positioned toward the apex (4). The catheters were connected to two Sigma-5 DF signal processors (CD-Leycom, Zoetermeer, The Netherlands), in one of which the excitation frequency was modified from 20 to 15 kHz to avoid electrical interference between the two systems and to enable simultaneous LV and RV volume measurements. The conductance catheters were calibrated as previously described using thermodilution for cardiac output and saline injection for parallel conductance volume (1, 10). LV parallel conductance was determined from the same saline injection used for RV parallel conductance by analyzing the LV signal during the subsequent passage of the bolus through the LV (37). After instrumentation, a 10-min stabilization period was allowed before baseline measurements were obtained. Data acquisition was performed as described elsewhere (10). At the end of the experiment, the animals were killed under adequate anesthesia by lethal injection of KCl.

Pulmonary artery banding operation. Pulmonary artery banding (PAB) was performed in eight lambs (2–3 wk old; mean body mass 6.4 ± 1.7 kg), which were anesthetized with propofol (4–6 mg/kg) while they were preoxygenated with 100% oxygen. The lambs were intubated and mechanically ventilated with 0.5–1.5% isoflurane in a room air and 80–100% oxygen mixture. General anesthesia was maintained with isoflurane and continuous intravenous infusion of propofol (6–18 mg·kg⁻¹·h⁻¹). Tomanol (a combination of ramifennazon and fentanylbuzon; 0.03 ml/kg iv) was given for analgesia.

Under sterile conditions, two reservoirs (0.25 ml; UNO, Zevenaar, The Netherlands) with pressure lines attached (2.1-mm OD × 1.0-mm ID) were placed subcutaneously in the neck of the animal. The distal end of one pressure line was surgically inserted into the right carotid artery and fixed. The chest was opened by a median thoracotomy, and the heart was exposed in a pericardial cradle. The distal end of the second pressure line was introduced into the RV through a minor stab wound in the RV free wall and fixed. The pulmonary trunk was mobilized by blunt dissection, and 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 right lateral wall of the thorax and connected to a third subcutaneous reservoir (0.25 cc), fixed on the underlying muscles. The pericardium was approximated for two-thirds to support the heart during the period of RV pressure overload, and the thorax was closed in layers. The presence of the PA cuff, however, did not allow complete closure of the pericardium.

Approximately 7 days after the operation, when recovery had occurred, RV pressure overload was initiated by stepwise inflation of the PA cuff via hypertonic saline injections into the third reservoir. RV and aortic pressures were monitored twice a week by connecting both subcutaneous reservoirs in the neck to a pressure transducer (model 56S; Hewlett Packard, Andover, MA) under local (skin) anesthesia. RV peak systolic pressure was matched with aortic peak systolic pressure by adjusting the PA cuff (inflated or deflated). After the measurements, the pressure lines were filled with heparin solution (500 IU/ml) to prevent clotting. Two animals died during the PAB operation. One animal, in which PAB adjustment and RV pressure monitoring failed, died 33 days after the banding operation with clinical signs of heart failure.

After at least 8 wk of PA constriction (mean 64 ± 8 days), the surviving five animals (mean body mass at time of hemodynamic studies 16.6 ± 3.7 kg, mean age 84 ± 5 days) were studied according to the protocol described for the control lambs in Protocol for hemodynamic studies. The pericardium was reopened, and the heart was exposed in a pericardial cradle. To achieve this, we completely removed all adhesions between the pericardium and the heart.

Calculations. Baseline biventricular function was quantified with various hemodynamic parameters obtained from 10-s recordings of steady-state signals. To avoid misunderstanding, all dP/dt values obtained by differentiation of the pressure signal are shown as absolute (positive) values. dP/dt was calculated as the time constant of monoexponential pressure decay during isovolumic relaxation. The isovolumic period was defined as the period between the time point of dP/dtmin and the time point at which dP/dt reached 10% of the dP/dtmin value as illustrated in Fig. 1. To determine whether calculated τ depends on the selected period, τ was also calculated by selecting the end point at 5%, 20%, and 30% of dP/dtmin. As discussed in Diastolic function in normal RV and LV, we chose the 10% range to calculate all τ values.

