Left ventricular underfilling and not septal bulging dominates abnormal left ventricular filling hemodynamics in chronic thromboembolic pulmonary hypertension

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Am J Physiol Heart Circ Physiol 299: H1083–H1091, 2010. First published July 30, 2010; doi:10.1152/ajpheart.00607.2010.—Chronic thromboembolic pulmonary hypertension. Am J Physiol Heart Circ Physiol 299: H1083–H1091, 2010. First published July 30, 2010; doi:10.1152/ajpheart.00607.2010.—Chronic thromboembolic pulmonary hypertension (CTEPH) is associated with abnormal left ventricular (LV) filling hemodynamics [mitral early passive filling wave velocity/late active filling wave velocity (E/A) < 1]. Pulmonary endarterectomy (PEA) acutely reduces pulmonary vascular resistance, resulting in an increase of mitral E/A. The abolishment of leftward septal bulging and an increase in right ventricular (RV) output are thought to be responsible for the increase of mitral E/A. In this study, we quantified the separate effects of leftward septal bulging and RV output on LV hemodynamics. In 39 CTEPH patients who underwent PEA, transmitral flow velocities and RV hemodynamic data were obtained pre- and postoperatively. A mathematical model describing the mechanics of ventricular interaction was fitted to the preoperative average values of cardiac output (CO; 4.4 l/min), mean pulmonary artery pressure (mPAP; 50 mmHg), mitral E/A (0.74), and mean left atrial pressure (mLAP; 9.8 mmHg). Starting from this preoperative reference state with leftward septal bulging, PEA was simulated by changing mPAP and CO to average postoperative values (28 mmHg and 5.7 l/min, respectively). Simulated and postoperatively measured data on E/A (1.27 vs. 1.48), mLAP (12.6 vs. 11.5 mmHg), and septal curvature (both rightward) were consistent. When an exclusive decrease of mPAP was simulated, mitral E/A increased 26%, mLAP decreased 16%, and septal curvature became rightward. When an exclusive increase of CO was simulated, mitral E/A increased 53% and mLAP increased 62%, whereas leftward septal bulging persisted. Thus, our simulations suggest that the increase of mitral E/A with PEA is caused two-thirds by an increase of RV output and one-third by the abolishment of leftward septal bulging.

IN PATIENTS with chronic thromboembolic pulmonary hypertension (CTEPH), pulmonary vascular resistance (PVR) is chronically increased due to resistive lesions in the pulmonary vascular bed. The chronic increase of right ventricular (RV) afterload in these patients is associated with an abnormal left ventricular (LV) filling pattern (10, 15, 31, 35), i.e., peak blood flow velocity of the early passive mitral filling wave (E wave) is smaller than that of the atrial contraction-induced late active filling wave (A wave). Successful treatment with surgical pulmonary endarterectomy (PEA) leads to an acute reduction of PVR associated with a decrease of mean pulmonary artery pressure (mPAP) and with an increase of cardiac output (CO) (10, 31). Consequently, PEA results in an acute improvement of cardiac pump function (18, 35, 44). Furthermore, mitral E wave velocity increases, so that mitral E wave velocity/A wave velocity (E/A) changes from an abnormal value (E/A < 1) to a normal physiological value (E/A > 1).

Generally, two different mechanisms have been hypothesized to be responsible for the acute change of the LV filling pattern in CTEPH patients undergoing PEA. The first mechanism comprises the effect of PEA on LV filling via the pulmonary circulation, i.e., the reduction of RV afterload leads to an increase of RV output and, thus, to an increase of LV preload. The second mechanism comprises the effect directly transmitted by the interventricular septum, i.e., the reduction of RV afterload is associated with the reestablishment of the normal transseptal pressure gradient (LV pressure > RV pressure) and, thus, with the abolishment of leftward septal bulging. This acute change of septal geometry is assumed to facilitate LV filling.

In the present study, we aimed to quantify the separate contributions of both mechanisms to the change of LV filling hemodynamics in CTEPH patients that underwent PEA.

MATERIALS AND METHODS

In this study, clinical measurements, as obtained from a group of CTEPH patients that underwent PEA, were combined with a computational modeling approach that allows quantitative discrimination between the effect of increased RV output and of decreased leftward septal bulging on LV filling hemodynamics in these patients. All participants gave written, informed consent before entering the research study. The research study protocol and the informed consent document were reviewed and approved by the University of California-San Diego Medical Center’s Institutional Review Board before the enrollment of participants.

