Right Atrial and Ventricular Adaptation to Chronic Right Ventricular Pressure Overload

Sydney L. Gaynor, MD; Hersh S. Maniar, MD; Jeffrey B. Bloch; Paul Steendijk, PhD; Marc R. Moon, MD

Background—Increased mortality in patients with chronic pulmonary hypertension has been associated with elevated right atrial (RA) pressure. However, little is known about the effects of chronic right ventricular (RV) pressure overload on RA and RV dynamics or the adaptive response of the right atrium to maintain RV filling.

Methods and Results—In 7 dogs, RA and RV pressure and volume (conductance catheter) were recorded at baseline and after 3 months of progressive pulmonary artery banding. RA and RV elastance (contractility) and diastolic stiffness were calculated, and RA reservoir and conduit function were quantified as RA inflow with the tricuspid valve closed versus open, respectively. With chronic pulmonary artery banding, systolic RV pressure increased from 34±7 to 70±17 mm Hg (P<0.001), but cardiac output did not change (P>0.78). RV elastance and stiffness both increased (P<0.05), suggesting preserved systolic function but impaired diastolic function. In response, RA contractility improved (elastance increased from 0.28±0.12 to 0.44±0.13 mm Hg/mL; P<0.04), and the atrium became more distensible, as evidenced by increased reservoir function (49±14% versus 72±8%) and decreased conduit function (51±14% versus 28±8%; P<0.002).

Conclusions—With chronic RV pressure overload, RV systolic function was preserved, but diastolic function was impaired. To compensate, RA contractility increased, and the atrium became more distensible to maintain filling of the stiffened ventricle. This compensatory response of the right atrium likely plays an important role in preventing clinical failure in chronic pulmonary hypertension. (Circulation. 2005;112[suppl I]:I-212–I-218.)

Key Words: atrium ● hypertension, pulmonary ● pulmonary heart disease

Chronic pulmonary hypertension (CPH) is a devastating disease. With relentless progression, initial symptoms of mild dyspnea and fatigue culminate in right heart failure and death in the majority of patients. Increased mortality has been associated with elevated right atrial (RA) pressure;1,2 however, little is known about the effects of chronic pulmonary hypertension on RA dynamics or the compensatory response of the right atrium to persistent right ventricular (RV) pressure overload. Previous investigators have shown that RV systolic function is initially preserved with RV pressure overload, but diastolic dysfunction occurs as a consequence of myocardial hypertrophy and remodeling.3–7 With time, as the ventricle thickens, RV filling becomes more dependent on RA performance, which, if impaired, will lead to right heart failure.

Historically, the right atrium has been difficult to study because of its amorphous architecture and the complex interplay that occurs among the atrium, ventricle, and systemic and coronary venous circulation during both systole and diastole. Therefore, studies evaluating both normal and pathophysiologic RA mechanics are limited.8–12 and the impact of CPH on RA function remains unknown. If the right atrium is more sensitive to CPH than the ventricle, unfavorable changes in compliance may impair RV filling, but if the atrium is less sensitive than the ventricle, changes in compliance may be protective as the atrium compensates to maintain cardiac output. In an elegant computer model, Sugii13 suggested that atrial distensibility may substantially influence cardiac performance, but our understanding of this relationship under pathologic conditions is limited. The purpose of the current investigation was to use conductance technology to study RA and RV function simultaneously during chronic RV pressure loading to determine the pathophysiologic sequelae of CPH that portend right heart failure.