Data recorded during the vena cava occlusions were used to construct LV and RV EDPVVs by fitting end-diastolic pressure (PED) and volume (VED) from the vena cava occlusa-
Diastolic function in normal RV and LV. Average steady-state parameters are listed in Table 1. No significant differences between average RV and LV \( P_{ED} \) (4 ± 3 and 6 ± 2 mmHg, respectively) were found, whereas RV \( V_{ED} \) tended to be smaller than in the LV (37.7 ± 6.7 and 51.1 ± 14.4 ml, respectively; \( P = 0.07 \)).

The average \( b \), derived from the EDPVRs, was 0.14 ± 0.05 ml⁻¹ in the RV and 0.12 ± 0.05 ml⁻¹ in the LV [not significant (NS)]. Typical RV and LV examples of EDPVRs acquired during a veno-cava occlusion are illustrated in Fig. 2A. Figure 3 depicts the average RV and LV EDPVRs for both groups. \( dP/dt_{min} \) was eightfold lower in the RV than in the LV (188 ± 44 vs. 1,590 ± 472 mmHg/s; \( P < 0.01 \)). We used the pressure decay during the time interval from \( dP/dt_{min} \) to the point where \( dP/dt \) reached 10% of \( dP/dt_{min} \) value to calculate \( \tau \) (Fig. 1). Longer (up to 5%) of \( dP/dt_{min} \) or shorter (20% or 30%) time intervals did not yield significantly different calculated \( \tau \) values. The onset of RV relaxation was delayed by 13 ms compared with the onset of LV relaxation, but this shift was not statistically significant (\( P = NS \)). \( \tau \) averaged 27.8 ± 3.8 ms in the RV and 40.1 ± 6.8 ms in the LV (\( P < 0.05 \)), indicating that isovolumic relaxation time during early diastole is shorter in the RV than in the LV. Despite its later onset, the period of RV isovolumic relaxation occurs completely within the period of LV isovolumic relaxation.

Load dependence of \( dP/dt_{min} \). In Table 2, the average slopes of the load dependence of \( dP/dt_{min} \) in the control group together with the average linear correlation coefficients \( (R^2) \) for the load dependence relationships in the RV and LV are listed. The average (±SD) slopes of these relationships represent a measure of sensitivity to changes in loading conditions. Figure 4 illustrates the average load dependence relationships of \( dP/dt_{min} \) in both ventricles. In the RV, positive and significant dependence of \( dP/dt_{min} \) with \( P_{ES} \) was found, i.e., as load decreases during caval occlusion, \( dP/dt_{min} \) also decreases. In the LV, similarly significant correlations were found, demonstrating \( dP/dt_{min} \) dependence on load in the normal RV as well as in the normal LV.

Load dependence of \( \tau \). Table 2 also shows the load dependence of \( \tau \) in the RV and LV of the control group, together with average \( R^2 \) in the RV and LV. Although the substantially lower \( R^2 \) value (0.54) in the control RV indicates a wider scatter in the RV data points, the load dependence in both ventricles was described by inverse linear relationships as illustrated by Fig. 5. The largest dependence of \( \tau \) on \( P_{ES} \) was found in the
control RV. In the control LV, the load dependence was lower by a factor of 4.