Patient Data

Patient characteristics and a full description of data acquisition have been previously published (31). For the present study, relevant details of the patient population, echocardiographic and catheterization measurements, and statistical analysis are summarized below.

Patient population. The patient group consisted of 39 consecutive patients (24 men and 15 women, mean age: 55 ± 11 yr) with surgically accessible CTEPH who underwent successful PEA. All patients were classified as New York Heart Association class III and IV.

Echocardiography. All patients underwent a standard echocardiographic examination 10 ± 7 days (mean ± SD) before PEA. Pulsed-
Table 1. Catheterization and echocardiographic data obtained in CTEPH patients before and after PEA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before PEA</th>
<th>After PEA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheterization data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO, l/min</td>
<td>4.4 ± 1.1</td>
<td>5.7 ± 0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>50 ± 11</td>
<td>28 ± 9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>9.8 ± 5.0</td>
<td>11.5 ± 4.5</td>
<td>0.04</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>93 ± 6</td>
<td>95 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E, cm/s</td>
<td>52.5 ± 20.5</td>
<td>82.5 ± 18.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A, cm/s</td>
<td>68.0 ± 17.9</td>
<td>60.1 ± 17.1</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>0.74 ± 0.22</td>
<td>1.48 ± 0.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>80 ± 16</td>
<td>81 ± 15</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 39 chronic thromboembolic pulmonary hypertension (CTEPH) patients. These patient data have been previously published by Mahmud et al. (31). PEA, pulmonary endarterectomy; CO, cardiac output; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial blood pressure; E, peak flow velocity of the early mitral filling wave; A, peak flow velocity of late mitral filling wave; HR, heart rate; NS, parameter was not significantly different after PEA.

Right heart catheterization. All patients underwent right heart catheterization within 48 h of preoperative echocardiography. A 7.5-Fr Swan Ganz catheter was used for the invasive measurement of mPAP and mean pulmonary capillary wedge pressure. Cardiac output (CO) was obtained by the thermodilution method. Mean arterial blood pressure (MAP) was measured noninvasively. This catheterization protocol was repeated postoperatively within 72 h of the postoperative echocardiogram.

Statistics. Echocardiographic and hemodynamic patient data are expressed as means ± SD and are shown in Table 1. A two-tailed Student t-test for paired populations was used to compare pre- and postoperative measurements of echocardiographic and hemodynamic parameters. P values of <0.05 were considered statistically significant.

Computer Simulations

Model design. For the present study, the TriSeg model (29) of ventricular mechanics was embodied in the CircAdapt model describing mechanics of the whole human circulation (2).

The TriSeg model of ventricular mechanics, previously described in more detail by Lumens et al. (28, 29), incorporates mechanical interactions of the LV free wall, RV free wall, and interventricular septum, resulting in realistic coupling characteristics of LV and RV pump mechanics. Briefly, three thick-walled spherical segments, representing the ventricular walls, join in a common junction so that they encapsulate the LV and RV cavity. Given the LV and RV cavity volume, the area and curvature of the LV and RV free wall are estimated while assuming an initial estimate of septal geometry. From wall geometry, representative myofiber strain is calculated for each wall. From myofiber strain and strain rate, myofiber stress is determined using constitutive equations derived from experiments on isolated cardiac muscle (8, 43). The latter experiments showed that the velocity of sarcomere shortening increases with passive stretch, that the strength of activation increases with sarcomere length, and that the duration of activation increases with sarcomere length. Using myofiber stress and geometry of the LV free wall, septum, and RV free wall, total tension acting on the common junction is calculated. Using numerical optimization, septal geometry (initially estimated) is adjusted so that equilibrium of tensile force in the junction is satisfied.

As a result, geometries of the three ventricular walls are known, together with myofiber stresses, wall tensions, and ventricular cavity volumes and pressures. In summary, the TriSeg model relates global LV and RV pump mechanics to local myofiber mechanics in the three ventricular walls. An important property of the model is that the principle of conservation of energy is satisfied, meaning that summated ventricular pump work equals summed mechanical work as generated by the myofibers in the ventricular walls.

