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A Computational Cardiac Model for the Adaptation to Pulmonary Arterial Hypertension in the Rat

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Abstract

Pulmonary arterial hypertension (PAH) imposes pressure overload on the right ventricle (RV), leading to RV enlargement via the growth of cardiac myocytes and remodeling of the collagen fiber architecture. The effects of these alterations on the functional behavior of the right ventricular free wall (RVFW) and organ-level cardiac function remain largely unexplored. Computational heart models in the rat (RHMs) of the normal and hypertensive states can be quite valuable in simulating the effects of PAH on cardiac function to gain insights into the pathophysiology of underlying myocardium remodeling. We thus developed high-fidelity biventricular finite-element RHMs for the normal and post-PAH hypertensive states using extensive experimental data collected from rat hearts. We then applied the RHM to investigate the transmural nature of RVFW remodeling and its connection to wall stress elevation under PAH. We found a strong correlation between the longitudinally-dominated fiber-level adaptation of the RVFW and the transmural alterations of relevant wall stress components. We further conducted several numerical experiments to gain new insights on how the RV responds both normally and in the post-PAH state. We found that the effect of pressure overload alone on the increased contractility of the RV is secondary to the effects of changes in the RV geometry and stiffness. Furthermore, our RHMs provided fresh perspectives on long-standing questions of the functional role of the interventricular septum in RV function. Specifically, we demonstrated that an inaccurate identification of the mechanical adaptation of the septum can lead to a significant underestimation of RVFW contractility in the post-PAH state. These findings showed that how integrated experimental-computational models can facilitate a more comprehensive understanding of the cardiac remodeling events during PAH.

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Keywords

Pulmonary hypertension; in-silico biventricular model; fiber reorientation; wall stress; contractility

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by a prolonged elevated pressure in the right ventricle (RV). To cope with this pressure overload, the RV undergoes a series of remodeling events that take place at multiple length scales. The remodeling primarily manifests as an early-stage compensatory hypertrophy to a maladaptive dilation of the RV at the organ-level and regional mechanical and structural alterations at the fiber-level. Several recent studies [1–4] have characterized remodeling processes at tissue- and fiber-level scales, revealing stiffening of the tissue and reorientation of the myofibers. However, details of how the remodeling at multiple scales influence and interact with each other and the existence of a common trigger to regulate these events remain largely unknown. Computational models of the heart can bridge the gap between local microstructural and mechanical alterations in organ-level cardiac function. Hence, these models provide means to gain a detailed understanding of the heart remodeling under PAH, and may ultimately be used to predict the prognosis of PAH in an expeditious manner.

Experimental studies on normal and hypertensive hearts [1, 2, 5] support the view that the myocardial wall stress is the primary mediator of right ventricular growth and remodeling (G&R) responses. Moreover, reduction of wall stress to homeostatic values constitutes a feedback mechanism governing ventricular adaptation and remodeling in hypertensive hearts. In a recent study [5], using a basic Laplace model of biventricular heart based on gross dimensional changes (collected from rat pulmonary arterial banding, or PAB, model of PAH), we showed that the average stress in a central region of the RV free wall (RVFW) and along the apex-to-base direction remained markedly above the estimated homeostatic range. This observation was consistent with localized adaptations of the wall constituents including alignment of both myofibers and collagen fibers towards the apex-to-base direction and stiffening of collagen fiber. Furthermore, these adaptations were concentrated in the midwall portion of the RVFW. Although this study provided preliminary insights into the role of in-vivo wall stress on the fiber-level adaptations in the RVFW, the need to fully quantify the stress distribution in the wall and gain a detailed understanding of stress-driven growth and remodeling process in the RV still remains. Image-based finite element (FE) modeling of heart is most likely the best approach for obtaining a realistic quantitative assessment of regional values of ventricular wall stress, enabling to characterize the relationships between the wall stress alterations, transmural structural and mechanical remodeling of the RVFW, and changes in the organ-level cardiac function.

The development of animal-specific computational models of the heart has markedly progressed in recent years, and can now accurately account for heart anatomy and fibrous structure to be able to describe the hemodynamics and active behavior of the normal animal heart. However, except a few recent studies [6, 7], the use of image-based ventricular computational models to study heart remodeling under PAH and explore the possible

reversibility of the remodeling has not been reported. In a recent study, Xi et al. [7] developed anatomically image-based biventricular computational models from normal and PAH patient human subjects. Using a hyperelastic warping method [8], they found that the contractile circumferential strain in the RVFW during systole is substantially smaller than that of normal case confirming the weaker contractility of the PAH heart in the circumferential direction. They used the fitted heart model to explore the anatomical adaptation of septum during PAH, and showed that how the PAH-induced change in the transseptal pressure difference (between right and left ventricles) accounted for observed septal curvature leading to the “bowing” of the septum towards the left ventricle (LV) under PAH.