**PAB effects.** Chronic pressure overload resulted in considerable RV hypertrophy, characterized by a significant increase in the RV-to-LV wall thickness ratio from $0.43 \pm 0.04$ in the control group to $0.94 \pm 0.15$ in the banding group ($P < 0.01$). RV PES was $64 \pm 8$ mmHg in the PAB group, which was fivefold higher than in the control group ($12 \pm 3$ mmHg; $P < 0.01$). LV PES was not significantly different (control: $78 \pm 15$ mmHg, PAB: $66 \pm 13$ mmHg; $P = \text{NS}$). RV VED was unchanged (control: $37.7 \pm 6.7$ ml, PAB: $32.6 \pm 8.8$ ml; $P = \text{NS}$), whereas LV VED was smaller by a factor of 2 in the banding group (control: $51.1 \pm 14.4$ ml, PAB: $26.5 \pm 2.9$ ml; $P < 0.01$; Table 1). Both RV P ED (control: $4 \pm 3$ mmHg, PAB: $7 \pm 2$ mmHg; $P = \text{NS}$) and LV P ED (control: $6 \pm 2$ mmHg, PAB: $7 \pm 2$ mmHg; $P = \text{NS}$) were unchanged. Cardiac output was significantly lower in the PAB group (control: $2.6 \pm 0.8$ l/min, PAB: $1.6 \pm 0.3$ l/min; $P < 0.05$), whereas heart rate was unaffected ($117 \pm 29$ vs. $118 \pm 25$ beats/min).

**Table 1. Steady-state parameters**

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<tr>
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<th>Control</th>
<th>Banding</th>
<th>Banding Effect</th>
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<tr>
<td></td>
<td>LV</td>
<td>RV</td>
<td></td>
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<tr>
<td>PVED (ml)</td>
<td>$6 \pm 2$</td>
<td>$4 \pm 3$</td>
<td>$2.25$</td>
</tr>
<tr>
<td>VVED (ml)</td>
<td>$51.1 \pm 14.4$</td>
<td>$37.7 \pm 6.7$</td>
<td>$0.07$</td>
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<tr>
<td>$b$</td>
<td>$0.12 \pm 0.05$</td>
<td>$0.14 \pm 0.05$</td>
<td>$0.11$</td>
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<td>$dP/dt_{min}$</td>
<td>$1,590 \pm 472$</td>
<td>$188 \pm 44$</td>
<td>$&lt;0.01$</td>
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<tr>
<td>$\tau$</td>
<td>$40.1 \pm 6.8$</td>
<td>$27.8 \pm 3.8$</td>
<td>$&lt;0.05$</td>
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</table>

Values are means $\pm$ SD of steady-state parameters in the control and banding groups. $P$ values denote the statistical significances for the differences between left ventricular (LV) and right ventricular (RV) parameters within 1 group. Banding Effect denotes the statistical significances for the differences between the control and banding groups for each ventricle. PED, end-diastolic pressure (mmHg); VED, end-diastolic volume (ml); $b$, chamber stiffness constant (ml$^{-1}$); $dP/dt_{min}$, minimum first derivative of pressure vs. time (mmHg/s); $\tau$, time constant of isovolumic relaxation (ms).

![Fig. 2](http://ajpheart.physiology.org/). Typical examples of end-diastolic pressure-volume relationships (EDPVRs) of 1 animal in the left ventricle (LV; left) and the RV (right) in the control (A) and banding (B) groups, obtained by fitting the individual data points to a monoexponential function with variable asymptote. In each panel, the rightmost data point represents the steady-state value and the other data points were found during gradual preload reduction. Note that the scale on the volume axis is not identical in the 4 examples.
Table 2. Load dependencies of dP/dt_{min} and τ

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>P</th>
<th>Banding</th>
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<th>Banding Effect</th>
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<td></td>
<td>LV</td>
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<td></td>
<td>LV</td>
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<tr>
<td>Slope</td>
<td>21.1 ± 10.4</td>
<td>13.7 ± 1.9</td>
<td>0.15</td>
<td>24.0 ± 2.5</td>
<td>13.0 ± 4.4</td>
<td>&lt;0.01</td>
<td>0.56</td>
</tr>
<tr>
<td>R^2</td>
<td>0.85 ± 0.18</td>
<td>0.91 ± 0.15</td>
<td></td>
<td>0.91 ± 0.04</td>
<td>0.95 ± 0.03</td>
<td></td>
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<tr>
<td>τ</td>
<td>−0.6 ± 1.0</td>
<td>−2.3 ± 1.4</td>
<td>&lt;0.05</td>
<td>−1.2 ± 1.1</td>
<td>−0.6 ± 0.5</td>
<td>0.08</td>
<td>0.37</td>
</tr>
<tr>
<td>R^2</td>
<td>0.73 ± 0.27</td>
<td>0.54 ± 0.14</td>
<td>&lt;0.05</td>
<td>0.70 ± 0.17</td>
<td>0.70 ± 0.13</td>
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Values are means ± SD of LV and RV dP/dt_{min} and τ characteristics in the control and banding groups. Banding Effect denotes the statistical significance (P-value) for the difference between the control and banding groups for each ventricle. Slope describes the relationship of dP/dt_{min} (s^{-1}) or τ (ms/mmHg) with load, respectively. R^2, linear correlation coefficient of the associated average relationship.