The CircAdapt model of the whole circulation (2) creates the required physiological environment (circulatory boundary conditions) for the ventricles as represented by the TriSeg model. The CircAdapt model consists of a network of modules, representing myocardial walls, valves, large blood vessels, and peripheral resistances. It allows beat-to-beat simulation of time-dependent ventricular mechanics and hemodynamics, e.g., volumes and pressures of the ventricular cavities, geometries and myofiber mechanics of the three ventricular walls, as well as flows through valves. An important feature of the CircAdapt model is that the number of independent parameters is reduced by incorporating adaptation of cardiac and vascular wall size and wall mass to mechanical load so that stresses and strains in the walls of heart and blood vessels are normalized to tissue-specific physiological standard levels (2, 29).

The pulmonary peripheral microcirculation is modeled as a nonlinear resistive module connecting the compliant pulmonary arterial and venous blood vessel modules (2). The instantaneous pulmonary arteriovenous pressure drop (pulmonary artery pressure – pulmonary venous pressure) is proportional to the square root of instantaneous blood flow through the pulmonary resistance module. This pulmonary pressure-flow relation is scaled by a proportionality factor expressing mean PVR. The nonlinearity of this pressure-flow relationship is in agreement with that measured in the human and canine lung with normal as well as increased pulmonary peripheral resistance due to pulmonary vascular disease (17, 19, 45).

The systemic peripheral microcirculation is modeled as a linear resistive module (2). The instantaneous systemic arteriovenous pressure drop is directly proportional to instantaneous blood flow through the systemic resistance module. This systemic pressure-flow relation is scaled by a proportionality factor expressing mean systemic vascular resistance (SVR).

The combined CircAdapt/TriSeg model has been used to simulate cardiovascular mechanics and hemodynamics under normal healthy ventricular loading conditions (normal simulation) and under CTEPH conditions before (CTEPH simulation) and after (post-PEA simulation) pulmonary endarterectomy. Furthermore, simulations have been performed to quantify the effects of either a decrease of mPAP (post-mPAP simulation) or an increase of CO (post-CO simulation) on LV filling hemodynamics in CTEPH. In all simulations, MAP and HR were set to their preoperatively measured values (93 mmHg and 80 beats/min, respectively), because MAP and HR did not change significantly with PEA in the patients (Table 1). Furthermore, in our model, RV stroke volume was equal to LV stroke volume under steady-state conditions. For each simulation, CO and mPAP were fitted to pre- or postoperatively measured values (Table 2).

Normal simulation. The normal simulation rendered human cardiovascular mechanics and hemodynamics under normal ventricular loading conditions at rest. The size and mass of cardiac walls and large blood vessels were adapted to normalize mechanical load in the tissues. The methods used for the simulation of normal ventricular mechanics and hemodynamics have been published in detail elsewhere (29). In the normal simulation, CO was set to the average value measured postoperatively in the CTEPH patients (Tables 1 and 2).

Figure 1 shows a schematic representation of the simulation protocol as followed to simulate the different patient conditions as described below.

CTEPH simulation. Using the normal simulation as point of departure, the CTEPH simulation was obtained in two steps. First, PVR...
was increased so that mPAP was equal to 25 mmHg. Up to this level of RV afterload, we assumed the heart and large blood vessels to be able to adapt their wall size and wall mass so that stresses and strains in the walls are normalized to tissue-specific physiological levels. Moreover, this value of mPAP was chosen because pulmonary hypertension is clinically defined as mPAP > 25 mmHg at rest (14). The adaptation led to a 25% increase of the mass of the RV free wall. Moreover, this value of mPAP was chosen because pulmonary hypertension is clinically defined as mPAP > 25 mmHg at rest (14). The adaptation led to a 25% increase of the mass of the RV free wall.

During the fitting procedure, no further adaptation of cardiac and vascular walls to mechanical load was performed. Similar to that observed in previous studies (27, 29), the increase of mPAP from 25 to 50 mmHg without adaptation led to RV decompensation, characterized by interventricular mechanical asynchrony, an increase of RV end-diastolic volume, and an increase of RV filling pressure (Table 2). It was assumed that pulmonary capillary wedge pressure was a reasonable accurate surrogate of mLAP in the present patient group (3). The resulting CTEPH simulation served as the reference state for each of the remaining three simulations, i.e., post-PEA, post-mPAP, and post-CO.

