Right ventricular free wall pacing improves cardiac pump function in severe pulmonary arterial hypertension: a computer simulation analysis

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IN PULMONARY ARTERIAL HYPERTENSION (PAH), progressive increase of pulmonary vascular resistance causes chronic elevation of right ventricular (RV) pressure. When left untreated, PAH leads to right heart failure and premature death (18, 24). Several studies showed that morbidity and mortality of PAH patients are determined by the ability of the RV to maintain normal stroke volume and cardiac output (6, 23).

In PAH, structural remodeling (hypertrophy and dilatation) is limited to the RV free wall (RVfw) (5, 19), suggesting an inhomogeneous distribution of myocardial tissue load. Therefore, local reduction of mechanical load of the RVfw may be another therapeutic option, in addition to conventional reduction of pulmonary vascular resistance (8).

Marcus et al. (17) demonstrated the presence of interventricular mechanical asynchrony in severe PAH patients, evidenced as prolonged duration of shortening and delayed peak shortening in the RVfw compared with that in the left ventricular (LV) free wall (LVfw) and the interventricular septum (Sept). RVfw shortening even continued after pulmonary valve closure and appeared related to leftward septal motion during LV isovolumic relaxation. As a potential treatment, early RVfw pacing was suggested to improve interventricular mechanical synchrony and, thereby, cardiac pump function (2, 12, 17). This seems logical, because, during ventricular pacing, mechanical myofiber work is significantly decreased in early-activated regions, whereas it is increased in late-activated regions (21).

To explore the idea of RVfw pacing in PAH, we used a mathematical model (16) to simulate ventricular mechanics and hemodynamics under normal and PAH conditions. The hypothesis was assessed that, in severe PAH, early pacing of the RVfw decreases mechanical myofiber load in the RVfw and thereby improves RV pump function.

MATERIALS AND METHODS

Model Design

For the present study, the TriSeg model (16), describing ventricular mechanics, including mechanical interaction of the ventricular walls, was embodied in the CircAdapt model of the whole circulation (1).

The TriSeg model of ventricular mechanics, previously described in more detail by Lumens et al. (15, 16), incorporates mechanical interaction of the LVfw, RVfw, and Sept, resulting in realistic coupling characteristics of LV and RV pump mechanics. In short, three thick-walled spherical segments representing the ventricular walls join in a common junction so that they encapsulate the LV and RV cavity. Given LV and RV cavity volume, area and curvature of the LVfw and RVfw are calculated while assuming an initial estimate of Sept geometry. From wall geometry, representative myofiber strain is calculated for each wall. From myofiber strain, myofiber stress is determined using constitutive equations describing sarcomere mechanics. This latter empirical model incorporates sarcomere properties as derived from experiments on isolated cardiac muscle (7, 26), i.e., velocity of sarcomere shortening increases with passive stretch, strength of activation increases with sarcomere length, and duration of activation increases with sarcomere length. Using myofiber stress and wall geometry, total radial and axial force components of tension acting on the junction are calculated. Then septal geometry (initially estimated) is adjusted so that equilibrium of tensional 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. Summarizing, the TriSeg model relates global LV and RV pump mechanics to local myofiber...
mechanics in the three ventricular walls. This relation is based on the principle of conservation of energy, meaning that summed ventricular pump work equals summed mechanical work as generated by the myofibers in the ventricular walls.

The CircAdapt model of the whole circulation (1) 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 mechanics and hemodynamics, e.g., volumes and pressures of the ventricular cavities, geometries and myofiber mechanics of the three ventricular walls, and 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 (1, 16).

Pulmonary peripheral resistance was modeled as a nonlinear resistive module connecting the compliant pulmonary arterial and venous blood vessels. Pulmonary flow was proportional to the squared pulmonary arteriovenous pressure drop, which was prescribed for each simulation in the present study. This relation is in agreement with the pressure-flow relationship as measured in the human and canine lung with normal as well as with increased peripheral pulmonary resistance due to pulmonary vascular disease (11, 14, 28).

Simulations

Cardiovascular mechanics and hemodynamics were simulated under normal ventricular loading conditions at rest (NORM), with compensated mild PAH (PAHComp), with moderately (PAHDecomp Mod) and severely (PAHDecompSev) decompensated PAH, and with additional pacing of the RVfw. Details of the methods used for simulation of ventricular mechanics and hemodynamics under normal and pulmonary hypertensive loading conditions have been published previously (16).