Methods

Initial Surgical Preparation
Seven adult dogs of either sex (20 to 25 kg) were anesthetized with propofol (5 to 7 mg/kg IV) and intubated and ventilated (Siemens) with supplemental inhalational isoflurane (2% to 3%). Animals were monitored continuously throughout the procedure with pulse oximetry, surface ECG, and frequent arterial blood gases. Supplemental oxygen and sodium bicarbonate were administered as necessary to maintain a normal acid-base balance and arterial oxygen tension between 100 and 200 mm Hg, and a table warmer was used to ensure...
normothermia. Micromanometer-tipped pressure catheters (Millar Instruments, Inc) were zeroed in a 37°C water bath for 30 minutes before insertion. A median sternotomy was performed, leaving the pericardium intact. A 7-Fr pressure catheter (Millar MPC-500) was advanced through the left mammary artery to the arch to record central aortic pressure. Ultrasonic flow probes (10- to 12-mm perivascular probes with a T206 Flowmeter, Transonic Systems) were placed around the superior (SVC) and inferior (IVC) vena cava ~1 cm from the caval-atrial junction to measure RA inflow. A tonourset was positioned around the IVC to allow transient caval occlusion (preload alteration during data collection). A 1-cm incision was made in the pericardium over the anterior RV free wall, and a 6-Fr combined pressure volume (PV) conductance catheter (Millar SPR-843) was introduced through a purse-string suture just below the pulmonary valve and positioned toward the apex. The RV catheter measured RV pressure (RVP) and RV chamber conductance using dual-field technology with 10 electrodes 4 mm apart. A second 1-cm incision was made in the pericardium over the RA appendage, and a 5-Fr combined PV conductance catheter (Millar SPR-766) was positioned along the long axis of the right atrium so that its tip rested at the RA-IVC junction. The RA catheter measured RA pressure (RAP) and RA chamber conductance using dual-field technology with 10 electrodes 4 mm apart. These catheters were connected to 2 signal conditioner processors (Sigma 5DF, CD Leycom) to convert instantaneous conductance signals were acquired at 200 Hz and processed using custom-designed computer software. The RAP and RVP signals were differentiated with respect to time to calculate instantaneous RA dp/dt and RV dp/dt. To minimize the effects of intrathoracic pressure variation, the respirator was temporarily interrupted at end expiration during data collection for 10 to 15 seconds. Initially, hypertonic saline (3 mL, 10% solution) was injected into the cephalic vein and PV loops recorded for 15 to 20 seconds to determine RA and RV parallel conductance and calibrate volume calculations (see below). Then, after steady-state data were obtained (3 to 5 beats), slow, progressive vena cava occlusion was performed to generate RA and RV PV loops over a wide physiological range of filling pressures. Data acquisition runs were repeated in triplicate, and all of the runs containing premature ventricular contractions were excluded from future analysis. Sufficient time was allowed between runs for hemodynamic stabilization (2 to 4 minutes).

Baseline Data Acquisition
Baseline data were recorded during steady-state conditions with the pericardium intact. During each data acquisition run, ECG, RAP, RVP, aortic pressure, SVC flow, IVC flow, and RA and RV conductance signals were acquired at 200 Hz and processed using custom-designed computer software. The RAP and RVP signals were differentiated with respect to time to calculate instantaneous RA dp/dt and RV dp/dt. To minimize the effects of intrathoracic pressure variation, the respirator was temporarily interrupted at end expiration during data collection for 10 to 15 seconds. Initially, hypertonic saline (3 mL, 10% solution) was injected into the cephalic vein and PV loops recorded for 15 to 20 seconds to determine RA and RV parallel conductance and calibrate volume calculations (see below). Then, after steady-state data were obtained (3 to 5 beats), slow, progressive vena cava occlusion was performed to generate RA and RV PV loops over a wide physiological range of filling pressures. Data acquisition runs were repeated in triplicate, and all of the runs containing premature ventricular contractions were excluded from future analysis. Sufficient time was allowed between runs for hemodynamic stabilization (2 to 4 minutes).

Creation of Chronic RVP Overload
Following baseline data collection, the RA and RV PV catheters were removed, and a 5-Fr pressure catheter (Access Technologies) was introduced into the RV-free wall and secured in place. An inflatable silastic band (16-mm diameter, Access Technologies) was secured around the distal main pulmonary artery (PA). The PA band and RVP catheters were tunneled through the left and right lateral chest walls, respectively, and connected to small reservoirs covered with silicone membranes that allowed injection of saline and pressure monitoring. Each reservoir was buried in a subcutaneous pocket. The sternum was reapproximated with wires, and the overlying soft tissue was closed in layers after placing a 28-Fr chest tube for drainage. Approximately 1 week after the baseline operation, when the animal was fully recovered, RVP overload was initiated in a stepwise manner with progressive inflation of the PA band via saline injection into its reservoir. With the animals resting comfortably, RVP was monitored by connecting its reservoir to a pressure transducer. Approximately 0.3 to 0.5 mL of saline was injected into the PA band reservoir to increase inflation. Inflation of the PA band was performed weekly, increasing RVP by 10 to 20 mm Hg at each inflation until near-systemic pressures were achieved. The RVP reservoir was flushed with heparinized saline to prevent clotting between inflation intervals.