**Post-PEA, post-mPAP, and post-CO simulations.** The post-PEA simulation, representing the average CTEPH patient after PEA, was obtained by simultaneously applying two acute interventions (Fig. 1), as derived from the patient data (Table 1): 1) PVR was decreased so that mPAP decreased from 50 to 28 mmHg and 2) SVR was decreased so that CO increased from 4.4 to 5.7 l/min, whereas MAP was kept constant at 93 mmHg.

The post-mPAP simulation was obtained by decreasing mPAP to the postoperative value, whereas CO was set to the preoperative value. This exclusive decrease of mPAP was achieved by decreasing PVR, whereas SVR was slightly adjusted to keep CO constant. Similarly, the post-CO simulation was obtained by increasing CO to the postoperative value, whereas mPAP was kept constant at the preoperative value. This exclusive increase of CO was achieved by decreasing SVR, whereas PVR was slightly adjusted to keep mPAP constant. All other changes of ventricular mechanics and hemodynamics (e.g., local myofiber contractility or ventricular diastolic pressures and volumes) resulting from these changes of PVR and SVR are simulation results satisfying constitutive equations describing sarcomere mechanics in the cardiac walls and satisfying physical laws of mechanical equilibrium relating sarcomere mechanics to ventricular pump mechanics and cardiovascular system hemodynamics, i.e., conservation of energy and force equilibrium in the junction of the ventricular walls, as previously published by Lumens et al. (29).

**Assessment of septal geometry.** To assess the effect of PVR on septal geometry, average septal curvature during the early mitral filling wave (Csens) was quantified. This curvature was defined as the reciprocal of the radius of curvature and was defined as positive for physiological septal bulging toward the RV cavity.

**Sensitivity analysis.** The CTEPH, post-mPAP, and post-CO simulations were used to quantify the relative sensitivity (RS) of the dependent parameter (DP) for changes of the independent parameters mPAP and CO. For example, $\text{RS}_{\text{DP,mPAP}}$ indicates the relative sensitivity of DP for changes of mPAP, as follows:

$$\text{RS}_{\text{DP,mPAP}} = \frac{\log \left( \frac{\text{DP}_{\text{POST,mPAP}}}{\text{DP}_{\text{CTEPH}}} \right)}{\log \left( \frac{\text{mPAP}_{\text{POST,mPAP}}}{\text{mPAP}_{\text{CTEPH}}} \right)},$$

where the denominator is a constant value of $-0.58$. Analogously, $\text{RS}_{\text{DP,CO}}$ indicates the relative sensitivity of DP for changes of CO, as follows:

$$\text{RS}_{\text{DP,CO}} = \frac{\log \left( \frac{\text{DP}_{\text{POST,CO}}}{\text{DP}_{\text{CTEPH}}} \right)}{\log \left( \frac{\text{CO}_{\text{POST,CO}}}{\text{CO}_{\text{CTEPH}}} \right)},$$

where the denominator is a constant value of 0.26. A value of 1, 0, and $-1$ for RS indicates a proportional, independent, and reciprocal relationship, respectively. Septal curvature can be zero or negative.
with pulmonary hypertension. Consequently, RS could not be quantified for $C_{\text{sept}}$ because only positive real numbers have real-valued logarithms.

RESULTS

Figure 2 shows measured as well as simulated LV filling parameters in CTEPH patients before and after PEA. Similar to the results in patients, the model predicted an increase of mitral $E$, mitral $E/A$, and mLAP and little change of mitral $A$ with PEA in CTEPH patients. Simulation data indicated that the increase of mitral $E/A$ was predominantly caused by an increase of CO (Fig. 2C, blue line) and, to a lesser degree, by a decrease of mPAP (Fig. 2C, red line). An increase of CO and a decrease of mPAP have opposite effects on mLAP (Fig. 2D). The increase of mLAP with CO (Fig. 2D, blue line) was much larger than the decrease with mPAP (Fig. 2D, red line), resulting in a net increase of mLAP with PEA.