NORM simulation. The NORM simulation represents the human circulation under normal ventricular loading conditions with regular resting values of heart rate (70 beats/min), cardiac output (5 l/min), and mean arterial blood pressure (92 mmHg). The heart and large blood vessels were fully compensated by adaptation to mechanical load (16). The three ventricular walls were activated synchronously.

PAH simulations. The PAHComp simulation represents a state of mild compensated PAH. Mean pulmonary arterial pressure was increased by 11 mmHg (1.5 kPa) to 26 mmHg (3.5 kPa), so that mean pulmonary artery pressure (mPAP) increased from 18 mmHg (NORM) to 32 mmHg. Subsequently, size and mass of the heart and large blood vessels were fully compensated by adaptation to normalize mechanical load of the constituting tissues. This adaptation resulted in a 40% increase of RVfw mass. More details of the simulation protocol during adaptation have been published previously (16). The PAHDecompMod and PAHDecompSev simulations represent a moderate and a severe state of decompensated PAH, respectively. This pathological condition was achieved by further increase of mean pulmonary arteriovenous pressure drop to 49 mmHg (6.5 kPa, PAHDecompMod) and 71 mmHg (9.5 kPa, PAHDecompSev), so that mPAP increased to 55 and 79 mmHg, respectively. In the PAHDecomp simulations, no further adaptation of ventricular and atrial walls to mechanical load was performed compared with the PAHComp simulation, thus introducing partial RV decompensation. The three ventricular walls were activated synchronously.

RVfw pacing simulations. To study the acute effect of early RVfw pacing on ventricular mechanics in severely decompensated PAH, the RVfw in the PAHDecompSev simulation was activated 20, 40, and 60 ms earlier than the LVfw and the Sept. No adaptation was applied. Finally, the same pacing protocol was applied to the NORM simulation as control measurement and to the PAHDecompMod simulation to investigate whether the effect of RVfw pacing in PAH depends on degree of decompensation.

Data Analysis

To test whether the model realistically describes ventricular mechanics in PAH, simulated time courses of circumferential strain in the ventricular walls were compared with clinical strain data obtained in healthy subjects and severe PAH patients by Marcus et al. (17). In our simulations, for each ventricular wall, circumferential strain was quantified as the percent change in sarcomere length with respect to reference sarcomere length at the moment of aortic valve opening.

For each simulation, LV and RV pressure waveforms were normalized to their maximum values and plotted as function of time. These normalized pressure curves were used to quantify timing difference between LV and RV pressure decay (Δtdec) at half-maximum pressure. This timing difference was defined positive when RV pressure decay precedes LV pressure decay.

For each ventricular wall segment, mechanical myofiber load was represented by natural myofiber strain and Cauchy myofiber stress. The area of the obtained myofiber stress-strain loop represents stroke work density, defined as contractile myofiber work per unit of tissue volume (unit: Pa = J/m³) per beat.

RESULTS

Below, we first compare simulated and measured circumferential strain patterns under normal healthy and under severe PAH conditions (Fig. 1). Next, we evaluate the effect of compensated and decompensated PAH on cardiac pump function in Figs. 2, 3, and 4. Finally, we evaluate the effect of RVfw pacing in PAHDecompSev on cardiac pump function in Figs. 5, 6, 7, 8, and 9.

NORM and PAH Simulations

In the NORM simulation, as well as in the healthy subject, time courses of circumferential strain showed synchronous shortening of the ventricular walls during ejection, synchronous lengthening during filling, and similar values of peak circumferential shortening in the three walls (Fig. 1, left). Also under severely decompensated PAH conditions, simulated and measured circumferential strain patterns were similar (Fig. 1, right), with RVfw peak shortening being delayed with respect to LVfw and Sept peak shortening, and with prolonged RVfw shortening that continues after aortic and pulmonary valve closure. During LV isovolumic relaxation, leftward bulging of the Sept was associated with lengthening of myofibers in the Sept and LVfw. Maximal leftward septal bulging occurred at the moment of RVfw peak shortening. Furthermore, simulated as well as measured RV isovolumic relaxation phase was prolonged and delayed in severe PAH compared with that in the normal situation (horizontal bar plots in Fig. 1).