A unique advantage of computational modeling approaches is that they provide a powerful tool to explore the link between remodeling events and changes in heart hemodynamic characteristics. They also can evaluate the independent effects of specific remodeling events on RV function. Along these lines, Gomez et al. [6] performed numerical experiments using a computational heart model (based on a PAB model of PAH) and demonstrated the longitudinal alignment of cardiac fibers as a compensatory mechanism could improve the ejection fraction of the RV. This observation was also consistent with our recent findings [5] that the fibers tend to align towards the apexto-base direction, concentrated in the midwall portion of the heart. Growing interest in the use of computational heart models to improve our understanding of PAH has inspired studies with a focus on capturing the overall tissue- and organ-level adaptations. Yet there is still a pressing need to investigate the heterogeneity of the RVFW adaptation and make connections between remodeling events at multiple scales ranging from fiber to organ.

Herein, we developed a computational rat heart model, and applied it to normal and post-PAH states, to: (i) understand the correlation between the changes in local in-vivo wall stress and the fiber-level remodeling of the RVFW, and (ii) investigate the transmural of the remodeling events on the organ-level performance. In addition, we used the RHMs to gain further insight into the role of the interventricular septum on normal and post-PAH RV's function. In contrast to large animal models, RHMs are less costly and more efficient to develop, validate and implement. In addition, rat species offer the possibility of genetic modification with the genetic consistency of inbred strains, altogether making them attractive candidates for the development of in-silico heart models. Building on the RHM presented here, our long-term goal is to develop animal-specific RHMs that can address the critical need to predict the *continuous* progression of PAH starting from the normal state.

2. Methods

2.1. Overview of Approach

We developed two implementations of the finite-element (FE) biventricular RHM using extensive datasets from a normal and a post-PAH rat heart in order to simulate and understand the local and organ-level remodeling of the RV in response to PAH. Terminal hemodynamic datasets were collected at the Molecular Cardiology Research Laboratory (Texas Heart Institute) from control (normal) hearts (n=4) and 4-weeks post-PAH hearts (n=4) developed using monocrotaline (MCT) injection [9]. Magnetic resonance imaging

(MRI) and diffusion tensor MRI (DT-MRI) scans [10] were acquired from the same hearts at the Small Animal Imaging Core Facility (University of Utah).

2.2. Animal Model

Both animal groups were treated in accordance with the Texas Heart Institute IACUC (Protocol 13021226). A total of 8 male Fischer-344 rats, eight weeks old at the start of the experiment, were used in this study. The hypertensive group rats (n=4; referred to as PAH thereafter) received a moderate dose of MCT (60 mg/kg body wt) in a single subcutaneous injection of MCT. Control group rats (n=4) were injected with an equal volume of phosphate buffered saline.

2.3. Hemodynamic measurements and heart fixation

At four weeks post PAH the pressure-volume (P-V) measurements of the RV and LV were collected. After sacrifice, blood was flushed out from the heart using heparinized saline, then two small catheters, inserted into aortic and pulmonary arteries, were used to infuse 2% alginate solution to close mitral valve and tricuspid valve and maintain the internal geometry of both ventricles at about the end-diastolic (ED) pressure. Heart tissues were immediately put in a 10% formalin solution for fixation. Additional details on the animal model and pressure measurement are provided in the supplementary materials.

2.4. Acquisition of Geometry and Fiber Distribution

The shape of ventricles and fibrous structure of myocardial tissues play critical roles in cardiac mechanics and remodeling process under PAH, that is, an accurate reconstruction of both the heart anatomy and the local anisotropy of myocardium is essential in capturing the pathophysiology of local tissue adaptations [11]. In this study, a high-resolution cardiac MRI scan was performed on the prepared hearts using a Bruker Biospec 7T (Billerica, MA) scanner. Also, DT-MRI scans were performed at the same configuration as in the MRI scans. Myofiber and sheet orientations were determined after post-processing the local diffusion tensors obtained from the DT-MRI data [11]. All the scans were performed at an isotropic 100 μm resolution (FOV $17.5 \times 15 \times 22.5$ mm, TR 500 ms, and TE 23 ms) over a period of 12 hrs. The DT-MRI accuracy was 5deg (see [12] for more detail). More detail on DT-MRI scans is also provided in the supplementary materials.