In the RV, banding significantly increased the average b value (control: 0.14 ± 0.05 ml^{-1}, PAB: 0.25 ± 0.09 ml^{-1}; P < 0.05; Table 1) as illustrated in Fig. 3. Also, in the LV, b was significantly higher in the banding group than in the control group (control: 0.12 ± 0.05 ml^{-1}, PAB: 0.37 ± 0.18 ml^{-1}; P < 0.05; Table 1). Typical examples of biventricular EDPVRs before and after banding are shown in Fig. 2.

RV dP/dt_{min} was significantly higher in the PAB group than in the control group (control: 188 ± 44 mmHg/s, PAB: 725 ± 224 mmHg/s; P < 0.01), whereas in the LV dP/dt_{min} tended to be lower (control: 1,590 ± 472 mmHg/s, PAB: 1,094 ± 230 mmHg/s; P = 0.07; Table 1). Whereas in the control group RV dP/dt_{min} was significantly lower than LV dP/dt_{min}, in the banding group the difference between the RV and LV dP/dt_{min} was just not significant (P = 0.06).

Table 2 shows the average slopes of the relationships of dP/dt_{min} with load for both ventricles in the banding group, together with the average R^2. The average slopes of these relations in the RV and LV were all significantly different from zero, indicating that, just as in the control group, in the banding group dP/dt_{min} was significantly dependent on load. Strikingly, the average slopes, both for the RV and the LV, hardly differed between the two groups, indicating that the
CHRONIC RV PRESSURE OVERLOAD AND DIASTOLIC FUNCTION

In this study we determined indexes of diastolic function, which are commonly used for LV analysis, in the normal and chronic pressure-overloaded RV. Because diastole is characterized by a complex set of separate but interrelated phases (i.e., relaxation, filling, and end diastole), its function cannot be described by a single parameter (27). Evaluation of the time course of pressure fall during isovolumic relaxation provides an important measure of early diastolic performance and can be described by the peak rate of pressure decline (dP/dt_{min}) and the time constant of isovolumic pressure decay (τ). At the end of diastole, when relaxation is complete and filling has ended, passive chamber properties can be adequately described by the EDPVR and characterized in particular by the chamber stiffness constant b (20, 28, 32). Our results demonstrate that both dP/dt_{min} and τ are lower in the normal RV than in the normal LV whereas diastolic stiffness is similar in both ventricles. We have also demonstrated that, as in the LV, in the normal RV dP/dt_{min} is strongly dependent on load. In addition, τ was found to be dependent on load in the normal RV, just as has been reported for the normal LV (15, 19, 33, 42).

Chronic RV pressure overload at the systemic level resulted in significantly increased RV pressure development and RV wall thickness, whereas cardiac output was significantly decreased compared with the control group. Banding resulted in a significantly prolonged RV τ and increased diastolic RV stiffness, both of which are most likely related to hypertrophy of the RV wall. Banding did not result in a prolonged RV systolic time interval but in a decreased LV systolic time interval compared with the control group.

As illustrated in Fig. 4, in the PAB group RV dP/dt_{min} was considerably higher than in control, but this was directly related to the increased pressure in the banding group through the established load dependence. τ was also prolonged in response to chronic pressure overload but, as shown in Fig. 5, this cannot be explained by its load dependence because the relationships differ substantially in slope and position.