In Fig. 2, top, time courses of ventricular pressures show that RV pressure increased with PAH. In the PAHDecompSev simulation, RV pressure even exceeded LV pressure during diastole and late systole. The time courses of normalized LV and RV pressures show that LV and RV pressure rise synchronously in NORM, PAHComp, PAHDecompMod, and PAH DecompSev (Fig. 2, middle). PAH hardly affected timing of LV pressure rise and decay. RV pressure decay, on the other hand, delayed with increase of PAH. RV pressure decay preceded LV pressure decay in NORM and PAHComp, as reflected by positive values of Δtdec, whereas decay of LV...
pressure preceded that of the RV in decompensated PAH, as reflected by negative values of \( \Delta t_{\text{dec}} \). This delay of RV pressure decay was associated with delayed RV isovolumic relaxation.

In the NORM and PAHComp simulations, time courses of circumferential strains (Fig. 2, bottom) showed relatively synchronous and uniform strain patterns in the three ventricular walls. In each wall, peak shortening was reached at end-ejection. Peak shortening was 16% in the LVfw, as well as in the Sept, and 17% in the RVfw. However, with decompensation (PAHDecompMod and PAHDecompSev), circumferential strain patterns changed. During isovolumic contraction, the LVfw and Sept shortened, whereas the RVfw lengthened. Consequently, onset of RVfw shortening was delayed compared with that of the LVfw and Sept. Peak RVfw shortening was also delayed until the moment of mitral valve opening, whereas peak shortening of the LVfw and Sept still occurred at the moment of aortic valve closure. The delay of RVfw peak shortening with respect to that of the LVfw was 106 and 136 ms for the PAHDecompMod and PAHDecompSev simulations, respectively. Duration of RVfw shortening increased from 212 ms in the NORM and PAHComp simulations to 294 and 318 ms in the PAHDecompMod and PAHDecompSev simulations, respectively, whereas duration of LVfw and Sept shortening was similar (282 ms) in the NORM and the three PAH simulations.

As shown in Fig. 3A, RV end-diastolic pressure increased from 4 mmHg in the NORM to 15 mmHg in the PAHDecompSev simulation. LV end-diastolic pressure increased less, from 10 mmHg in the NORM and PAHComp simulations to 11 mmHg in PAHDecompMod and 13 mmHg in PAHDecompSev. In the PAHComp simulation, RVfw mass and end-diastolic thickness were increased by 38 and 50%, respectively, whereas LV and RV end-diastolic volumes were not changed with respect to the NORM simulation (Fig. 3B). With decompensation, however, RV end-diastolic volume increased by 54% and LV end-diastolic volume decreased by 9% in PAHDecompSev. Compared with the NORM simulation, LV maximal rate of pressure rise (dP/dt\text{max}) decreased by 7% in PAHDecompSev (Fig. 3C), whereas RV dP/dt\text{max} increased by 175%.

In the NORM and PAHComp simulations, mechanical load was distributed homogeneously over the ventricular walls, as indicated by similarity of myofiber stress-strain relations (Fig. 4). In PAHDecompMod and PAHDecompSev, however, mechanical load was inhomogeneously distributed over the ventricular walls. In the PAHDecompSev simulation, RVfw myofiber work density was increased by 182% with respect to that in the NORM simulation (Fig. 3D and 4), whereas Sept and LVfw myofiber work densities were decreased by 27 and 18%, respectively, predominantly due to myofiber lengthening during LV isovolumic relaxation (Fig. 4). Peak RVfw myofiber stress was three times higher than in the NORM simulation. Furthermore, with decompensation, the RVfw myofiber stress-strain relation was shifted to the right, reflecting increase of mean RVfw sarcomere length from 1.9 \( \mu \text{m} \) in the NORM and

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**Fig. 1.** Time courses of circumferential strain in a healthy subject and a pulmonary arterial hypertension (PAH) patient: measurements (top) [adapted from Marcus et al. (17)] and simulations (bottom).

Both measurements and simulations show uniform strain curves under normal loading conditions and show interventricular mechanical asynchrony with severe PAH, i.e., prolonged duration of right ventricular (RV) free wall (RVfw) shortening, delayed RVfw peak shortening, and lengthening of the septum (Sept) and left ventricular (LV) free wall (LVfw) during LV isovolumic relaxation. Timing of LV and RV filling (FILL), isovolumic contraction (IC), isovolumic relaxation (IR), and ejection (EJ) are indicated in the horizontal bar plots. NORM, normal ventricular loading conditions at rest; PAHDecompSev, severely decompensated PAH condition.
PAHComp simulations to 2.0 and 2.2 μm in the PAHDecomp Mod and PAHDecompSev simulations, respectively.