Data Acquisition after Creation of Chronic RVP Overload
Animals underwent a second data acquisition study an average of 101 ± 44 days after the initial baseline study. Animals were again anesthetized with propofol for induction (5 to 7 mg/kg IV) and intubated and ventilated using propofol for maintenance (0.5 mg/kg/min). A repeat median sternotomy was performed to access the heart. The pericardium was again left intact except for 2 small openings to allow placement of the RA and RV PV catheters. Hypertonic saline injection was again performed to determine RA and RV parallel conductance and calibrate volume measurements. Data were then collected as described above during steady-state conditions with slow IVC occlusion to alter preload and repeated in triplicate.

At the conclusion of the experiment, the animals were euthanized using sodium pentothal (1 g IV) followed (after 2 minutes) by potassium chloride (80 meq IV), and proper positioning of the catheters was confirmed. All of the animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health. The study was approved by the Washington University School of Medicine Animal Studies Committee and conducted according to Washington University policy.

Data Analysis
RA and RV Volume
Instantaneous RA and RV volumes were determined using the conductance catheter methods as described previously. Relative RA and RV volumes were converted into absolute RA and RV volumes by subtracting Vc, the parallel conductance factor, and multiplying by α, the conductance gain factor. The parallel conductance factor, Vc, which accounts for conductance of the surrounding structures, was calculated for both chambers using the PV loops created during injection of hypertonic saline. The conductance gain factor, α, was determined for the RV by comparing uncalibrated conductance catheter values to stroke volumes obtained by integrating RA inflow throughout the cardiac cycle. For the RA, stroke volumes were compared only during RA filling, when the tricuspid valve was closed. Changes in RA chamber volume do not equal RA inflow when the valve is open because of direct caval flow into the ventricle. Separate values were obtained for Vc and α during the baseline and chronic studies.

RA Elastance (Contractility)
RA contractile performance was assessed using the “atrial-end-systolic” pressure-volume relationship (RA-ESPVR, chamber elastance). Atrial-end-systolic pressure (RAPα,ES) and volume (RA-Volα,ES) points were determined for each cardiac cycle during preload reduction, and, by least-squares linear regression, a straight line was fitted to the following equation:

\[ RAPα,ES = Eα,ES \cdot (RA-Volα,ES - V0) \]

where Eα,ES (mm Hg/mL) and V0 (mL) are the slope (RA chamber elastance) and volume-axis intercept, respectively.

RA Stiffness
Static RA stiffness was defined as the slope of the “atrial-end-diastolic” P-V relation. Atrial-end-diastolic pressure (RAPα,ED) and volume (RA-Volα,ED) points were determined at the time of maximum RA volume (corresponding to tricuspid valve opening and the RAP V-wave) for each cardiac cycle during preload reduction. By
Figure 1. Typical hemodynamic data obtained during baseline and with chronic RVP overload (PA banding). Three steady-state beats are illustrated. The reservoir phase extends from the ECG R-wave to the time of maximum RA volume (corresponding with tricuspid valve opening). The conduit phase extends from the time of maximum RA volume to the end of RV filling (the subsequent ECG R-wave).

Baseline

Chronic PA Banding

steep-state hemodynamic changes for all of the animals. With chronic PA banding, maximum RVP doubled from 34±7 mm Hg to 70±17 mm Hg (P<0.001), but there was no change in minimum RVP (P>0.24), mean RAP (P>0.46), mean aortic pressure (P>0.46), heart rate (P>0.27), stroke volume (total RA inflow; P>0.55), or cardiac output (P>0.31). There was no change in maximum RV (P>0.94) or RA (P>0.40) volume. Maximum RVP dP/dt tended to rise (P<0.06), but maximum RAP dP/dt did not significantly change (P>0.32).