Figure 3 illustrates that in response to chronic RV pressure overload, the stiffness of both ventricles is increased. The leftward shift of the EDPVR in the LV and the upward shift in the RV are both consistent with decreased chamber compliance. The two average RV EDPVRs in Fig. 3A show that the same level of filling can be reached only at the expense of an increase in PED. In the LV, the large decrease in volume indicates substantial remodeling: the same PED is reached at a much smaller V_{ED}.

Fig. 5. Representation of the average τ-P_{ES} relationships in the RV and LV of both groups. The rightmost point of each relationship represents the average (±SD) steady-state τ and P_{ES} values. Black lines represent the control group, and gray lines indicate the banding group. Solid lines indicate the RV, and gray lines indicate the LV. For all 4 relations, preload reduction results in an increase in τ, indicating an inverse load dependence. Note that preload reduction in the RV of the banding group results in a τ-P_{ES} relationship widely different from the relationship in the control group, indicating that the increase of τ in the banding group cannot be explained by the load dependence.

relationship between dP/dt_{min} and P_{ES} is unaffected by PAB. Figure 4 clearly shows that the RV dP/dt_{min}-P_{ES} relationships in both groups are in line with each other, from which it can be concluded that the strongly increased RV dP/dt_{min} value in the banding group is a direct result of the increased P_{ES} rather than being the result of intrinsic myocardial changes.

In response to PAB, average τ increased in the RV (control: 27.8 ± 3.8 ms, PAB: 44.4 ± 15.8 ms; P < 0.05) whereas in the LV (control 40.1 ± 6.8 ms, PAB: 47.6 ± 13.2 ms; P = NS) the increase was not significant (Table 1). In contrast to the control group, τ did not differ significantly between the RV and the LV in the banding group (P = NS).

The onset of isovolumic relaxation in the RV was significantly delayed by 29 ms compared with the onset of LV isovolumic relaxation (P < 0.05), and RV isovolumic relaxation extended beyond the period of LV isovolumic relaxation. Analysis of the duration of the systolic time interval revealed that the RV systolic interval was not prolonged but that LV systole ended earlier compared with that in the control group.

Table 2 also illustrates the average slopes of the τ-P_{ES} relationships for both ventricles in the banding group together with the average R^2. The load dependence of τ in the RV decreased (control: -2.3 ± 1.4 ms/mmHg, PAB: -0.6 ± 0.5 ms/mmHg; P < 0.05), whereas in the LV the load dependence showed a tendency to increase after PAB (control: -0.6 ± 1.0 ms/mmHg, PAB: -1.2 ± 1.1 ms/mmHg; P = NS). Despite these differences between both ventricles, the dependence in the PAB group was similar to that in the control group, i.e., as P_{ES} decreased, τ increased. Figure 5 summarizes the two changes that take place after PAB: first, the upward displacement of the RV τ-P_{ES} relationship as τ is increased after PAB and second, the decrease in slope of the dependence relationship. The rightward shift of the RV load dependence relationship in the control group is not surprising, because it was imposed by our study design.

DISCUSSION

In this study we determined indexes of diastolic function, which are commonly used for LV analysis, in the normal and chronic pressure-overloaded RV. Because diastole is characterized by a complex set of separate but interrelated phases (i.e., relaxation, filling, and end diastole), its function cannot be described by a single parameter (27). Evaluation of the time course of pressure fall during isovolumic relaxation provides an important measure of early diastolic performance and can be described by the peak rate of pressure decline (dP/dt_{min}) and the time constant of isovolumic pressure decay (τ). At the end of diastole, when relaxation is complete and filling has ended, passive chamber properties can be adequately described by the EDPVR and characterized in particular by the chamber stiffness constant b (20, 28, 32). Our results demonstrate that both dP/dt_{min} and τ are lower in the normal RV than in the normal LV whereas diastolic stiffness is similar in both ventricles. We have also demonstrated that, as in the LV, in the normal RV dP/dt_{min} is strongly dependent on load. In addition, τ was found to be dependent on load in the normal RV, just as has been reported for the normal LV (15, 19, 33, 42).