RVfw Pacing Simulations

As shown in Fig. 5, top, RVfw pacing did not affect the amplitude of ventricular pressures in severe PAH, RV pressure rise and decay occurred earlier with RVfw pacing in PAH, while timing of LV pressure rise and decay did not change (Fig. 5, middle). Timing difference \( \Delta t_{\text{dec}} \) increased when activating the RVfw earlier than the LVfw and Sept, indicating resynchronization of LV and RV pressure decay. Early RVfw pacing decreased RVfw peak shortening, increased Sept and LVfw peak shortening, resynchronized LV and RV isovolumic relaxation phases, and reduced lengthening of the Sept and LVfw during LV isovolumic relaxation (Fig. 5, bottom).

RVfw pacing decreased RV end-diastolic pressure and volume (Fig. 6). These parameters reached their minimal value (~7% and ~6% compared with PAHDecompSev, respectively) upon 40-ms RVfw preexcitation. In this latter simulation, LV end-diastolic pressure and volume were not changed. Furthermore, RV \( \frac{dP}{dt_{\text{max}}} \) was increased (+13%), and LV \( \frac{dP}{dt_{\text{max}}} \) was decreased (~25%), compared with the PAHDecompSev simulation.

With early RVfw pacing in severe PAH, RVfw myofiber work density decreased from pathologically increased level to normal physiological level (Fig. 6D). This decrease of RVfw myofiber work resulted from decrease of peak myofiber stress (up to 8% with 40-ms RVfw preexcitation) and shortening of the RVfw (decrease of myofiber strain) between mitral valve closure and aortic valve opening (Fig. 7). RVfw pacing also decreased myofiber shortening in the Sept and LVfw after aortic valve closure, whereas shortening during ejection increased (Fig. 7). As a consequence, RVfw pacing increased myofiber lengthening in the Sept and LVfw. Myofiber work was distributed most homogeneously over the ventricular walls upon 40-ms RVfw preexcitation (Fig. 6D).

The model predicted detrimental effects of RVfw preexcitation on ventricular pump function and myofiber mechanics under normal ventricular loading conditions (NORM simulation; Fig. 8): LV and RV end-diastolic pressures increased, LV \( \frac{dP}{dt_{\text{max}}} \) decreased, and myofiber work density became more inhomogeneously distributed because it decreased in the RVfw and Sept, whereas it increased in the LVfw.

Similarly, as observed in severely decompensated PAH (Fig. 6), RVfw preexcitation resulted in redistribution of myofiber work over the ventricular walls in moderately decompensated
PAH (PAHDecompMod simulation; Fig. 9). Under these moderate PAH conditions, myofiber work was distributed most homogeneously over the ventricular walls upon 20-ms RVfw preexcitation. This redistribution, however, was not associated with decrease of end-diastolic ventricular pressures or volumes. These simulation results show that, in our model, the beneficial effect of RVfw pacing on cardiac pump function in decompensated PAH increases with disease severity.

**DISCUSSION**

In the present study, a mathematical model describing mechanics of ventricular interaction was used to predict the effect of RVfw pacing on ventricular pump mechanics and hemodynamics in severe PAH. With severely decompensated PAH, the model predicted an inhomogeneous distribution of myofiber load over the ventricular walls, expressed by three times higher myofiber work in the RVfw than in the Sept and LVfw. Interestingly, the model predicted that early RVfw pacing decreases the exorbitantly high myofiber work in the RVfw and increases myofiber work in the LVfw and Sept, while global LV and RV pump work remain the same. Apparently, the mechanical interaction of the ventricular walls allowed local redistribution of myofiber work over the ventricular walls. In our simulations, an optimal moment of RVfw preexcitation was found, resulting in homogeneous distribution of myofiber work over the ventricular walls and moderate improvement of RV pump function.

**Comparison of Measured and Simulated Ventricular Geometry and Wall Mechanics in Compensated and Decompensated PAH**

Similarly, as observed in experimental animals with mild chronic RV pressure overload (19, 20), the RVfw was hypertrophied in the PAHComp simulation, while resting LV and RV end-diastolic volumes were not changed. Increasing pulmonary resistance without further cardiac load adaptation...
However, resulted in RV dilatation, decrease of LV volume, and prolonged as well as delayed RV isovolumic relaxation. All of these changes are in agreement with measurements obtained in patients with severe PAH (9, 25). The simulated circumferential strain patterns in the three ventricular walls were in close agreement with measurements in healthy subjects and PAH patients (17). Measurements in, and simulations of, severe PAH showed prolonged RVfw shortening associated with lengthening of the Sept and LVfw during LV isovolumic relaxation. All of these similarities between simulations and measurements show that our model enables realistic simulation (PAHDecompMod and PAHDecompSev simulations), however, resulted in RV dilatation, decrease of LV volume, and prolonged as well as delayed RV isovolumic relaxation. All of these changes are in agreement with measurements obtained in patients with severe PAH (9, 25). The simulated circumferential strain patterns in the three ventricular walls were in close agreement with measurements in healthy subjects and PAH patients (17). Measurements in, and simulations of, severe PAH showed prolonged RVfw shortening associated with lengthening of the Sept and LVfw during LV isovolumic relaxation. All of these similarities between simulations and measurements show that our model enables realistic simulation.