Typical RV PV loops during baseline and with chronic PA banding are illustrated in Figure 2 (same animal as depicted in Figure 1). Overall, with PA banding, RV elastance (contractility) increased from 0.48±0.17 to 1.65±0.68 mm Hg/mL (P<0.004) without a significant change in RV V0 (P>0.41) (Table 2 and Figure 3). Similarly, RV stiffness rose from 0.12±0.04 to 0.26±0.16 mm Hg/mL (P<0.05) but RV V Ed did not change (P>0.43).

Typical RA PV loops during baseline and with chronic PA banding are illustrated in Figure 4 (same animal as depicted in Figures 1 and 2). Overall, with PA banding, RA elastance

Table 1. Hemodynamic Effects of Chronic PA Banding

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Chronic PA Banding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>107±17</td>
<td>126±31</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>63±12</td>
<td>70±20</td>
</tr>
<tr>
<td>Maximum RV pressure (mm Hg)</td>
<td>34±7</td>
<td>70±17*</td>
</tr>
<tr>
<td>Minimum RV pressure (mm Hg)</td>
<td>9±5</td>
<td>7±3</td>
</tr>
<tr>
<td>Mean RA pressure (mm Hg)</td>
<td>7±2</td>
<td>8±5</td>
</tr>
<tr>
<td>Maximum RV volume (mL)</td>
<td>56±13</td>
<td>57±27</td>
</tr>
<tr>
<td>Maximum RA volume (mL)</td>
<td>33±13</td>
<td>28±13</td>
</tr>
<tr>
<td>Maximum RV dP/dt (mm Hg/s)</td>
<td>554±143</td>
<td>1077±647*</td>
</tr>
<tr>
<td>Maximum RA dP/dt (mm Hg/s)</td>
<td>55±17</td>
<td>82±55</td>
</tr>
<tr>
<td>Total RA inflow (mL/beat)</td>
<td>22±5</td>
<td>20±7</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>2.4±0.6</td>
<td>2.5±0.7</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.05 (Student t test).

Results

Figure 1 illustrates typical hemodynamic changes from 1 animal with chronic PA banding, and Table 1 summarizes the
(contractility) increased from 0.28±0.12 to 0.44±0.13 mm Hg/mL (P<0.04) without a significant change in RA V₀ (P>0.72) (Table 3 and Figure 5). Unlike the ventricle, there was not a significant change in RA stiffness (P>0.63) or RA Vₑₑₑₑ (P>0.17) with chronic PA banding.

Figure 1 illustrates typical changes in reservoir and conduit function with chronic PA banding. During RV systole, when the tricuspid valve was closed, RA inflow increased from 11±4 to 15±4 mL, corresponding with increased prominence of the RA inflow curve during the reservoir phase, but the change was not significant (P>0.24). However, during RV filling, when the tricuspid valve was open, RV inflow fell significantly from 11±4 to 5±4 mL (P<0.005), corresponding with flattening of the RA inflow curve during the conduit phase. Thus, with chronic PA banding, atrial distensibility increased as evidenced by a significant rise in reservoir function from 49±14% to 72±8% and a corresponding decline in conduit function from 51±14% to 28±8% (P<0.002) (Figure 6).

**Discussion**

The current study demonstrated that the RV compensatory response to chronic pressure overload is one of increased contractility but impaired diastolic function. Interestingly, there was no significant change in cardiac output with chronic PA banding when compared with baseline (2.4 versus 2.5 L/min; P>0.31). This is in contrast to Leeuwenburgh et al who reported a fall in cardiac output with chronic PA banding, despite a similar increase in RV contractility in young lambs. It is important to note, however, that the hypertrophic response to pressure overload is different in newborns than it is in adults. Assey et al found in humans with congenital aortic stenosis that LV wall stress remained low, even when the obstruction to flow persisted into adulthood. This is in contrast to the significant rise in wall stress they noted in subjects with adult-acquired aortic stenosis. Other reports in full-grown animals have shown that cardiac output is maintained during chronic RVP overload, as it was in the current report.