Time courses of simulated mitral and aortic blood flow velocities (Fig. 3A) showed that PEA predominantly affected the mitral $E$ wave and hardly affected the $A$ wave. The increase of CO (Fig. 3A, blue line) caused most of the increase of the $E$ wave, whereas the decrease of mPAP (Fig. 3A, red line) caused a relatively small shift of flow from the late $A$ wave to the early $E$ wave. The increase of CO as well as decrease of mPAP resulted in earlier opening of the mitral valve. PEA did not affect the timing of mitral and aortic valve closure. Consequently, the duration of the LV isovolumic relaxation phase decreased from 124 ms (CTEPH) to 90 ms (post-PEA). Furthermore, PEA resulted in relatively little changes of duration of LV ejection (increase from 234 to 244 ms) and LV isovolumic contraction (decrease from 46 to 34 ms). The LV Tei (or myocardial performance) index, defined as the sum of LV isovolumic contraction and relaxation time divided by LV ejection time (42), decreased significantly from 0.73 to 0.51.
Time courses of the simulated septal curvature (Fig. 3B) showed that the interventricular septum was relatively flat in the CTEPH simulation. After aortic valve closure, the septal curvature decreased quickly to negative value at the moment of mitral valve opening. This decrease of septal curvature corresponded with a rapid leftward septal motion during the LV isovolumic relaxation phase. As a result, the septum bulged toward the LV cavity during early LV filling. In the post-PEA simulation, septal curvature was increased to nearly normal values. The increase of septal curvature with PEA resulted almost entirely from a decrease of mPAP rather than from an increase of CO. The effect of PEA on septal motion is clearly shown in the echocardiographic movies (Supplemental Material\(^1\)), which show ventricular geometry in the parasternal short-axis view obtained pre- and postoperatively in a CTEPH patient. The first movie (Supplemental Material, Movie I) demonstrates a flat interventricular septum and rapid end-systolic leftward septal motion in a CTEPH patient before PEA. The second movie (Supplemental Material, Movie II) demonstrates the abolishment of septal flattening and leftward septal motion after PEA. For a qualitative comparison with these measurements, two additional movies demonstrate simulated ventricular geometry and time courses of ventricular pressures obtained from the CTEPH and post-PEA simulations (Supplemental Material, Movies III and IV, respectively).

Table 2 shows the values of several hemodynamic and geometric parameters in all simulations. These data show that mitral E/A, mitral E, C\(_{\text{sept}}\), LV end-diastolic volume, and LV and RV ejection fraction increased from subnormal values in the CTEPH simulation to normal values in the post-PEA simulation. Similarly, RV end-diastolic volume decreased from a pathologically high value to a normal physiological one. Moreover, mean right atrial pressure (mRAP) decreased 30%. However, mLAP did not decrease to a normal physiological value but increased by 29% from CTEPH to post-PEA. An exclusive increase of CO (post-CO simulation) resulted in a rightward shift on the RV end-diastolic pressure-volume relation as reflected by the increase of RV end-diastolic volume and mRAP, whereas an exclusive decrease of mPAP (post-mPAP simulation) caused a leftward shift on the RV end-diastolic pressure-volume relation, i.e., a decrease of RV end-diastolic volume and mRAP.

Table 2 also shows sensitivity analysis data as derived from the post-mPAP and post-CO simulations. The post-mPAP simulation revealed that mitral E increased less than proportionally with a decrease of mPAP, whereas the post-CO simulation revealed that mitral E increased more than proportionally with CO. Furthermore, mitral A decreased less than proportionally with mPAP, whereas it was not affected at all by CO. In summary, these data suggest that, in CTEPH, mitral E/A is four times more sensitive to relative changes of CO (\(R_{\text{SCO}} = +1.64\)) than to those of mPAP (\(R_{\text{SmPAP}} = -0.40\)). Apparently, the increase of mitral E/A with PEA resulted predominantly from the increase of RV output and not so much from the normalization of septal geometry.

**DISCUSSION**

In the present study, we assessed the effect of PEA on LV filling mechanics and hemodynamics in CTEPH patients by fitting a mathematical model of cardiovascular mechanics and hemodynamics, including ventricular interactions, to measurements obtained in a group of CTEPH patients before and after PEA. The model was made pathology specific by fitting it to average preoperative patient data. Starting from this preoperative reference state, PEA was simulated by decreasing mPAP and increasing CO acutely to average postoperative values. Simulated postoperative LV filling hemodynamics were in agreement with postoperative measurements (Fig. 2). The added value of our modeling approach was that the effect of leftward septal bulging and the effect of CO on LV filling could be separated quantitatively by exclusively decreasing mPAP and exclusively increasing CO to postoperative values, respectively. The latter model simulations suggested that 1) mitral E/A was about four times more sensitive to relative changes of CO than to those of mPAP, 2) mitral A was relatively insensitive to acute changes of CO and mPAP, and 3) septal curvature during early LV filling was very sensitive to changes of mPAP and relatively insensitive to changes of CO (Table 2). These simulation data suggest that the increase of mitral E/A with PEA in CTEPH patients is largely the effect of increased RV output and that the abolishment of leftward septal bulging is of minor importance.