**Fig. 5.** Time courses of simulated ventricular pressures and circumferential strains in PAHDecompSev with synchronous activation of the ventricular walls and with 20-, 40-, and 60-ms RVfw preexcitation. Top: LV and RV cavity pressures. Middle: normalized LV and RV pressure curves. Bottom: circumferential strain in the LVfw, Sept, and RVfw. Timing of FILL, IC, IR, and EJ are indicated in the horizontal bar plots. Vertical dashed lines indicate moment of aortic valve opening.

**Fig. 6.** Simulated LV and RV end-diastolic pressures (A), end-diastolic volumes (B), dP/dt_{max} (C), and myofiber work densities (D) in the LVfw, Sept, and RVfw in PAHDecompSev with synchronous activation of the ventricular walls and with 20-, 40-, and 60-ms RVfw preexcitation.
of ventricular mechanics under normal as well as pulmonary arterial hypertensive ventricular loading conditions. Despite these qualitative similarities, however, lengthening of the Sept and LVfw during LV isovolumic relaxation appeared underestimated in the PAHDecompSev simulation compared with the lengthening measured in the specific PAH patient of Fig. 1. Apparently, the interventricular mechanical asynchrony, as measured in the specific PAH patient, cannot be entirely explained by normal sarcomere physiology, as simulated by our sarcomere model (16). In the pathological PAH situation, the effect of decompensation on local myofiber mechanics may be more pronounced. This is in agreement with the fact that, in myocardial cells isolated from decompensated failing hearts, action potential duration is prolonged compared with that in normal cells under similar loading conditions (27).

In patients with severe PAH, LV end-diastolic volume is significantly smaller (≥25%) than in healthy controls (9, 17). In our PAHDecompSev simulation, however, we observed a smaller decrease (9%) (Fig. 3B). This discrepancy most likely resulted from the assumption of constant cardiac output for all simulations. This was assumed to study the isolated effect of increased pulmonary peripheral resistance on ventricular mechanics and hemodynamics. In a clinical study comparing healthy controls with severe PAH patients, cardiac output was significantly smaller in PAH patients (≥25%) (9). If we would assume a similar reduction of cardiac output in our simulations, a similar change of LV end-diastolic volume is expected.

Comparison of Measured and Simulated Effects of Pacing in Decompensated PAH

The beneficial effect of early RVfw pacing in chronically RV overworked hearts seems to be supported by experimental data published recently by Handoko et al. (10). In this study, the effect of RVfw pacing was investigated in a Langendorff setup of hearts isolated from rats with chronic pulmonary hypertension and right heart failure. Similarly, as observed in our simulations, with RVfw preexcitation, an optimal pacing setting was found, resulting 1) in maximal improvement of RV systolic function (8.5% increase of RV dp/dtmax); 2) in decrease of Δtpdec; and 3) in resynchronization of LV and RV peak pressure. Furthermore, in this study, RVfw pacing did not detrimentally affect LV pump...
function or coronary perfusion. Thus the results of our simulation study and of the experimental study by Handoko et al. mutually support and complement each other.

In an open-chest pig model of acute RV pressure overload and complete atrioventricular block, Quinn et al. (22) also showed a beneficial effect of RVfw pacing on cardiac performance. In this study, early activation of the RVfw with respect to the LVfw resulted in increase of cardiac output, decrease of LV dP/dt max, and increase of RV dP/dt max. In our simulations, the largest decrease of RV end-diastolic pressure and volume was observed with 40-ms RVfw preexcitation (Fig. 6). Similarly, in the experiments by Quinn et al., maximal increases of cardiac output and RV dP/dt max occurred when the RVfw was 37 ms earlier activated than the LVfw. Simulations as well as measurements showed that, during this optimal pacing setting, LV and RV pressure waveforms were resynchronized.