Studies examining RV function during acute RVP overload consistently report no significant change in RV diastolic performance, despite a 2- to 3-fold rise in RV elastance. However, with chronic RVP overload, RV diastolic dysfunction with prolonged diastolic relaxation times and increased RV diastolic stiffness is the norm. This is consistent with the 117% rise in RV diastolic stiffness measured in the current report. It has been proposed that in the acute setting, contractility increases through homeometric autoregulation without effecting diastolic function. But in the chronic setting, although pressure-induced ventricular hypertrophy continues to support increased RV contractile force, its effects on diastolic compliance and function may be detrimental. Furthermore, the in-series impact of these potentially negative RV diastolic changes suggests that RV filling becomes more dependent on RA function as RVP overload persists. If the atrium does not respond, cardiac output will likely fall, and clinical failure will manifest.

Focusing specifically on the right atrium in an earlier report from our laboratory, we measured a 33% rise in RA elastance and a 45% rise in RA diastolic stiffness during acute overload.
RVP overload. In the current report, the RA compensatory response to chronic RVP overload again included an increase in RA contractility as was the case for the ventricle, but unlike the acute setting, there was no longer a significant rise in RA diastolic stiffness, with the atrium acting more as a reservoir than a conduit. In an elegant computer model, Suga found that increased atrial compliance improved cardiac performance and concluded that a “flexible atrium” (increased receptacle capabilities) could substantially improve global cardiac output.

Exploring the impact of various hemodynamic interventions on RA reservoir and conduit function, we previously found in normal hearts that cardiac output was inversely related to the conduit:reservoir ratio in normal hearts. An increase in the reservoir contribution was associated with a higher cardiac output. In our previous report with acute RVP overload, we noted only a modest 8% rise in reservoir function from 56% to 64%, which did not reach statistical significance (P=0.09). However, in the current study, there was a substantial 23% rise in reservoir function from 49% at baseline to 72% with chronic RVP overload, consistent with the increase in atrial distensibility that others predicted would have a positive impact on cardiac output. Future histologic and biochemical studies will be necessary to elucidate the structural remodeling and receptor changes that are responsible for the adaptive physiological RA changes that allow it to both increase its contractile force and alter its distensibility.

Consistent with previous reports, heart rate did not change with chronic RVP overload in the current investigation. In addition, others have demonstrated that gradual PA banding can produce RVP overload without activation of the sympathetic nervous system or systemic renin-angiotensin system. These findings suggest that sympathetic stimulation is not the mechanism responsible for enhanced RV systolic performance in this setting. Chen et al noted increased α1- and β-adrenergic receptor density in dogs with pulmonary hypertension, both of which contribute significantly to the hypertrophic response of adult myocardium to stress and may, in part, play a role in the genesis of increased RV contractile force.

In an attempt to pharmacologically manipulate the adrenergic response of the right ventricle to chronic pressure overload, Hon et al administered Clenbuterol, a selective β2-adrenergic receptor agonist that has been shown to induce cardiac hypertrophy in rats, to sheep undergoing chronic PA banding. The Clenbuterol group demonstrated a 5-fold greater rise in RV elastance (212% increase over baseline) compared with control sheep that did not receive the drug during banding (43% increase over baseline). Hon et al, however, did not examine the effects of stimulated hypertrophy on RV diastolic properties nor its impact on the ability of the right atrium to become more distensible. Furthermore, despite the 5-fold increase in contractile force with Clenbuterol, there was no change in cardiac output in either group. It is possible that detrimental changes in the diastolic properties of the right ventricle and atrium could make pharmacologically stimulated hypertrophy less desirable long-term.

**Proposed Mechanism**

Little is known about the effects of chronic RVP overload on the right atrium and the pathophysiological changes that occur. In