The acute effect of PEA on LV filling hemodynamics as predicted by our model was qualitatively as well as quantitatively similar to the effect as measured postoperatively in the CTEPH patients (Fig. 2), whose average preoperative data were used as input for our model. Mitral E/A, mitral E, and

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\(^1\) Supplemental Material for this article is available online at the *American Journal of Physiology-Heart and Circulatory Physiology* website.
mLAP were increased, whereas mitral $A$ was relatively unaffected after PEA. The simulated effect of PEA on ventricular cavity volumes was also in close agreement with the effect as derived from pre- and postoperative MRI measurements in CTEPH patients that underwent PEA (37). These measurements as well as our simulations show that, under CTEPH conditions before PEA, LV end-diastolic volume, LV ejection fraction, and RV ejection fraction are significantly decreased, whereas RV end-diastolic volume is significantly increased, with respect to values simulated and measured under normal physiological conditions. Furthermore, simulated as well as measured ventricular end-diastolic volumes and ejection fractions changed to normal physiological values after PEA (37). In our simulations as well as in patients with CTEPH (34), the favorable effect of successful PEA on global LV performance is reflected by a significant decrease of the LV Tei index. Also, septal geometry was simulated realistically before and after PEA. Similar to results observed in CTEPH patients (20, 37), our simulations showed a major change of septal curvature with PEA (Fig. 3B and Table 2), i.e., from negative septal curvature (leftward septal bulging) to physiological positive septal curvature (rightward septal bulging) after aortic valve closure and during early LV filling. Since septal geometry directly depends on the transseptal pressure gradient (11), a decrease of mPAP rather than an increase of CO resulted in the abolishment of leftward septal bulging by reestablishment of the normal transseptal pressure gradient (LV pressure > RV pressure). Movies I–IV (Supplemental Material) showed strong similarity between simulated and measured septal motions before and after PEA in CTEPH. All these similarities between simulations and measurements show that our model enables a realistic simulation of ventricular mechanics and hemodynamics under pre- and postoperative CTEPH conditions.

Although the cardiovascular dynamics as described by our model are strongly nonlinear (2, 29), mitral $E/A$ appeared to vary linearly with CO ($<1\%$ deviation from linearity) and mPAP ($<3\%$ deviation from linearity) within the range investigated in this study. This linearity has been evaluated by the quantification of mitral $E/A$ after either increasing CO or decreasing mPAP in two equal steps from pre- to postoperatively measured values (Supplemental Material, Fig. S1). An exclusive increase of CO in two equal steps from preoperative (4.4 l/min) to postoperative (5.7 l/min) values resulted in an increase of $E/A$ by 26% and 53%, respectively (Table 2 and Supplemental Material, Fig. S1). An exclusive decrease of mPAP in two equal steps from preoperative (50 mmHg) to postoperative (28 mmHg) values resulted in an increase of mitral $E/A$ by 15% and 26%, respectively (Table 2 and Supplemental Material, Fig. S1).

Our post-mPAP and post-CO simulations showed how a decrease of RV afterload and an increase of RV output, respectively, affect clinical LV filling parameters as measured in CTEPH patients. In the post-mPAP simulation, the decrease of mPAP was associated with a 9% decrease of mitral $A$ and with a 14% increase of mitral $E$. Apparently, the acute abolishment of leftward bulging of the interventricular septum facilitates passive LV filling (increase in the mitral $E$ wave) and results in the redistribution of blood flow from the late to the early mitral filling phase, as evidenced by the 26% increase of mitral $E/A$ in the post-mPAP simulation (Figs. 2 and 3). In the post-CO simulation, however, an increase of CO did not affect mitral $A$ but resulted in a 54% increase of mitral $E$. In CTEPH patients, PEA resulted in a small (not significant) decrease of mitral $A$ and in a significant increase of pulmonary capillary wedge pressure (Table 1) (15, 31). In combination with these latter observations in patients, our simulations showed that a decrease of RV afterload and the associated abolishment of leftward septal bulging could only explain a relatively small part ($\approx 30\%$) of the increase of mitral $E/A$ observed in patients that underwent PEA. An increase of CO, however, accounted for most ($\approx 70\%$) of the increase of $E/A$ with PEA.