The simulations of RVfw pacing in a normal heart (Fig. 8) are in agreement with experimental findings on RV pacing as well as left bundle branch block, indicating the combination of impairment of LV pump function, decrease of Sept and, to a greater extent, of RVfw workload, increase of LVfw workload, and moderate increase of RV pump function (RV dP/dt max) (13, 21).

**Potential Mechanism Behind Interventricular Mechanical Asynchrony in PAH**

It is important to realize that, in the PAHDecomp simulations, all three ventricular walls were activated simultaneously, thus simulating a decompensated PAH condition without conduction delay. The mechanical asynchrony, especially the prolonged RVfw shortening observed in the PAHDecomp simulations, is explained by the basic property of our model (16), that duration of mechanical myofiber activation increases with sarcomere length. This latter property is well known from experiments on isolated cardiac muscle (26). Our simulation results suggest that interventricular mechanical asynchrony in PAH is a direct consequence of stretching the RVfw (RV decompen- sation). Therefore, it seems safe to assume that the interventricular mechanical asynchrony, as reported among patients with severe PAH by Marcus et al. (17), also indicates RV decompen- sation. A spin-off of the present study may, therefore, be that detection of mechanical interventricular asynchrony could be used as an index of RV decompen- sation.

**Study Limitations**

Obviously, conditions in a computer simulation may differ considerably from those in patients. In our model, each ventricular wall is lumped into a spherical wall segment containing a single contractile fiber describing representative passive and active sarcomere properties of the entire wall (16). Although this simplified setup allows inhomogeneity of material properties to some extent, i.e., between ventricular walls, it does not allow local inhomogeneities of material properties within a single wall. In our RVfw pacing simulations, the effect of activation spread away from the pacing site was not included. Mechanical activation time of the RVfw represented representative average activation time. Therefore, with this model, we were not able to test the effect of pacing at different locations within the RVfw. Nevertheless, the qualitative and sometimes quantitative agreement between our model simulations and experimental as well as clinical observations indicate that the simplifications made in the simulations may not obscure first-order effects of RVfw pacing on ventricular mechanics and pump function in severe PAH. The present study only focuses on the acute hemodynamic effects of RVfw pacing. Long-term effects are not considered. However, in analogy with cardiac resyn-
chronization in dysynchronous ventricles, acute hemodynamic effects can be expected to be maintained over time and may even lead to further improvements by reverse remodeling (3).

The effect of tricuspid regurgitation, which often exists in severe PAH and which leads to RV volume overload, is not included in the present simulations. RVfw pacing may aggravate tricuspid regurgitation by changing synchrony of RV papillary muscle activation, but may also decrease it by reducing RV end-diastolic volume and, thereby, tricuspid annular dilatation. Previous experimental studies showed that PAH leading to RV decompensation and heart failure is associated with structural remodeling of the RVfw myocardium [summarized in a review by Bogaard et al. (4)]. Ischemia and interstitial fibrosis may locally change active and passive myocardial material properties in severe PAH. Although such changes were not included in our simulations of decompensated PAH, we expect minor influence on the decreasing effect of early RVfw pacing on local mechanical work. Whether the translation of work homogenization to improvement of cardiac pump function, as observed in our simulations, is affected by such change of myocardial material properties is unknown. Nonetheless, Handoko et al. (10) showed acute improvement of RV pump function with RVfw pacing in remodeled and failing hearts of rats with PAH.

Clinical Implications

The present study may provide a theoretical framework for a novel therapeutic strategy for severely decompensated PAH patients. Although decrease of pulmonary vascular resistance remains the primary therapeutic target in PAH patients, RVfw pacing as an additional treatment may contribute to clinical improvement of the patient by unloading the RVfw and, thereby, delaying development of RV failure. Furthermore, it might be useful as a bridge to thoracic organ transplantation in these patients. Clearly, more experimental and clinical evidence is needed to prove that the predicted beneficial effect of RVfw pacing is clinically relevant for a PAH patient.

Conclusions

Our simulations of ventricular mechanics under pulmonary arterial hypertensive conditions show many similarities with data obtained in patients. Both simulations and measurements show interventricular mechanical asynchrony in severely decompensated PAH, associated with prolonged duration of RVfw shortening and inhomogeneous distribution of myofiber load over the ventricular walls. Early RVfw pacing results in more synchronous LV and RV pressure decay, more homogeneous distribution of myofiber load over the ventricular walls, and slight improvement of RV pump function. Our simulations suggest that RVfw pacing has the potential to be a novel therapeutic approach in PAH patients.

GRANTS

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