<table>
<thead>
<tr>
<th>TABLE 3. Effects of Chronic PA Banding on RA Elastance (Contractility) and Chamber Stiffness</th>
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<tbody>
<tr>
<td><strong>Variables</strong></td>
</tr>
<tr>
<td>RA elastance (mm Hg/mL)</td>
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<tr>
<td>RA V0 (mL)</td>
</tr>
<tr>
<td>Correlation coefficient (r²)</td>
</tr>
<tr>
<td>RA stiffness (mm Hg/mL)</td>
</tr>
<tr>
<td>RA V10 (mL)</td>
</tr>
<tr>
<td>Correlation coefficient (r²)</td>
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*P<0.05 (Student t test).
previous studies on the left atrium where left ventricular failure was induced by pacing, Hoit et al\textsuperscript{33} found that there was significant up-regulation of $\beta$-myosin heavy chain (MHC) in the body of the left atrium in response to chronic pressure and volume overload. This isoform ($\beta$-MHC) is associated with left atrial hypertrophy, increased atrial mechanical work, maintained force generation (maximum and end systolic elastance), and decreased velocity of left atrial contraction. In their study, they found that there was a transition from fast ($\alpha$) to slow ($\beta$) MHC isoform. It is believed that this was a physiologically important adaptation of the left atrium to pressure and volume overload.\textsuperscript{33}

The pathological changes that occur in the hypertrophied ventricle have been well described. These changes include early diastolic dysfunction followed by systolic impairment, interstitial fibrosis, and down-regulation of calcium-handling proteins sarcoplasmic reticulum Ca$^{2+}$-ATPase2a and phospholamban. These proteins are important regulators of intracellular calcium homeostasis and have been implicated in ventricular dysfunction; specifically, diastolic relaxation and reduction in these proteins are associated with increases in calcium-transient times.\textsuperscript{34} The accumulation of fibrillar collagen in the extracellular space, myocyte hypertrophy, perivascular fibrosis resulting in myocardial stiffness, and, ultimately, ventricular dysfunction are likely a result of cardiac fibroblast growth and enhanced collagen synthesis.\textsuperscript{35} Laks et al\textsuperscript{36} demonstrated an increase in oxygen in the hypertrophied right ventricle of dogs that were subjected to chronic PA banding. It is perceivable that similar changes occur within the RA tissue but at a slower rate than that occurring within the right ventricle. Hence, the right atrium is able to compensate for the failing right ventricle.

In this study, we did not quantify the degree of RV or RA hypertrophy, and histological evaluation of the right ventricle and right atrium was not done. However, in a previous study, Hsieh et al\textsuperscript{16} used a similar model to ours to induce pulmonary hypertension in dogs. On histological examination of the RV outflow tract, they found that there were quantitatively similar degrees of mild-to-moderate myocyte hypertrophy and mild fibrosis in the endocardium, subendocardium, and interstitium in both acute and chronic heart failure dogs at sacrifice.\textsuperscript{16} It is reasonable to assume that similar changes may have occurred in our study.

Potential Limitations

In previous studies of RA dynamics in sheep, the coronary sinus was ligated to prevent coronary venous return during periods of data collection.\textsuperscript{11,12} This was well tolerated, because sheep possess a unique collateral vessel between the coronary sinus and hemiazygous vein that prevents coronary venous distension after ligation. Dogs do not possess such a collateral; therefore, we did not feel that coronary sinus ligation would be safe long-term. This may have caused a small but presumably consistent error in reservoir-to-conduit calculations. In the clinical setting, the mean duration from the onset of symptoms to establishing the diagnosis of CPH is $\approx$2 years.\textsuperscript{37} The 3 month period of pulmonary hypertension in our model was relatively short compared with that of the clinical scenario. A more prolonged exposure to pulmonary hypertension may have resulted in myocyte hypertrophy, collagen formation, and changes in capillary density, which could have additionally altered both RV and RA function.

In summary, this study demonstrated that chronic RVP overload resulted in an increase in RV contractility, thus preserving RV systolic function. However, RV diastolic dysfunction occurred, likely the consequence of ventricular hypertrophy and remodeling. As a compensatory response to increased RV diastolic stiffness, which surely made it more difficult for the ventricle to fill, RA contractility increased to support the active atrial contribution to RV filling (atrial kick), and the atrium acted more as a reservoir than a conduit. RA reservoir function increased, representing increased atrial distensibility, which is an adaptive response that previous investigators conclude would have a positive impact on global cardiac output.\textsuperscript{13,23,24,28,29} These compensatory changes in RA function likely play an important role in maintaining RV filling and preload to preserve cardiac output and prevent right heart failure during chronic RVP overload.

Acknowledgments

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References

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