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These diastolic abnormalities are very likely related to changes in RV wall thickness and in biventricular geometry and may, in part, be responsible for the lower stroke volume (cardiac output) in the PAB group because biventricular filling is hampered by increased stiffness. These average EDPVRs also illustrate their direct clinical applicability: therapeutic administration of fluids to increase cardiac output in the banded hearts will result in a large increase in biventricular PED that will lead, via impaired filling, to a state of backward failure.

The number of reports concerning determination of diastolic parameters in the RV is scant. Darsinos et al. (8) reported that only quantitative differences exist in the behavior of dP/dt\textsubscript{min} between the human LV and RV, i.e., the higher dP/dt\textsubscript{min} value in the LV is a direct result of the higher LV pressure. Consistent with our findings, Stein et al. (38) found a significantly higher RV dP/dt\textsubscript{min} in patients with pressure-overloaded RVs than in healthy controls (670 ± 60 vs. 170 ± 20 mmHg/s). It is remarkable, however, that despite similar RV and LV pressures in the banding group (64 ± 8 and 66 ± 13 mmHg, respectively), dP/dt\textsubscript{min} still tends to be lower in the RV than in the LV. This finding suggests that besides ventricular pressure, another as yet unknown factor may influence the size of dP/dt\textsubscript{min}.

We studied the behavior of dP/dt\textsubscript{min} during the same preload reduction used to obtain the EDPVR in normal and pressure-overloaded RVs and found that, similar to its behavior in the LV, the increased RV dP/dt\textsubscript{min} value after banding can be explained almost totally by the increased RV pressure. Table 2 and Fig. 4 illustrate that the two average slopes of the dP/dt\textsubscript{min}-P\textsubscript{ES} relationships (in control and PAB) are practically identical, strongly suggesting that the dP/dt\textsubscript{min}-P\textsubscript{ES} relationships in the control and banding group are the same. Thus, although dP/dt\textsubscript{min} indicates a faster initial pressure drop as load increases, it does not adequately reflect changes in myocardial diastolic properties after chronic pressure overload. Therefore, dP/dt\textsubscript{min} should not be used for the analysis of ventricular diastolic function, at least not without taking into account its load dependence.

A tight coupling between contraction and relaxation was recently shown in patients undergoing coronary artery bypass surgery (9). To see whether a relationship exists between the size of dP/dt\textsubscript{min} and a measure of systolic function, we correlated the dP/dt\textsubscript{min} data with previous measurements of end-systolic elastance and dP/dt\textsubscript{max} (24). In both cases, good correlations were obtained (R\textsuperscript{2} = 0.95, P < 0.001 and R\textsuperscript{2} = 0.80, P < 0.001, respectively), indicating that dP/dt\textsubscript{min} reflects intrinsic contractile function.

The second parameter obtained during active myocardial relaxation is τ. Previous attempts to determine τ in the RV were hampered by the finding that dP/dt\textsubscript{min}, often used as a starting point for the calculation of τ, in the RV occurred relatively late on the downstroke of ventricular pressure (38). These authors argued that τ would represent only a small portion of the isovolumic relaxation period and could not, therefore, be measured reliably in the RV (38). This may well be related to the hypothesis that RV relaxation begins soon after maximal pressure has been reached, i.e., long before end ejection, quite unlike what is found in the LV. This is also evident in the behavior of RV dP/dt, which, unlike in the LV, becomes negative early during ejection (Fig. 1). Although our results also suggested that dP/dt\textsubscript{min} in the RV occurred at a later time than in the LV, the isovolumic period in the RV over which τ was calculated averaged 57 ± 11 ms in the control group and 66 ± 16 ms in the banding group. With a sample frequency of 250 Hz, the number of data points was sufficient (15 ± 4 and 17 ± 5 before and after PAB, respectively) to justify an exponential fit through these data points to calculate τ in the RV. Nevertheless, the accuracy of determining τ in the RV is lower than in the LV as exemplified by the larger scatter of data points and lower correlation coefficients when its value is plotted during load intervention.