Our finding that an exclusive 30% increase of CO (post-CO simulation) did not affect mitral $A$ and resulted in a 54% increase of mitral $E$ is in agreement with Doppler measurements obtained before and after hemodialysis in patients with renal insufficiency but without overt heart disease (41). In these patients, the decrease of circulating blood volume as a result of hemodialysis was associated with a 13% decrease of CO, whereas HR and systemic blood pressures did not change significantly. This decrease of CO was associated with an $\approx 30\%$ decrease of mitral $E$ and mitral $E/A$, whereas mitral $A$ remained unchanged. Although pulmonary artery pressure and septal geometry are unknown in this patient group, it is very unlikely that these parameters were significantly different before and after hemodialysis. Therefore, these data provide support for part of our simulation results, i.e., mitral $E$ and mitral $E/A$ vary proportionally with CO, whereas mitral $A$ appears not to be related to CO.

In animal models with chronic RV pressure overload, LV systolic function (contractility) appeared to be unaffected (12, 21, 22, 24). Thus, the increase of CO with PEA is most likely the result of improved RV systolic function. This latter improvement may have several causes. First, a decrease of RV afterload in decompen-sated pulmonary hypertension results in the reduction of interventricular mechanical dysynchrony (27, 30, 32) and, thus, in a more coordinated contraction of the three ventricular walls with less leftward septal bulging. This may, therefore, account for an indirect effect of decreased leftward septal bulging on LV filling hemodynamics via the improvement of RV output. Second, in patients with CTEPH, a decrease of RV afterload by PEA has been shown to significantly reduce tricuspid regurgitation (38). Third, PEA and the associated decrease of RV end-diastolic volume may result in an acute reduction of total heart volume and, thus, of pericardial constraint. An acute reduction of pericardial constraint has been shown to increase CO in various animal models of pulmonary hypertension (4, 5). Finally (and speculatively), PEA may lead to an improvement of RV coronary perfusion. Exorbitantly high RV pressure may increase intramyocardial pressure in the RV free wall and, thus, increase resistance of the RV coronary vasculature more than that of the LV. This may result in relatively reduced myocardial perfusion of the RV. The acute decrease of RV pressure with PEA may result in a decrease of RV coronary vascular resistance (facilitating RV myocardial perfusion) and also cause a decrease in RV mechanical myofiber load. Consequently, RV contractile function and stroke volume can improve.

Many studies have reported strong correlations between septal curvature and LV filling parameters, such as $E/A$, and have speculated on the potential detrimental effect of leftward septal bulging on LV filling in patients with pulmonary hyper-
tension (10, 23, 25, 31, 35, 36, 40). Although not proven, Gurudevan et al. (15) suggested that the increase of mitral $E/A$ with PEA predominantly resulted from an increase of LV preload rather than from a release of LV compression by the septum. However, the relative contributions of both mechanisms could not be quantified from the available patient data alone. Our simulations strongly suggest that the increase of mitral $E/A$ with PEA in CTEPH patients is largely the effect of increased RV output and that the abolishment of leftward septal bulging is of minor importance. However, whether normalization of septal geometry and motion also has an indirect effect on LV filling by increasing RV performance and, thus, RV output remains unknown. This cannot be tested using our model.

In addition to LV underfilling (6), increased HR has also been shown to be a potential cause of low mitral $E/A$ (16). In this study, we waited a few days after surgery to perform the postoperative echocardiography under hemodynamically stable conditions. During this postoperative echocardiography, HR appeared unchanged and can thereby be excluded as a potential cause of the increase of mitral $E/A$ with PEA in patients with CTEPH.

Obviously, conditions in a computer simulation may differ from those in patients. The mechanical properties of the myocardium under chronic pulmonary hypertensive loading conditions may be different than under normal conditions due to disease-related histological and geometrical changes, e.g., increased collagen content in the ventricular walls and hypertrophy of the RV free wall (22). In the procedure used to obtain the CTEPH simulation, we accounted for histological changes by varying passive stiffness of the left atrial and LV myocardium, so that mitral $E/A$ and mLAP, respectively, were in agreement with the measured preoperative values. Histological changes of the right atrial and RV myocardium were not accounted for in our simulations because little is known about right-sided hemodynamics in our patient group. Furthermore, geometric changes were assumed to be of minor importance, as previously described by Arts et al. (1). In this study (1), it was shown that the ratio between cavity and wall volume appeared to be the major determinant of the relation between ventricular pump mechanics and myofiber mechanics. The actual shape of the LV, being a truncated ellipsoid, a sphere, or a cylinder, appeared to be of minor importance.