τ might expectedly be influenced by chronic RV pressure overload. Chen et al. (6) created pulmonary hypertension in dogs by injection of monocrotaline. This resulted in severe RV hypertrophy after a period of 8 wk. In the RV, they found a significantly prolonged τ as well as increased b, indicating impaired RV diastolic function. Similar increases in RV τ were found by Maeda et al. (31), who studied RV diastolic function in patients with hypertrophic cardiomyopathy. These findings are comparable to our findings of increased RV τ and b. However, to our knowledge, load dependence of τ has not been studied before in the RV.

Recently, two groups of investigators found a nonlinear and biphasic relationship between τ and systolic load in the normal canine LV (26, 33). In the rabbit heart, the biphasic character was less pronounced (25). Although in this study we did find an inverse relationship between τ and systolic load, it was linear rather than biphasic, which may be related to species differences.

The systolic pressure of the banded RV in our study is, by design, similar to that of the normal LV. But does the banded RV also function as a normal LV? According to several parameters in this study (i.e., wall thickness, V\textsubscript{ED}, P\textsubscript{ES}, dP/dt\textsubscript{min}, τ), it appears that the banded RV bears more resemblance to the LV of the banding group than to the normal LV. Despite similar wall thickness, diastolic stiffness in the RV of the banding group is higher by a factor of 2 than that of the normal LV. Although we do not have specific data regarding the septal geometry and geometry of the LV in terms of septal-to-free wall distance and apex-to-base distance, several studies indicate that as result of a chronic RV pressure overload (and thus decreased septal pressure gradient), the septum is displaced toward the LV (12, 21). In addition, the septal-to-LV free wall distance is found to be decreased. A chronic study in open-pericardium dogs has shown that chronic RV pressure overload changed LV geometry into a more "spherical" shape in the sense that the ratio between measured anterior-posterior short-axis dimension and base-apex long-axis dimension is increased, whereas LV chamber...
stiffness is decreased (40). Whether similar geometric changes can also explain our findings of increased chamber stiffness remains speculative.

Study limitations. In this study, early and late filling parameters (i.e., the E and A peaks of flow during filling) were not measured because these would require differentiation of the conductance volume signals, which has not been validated so far, especially for the RV. Second, instead of occluding the PA acutely to increase RV afterload (which would have been practically impossible in the banded animals), we used the decrease in afterload, which is a concomitant result of the decrease in preload, to study the load dependence, an approach also used by Prabhu (33) and Ishizaka et al. (19). Moreover, separating a change in preload from that in afterload is virtually impossible in the intact circulation. Third, after careful consideration, we decided not to perform a sham operation in the control group. Because we studied ventricular function after a period of 8 wk, we consider it highly unlikely that placement of a small pressure line into the RV free wall affects ventricular function after this period. During the second operation, pericardial adhesions in the banding group were completely removed and the heart was exposed again in a pericardial cradle. Furthermore, it was shown previously that cardiovascular function in lambs had completely recovered after thoracotomy as soon as 3 days postoperatively (35). It does not appear to be justified to subject healthy animals to a thoracotomy when the effects of the operation are not expected until after 8 wk on cardiac function. Finally, the absence of the pericardium may have confounded our results. However, pericardiotomy-related ventricular dilatation (or absence of pericardial constraint) did not occur in our study because ventricular volume of both ventricles in the banding group remained fairly constant.

In conclusion, we have found that in the normal heart biventricular dP/dt<sub>min</sub> and τ are both dependent on load. Chronic RV pressure overload at systemic level results in changes in diastolic function, characterized by increased dP/dt<sub>min</sub>, prolonged τ, and decreased chamber compliance of both ventricles. However, the increased dP/dt<sub>min</sub> in the banding group can be explained by the increased systolic pressure alone (load dependence of dP/dt<sub>min</sub>) and has, therefore, limited applicability as a parameter of early diastolic relaxation. In contrast, despite its load dependence, τ seems to be a more suitable parameter to evaluate early diastolic relaxation in the RV. The EDPVR can be used to assess the passive properties of the ventricle at end diastole in the RV. Changes in this relationship, for the RV and even more so in the LV, are characteristic for decreased biventricular compliance and thus are likely to contribute importantly to reduced pump function in the chronic PAB situation.

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