**Clinical Implications**

There has been some debate concerning the relative importance of LV underfilling versus LV compression by septal bulging in the low-output state of advanced pulmonary hypertension (15, 33). The etiology of the LV “diastolic dysfunction” often present in CTEPH has also been controversial (26, 31, 39). The results of the present study strongly support the concept that perturbations in LV filling pressure, output, and Doppler flow patterns due to CTEPH are primarily caused by RV outflow obstruction and resultant LV underfilling. Although not negligible, the relative contribution of septal geometry and bulging is considerably less. Also, the increases in CO and LV filling explain the marked improvement in the LV Doppler diastolic filling pattern after PEA, rather than changes in septal geometry per se.

**Study Limitations**

An important limitation of our model is the fact that HR and ventricular stroke volume are prescribed independent model parameters. In reality, however, these parameters are mutually dependent and are tightly controlled to maintain MAP. Thus, the exact mechanism by which PEA results in an increase of CO cannot be studied with the present model. Nevertheless, the quantitative agreement between our postoperative simulation data and postoperative patient data on LV filling hemodynamics (Fig. 2) indicate that the simplifications made in the simulations may not obscure first-order mechanical effects of hemodynamic and mechanical ventricular interaction on LV filling characteristics in CTEPH patients undergoing PEA.

In our model, the external pressure surrounding the LV and RV free walls is assumed to be zero. The real heart is surrounded by the pericardium, which constrains the increase of total heart volume during volume overload. With acute pulmonary hypertension, pericardial constraint has been shown to significantly modulate ventricular mechanics and hemodynamics by ventricular interactions (4, 5). Under chronic pulmonary hypertensive conditions, however, the effect of the pericardium on ventricular mechanics is likely to be of minor importance, because measurements have demonstrated adaptive dilatation of the pericardium in experimental animals with chronic RV dilatation (13). Furthermore, it has been previously shown that complete surgical pericardiectomy in patients with CTEPH produces no significant change in cardiac geometry, ventricular diastolic pressure-volume relationships, and transmural flow velocity parameters (7). Moreover, in our simulations, total heart volume hardly changes as a result of PEA (<3% decrease). Therefore, the absence of the pericardium in our model is assumed to be of minor importance.

We acknowledge that further research is necessary to obtain experimental data supporting the findings derived from the post-CO and post-mPAP simulations. The highly controlled conditions represented by these simulations may be obtained in an animal model or an isolated heart setup.

Although the movies I–IV (Supplemental Material) showed qualitative agreement between simulated and measured changes of septal motion due to PEA, septal curvature was not quantified in our patients. Nevertheless, in a previous study (29), we have shown that the relation between septal curvature and transseptal pressure difference in our model is similar to the relation measured in a group of healthy volunteers and patients with pulmonary arterial hypertension (9).

Tricuspid regurgitation, which often exists in patients with CTEPH and which has been shown to be significantly reduced by PEA (38), was not included in our simulations. Since tricuspid regurgitation often leads to RV volume overload and, thus, to additional distortion of LV geometry in patients with CTEPH, its absence in our simulations should be considered when interpreting our simulation results.

**Conclusions**

The effect of PEA on LV filling hemodynamics as predicted by our model was surprisingly similar to the effect as observed in patients with CTEPH. Mitral $E/A$, mitral $E$, LV end-diastolic volume, and septal curvature increased from subnormal values in CTEPH before PEA to normal values after PEA, whereas RV end-diastolic volume decreased to a normal value. Our
model simulations suggest that 1) mitral E/A is about four times more sensitive to relative changes of CO than to those of mPAP, 2) mitral A is relatively insensitive to changes of CO and mPAP, and 3) septal curvature is almost solely dependent of mPAP and relatively independent of CO. Our simulation data suggest that one-third of the increase of mitral E/A with PEA in CTEPH patients can be explained by the mechanical effect of a decrease of RV pressure overload as transmitted by the septum. The remaining two-thirds increase of mitral E/A can be attributed to an increase of RV output.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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