2.5. Computational RHM Development

The construction of the rat-specific biventricular RHM consisted of four main steps: (i) reconstruction and meshing the biventricular geometry, (ii) mapping the myofiber orientation to the meshed geometry, (iii) incorporating the passive and active constitutive model into the model, and (iv) conducting an inverse modeling to produce the organ-level hemodynamic measurements. The detail of steps (i) and (ii) is given below, and steps (iii) and (iv) are further discussed in the supplementary materials.

2.5.1. Biventricular Geometry and Mesh—The segmentation and reconstruction of 3-D full heart geometry from the MRI scans with 100 μm resolution were performed using ScanIP (Simpleware, Exeter, UK). The geometries for both control and PAH hearts were

truncated below the valve plane (Fig. 1A) and meshed using quadratic tetrahedral elements. A simple Laplace-Dirichlet boundary-value problem with fixed values at the endo- and epicardial surfaces [13] was used to identify the LV and RV regions in the RHM (Fig. 1A) needed for parameter estimation purposes. The LV region consisted of the LV free wall (LVFW) and the interventricular septum, while the RV region included the RVFW only.

2.5.2. Fiber Distribution Registration—The pseudo geometry, reconstructed from DT-MRI scans and weighted by principle directions at each voxel, was registered to the corresponding ventricular mesh from the same heart (Fig. 2(a)). As the number of voxels were much higher than that of elements, a single preferred (fiber) direction for each element centroid was estimated by taking a weighted average of all the directions contained within a spherical neighborhood of each element centroid.

The transmural mean fiber orientation across the RVFW thickness was calculated using the meshed geometry with registered fiber directions at each element, and presented with respect to the fixed anatomical coordinate system (Fig. 2(b)). To this end, a Laplace-Dirichlet boundary-value problem on the separated RVFW regions (with boundary conditions on endo- and epicardial surfaces; see Fig. 1A) was used to divide the RVFW to three layers ranging from endocardium to epicardium.

2.6. Wall Stress Calculations

The fitted model was used to assess the transmural stress distributions in the right ventricular free wall. To present the transmural variation of the wall stress, the Cauchy stress was averaged in each of the three layers of the RVFW (Fig. 2c). A local orthonormal anatomical coordinate system Fig. 2(b), consisting of transmural, longitudinal (apicobasal), and circumferential axes, was chosen in each element to present the stress. Simple Laplace-Dirichlet boundary-value problems with appropriate boundary conditions were used to determine these axes that vary throughout the RVFW. To determine the transmural distribution of the stress and fiber orientation, the RVFW was divided to three layers consisting of endocardial, midwall and epicardial regions (Fig. 2(c)). The average stresses were then defined in terms of the volume average of the local Cauchy stress $\mathbf{T}$ as

$$\bar{T}_{ii}^L = \frac{1}{Vol(\Omega^L)} \int_{\Omega^L} T_{ii} d\Omega^L, \quad i = t, l, c, \quad L = endo, mid, epi, \quad (\text{no summation}) \quad (1)$$

where the subscripts t , l , and c denote the respective variable in the transmural, longitudinal and circumferential directions, respectively, Ω^L denotes the volume of the three layers, namely endocardial(endo), midwall(mid), and epicardial(epi) layers of the RVFW in the deformed configuration. The averaging procedure was carried out for the central part of the RVFW (Fig. 2(d)).

2.7. In-Silico Experiments

The biventricular control and PAH RHM were used to conduct numerical experiments to gain further insights into local RVFW adaptations under PAH and how RV functions in general. The following three studies were done:

2.7.1. Effect of Elevated Pressure in the Control RHM—To study the independent effect of an immediately elevated pressure in a normal heart, the pressures measured in the RV and LV of the PAH heart were applied to the biventricular control model. The estimated parameters were compared to those of the control and PAH RHMs. This experiment was intended to decouple the effects of elevated pressure from those of anatomical and structural adaptations on the RV contractile function in a PAH heart.

2.7.2. Effect of RVFW Transmural Alterations on the Organ-Level Function—The fitted PAH model was used to investigate the effect of transmural alterations in passive properties of RVFW. The RVFW was divided to endocardial, midwall and epicardial layers (Fig. 2(c)). Our recent biomechanical analyses of hypertensive RVFW specimens (from rat PAB models [2, 5]) suggested pronounced tissue-level stiffening in the midwall region. Motivated by this finding, instead of assuming uniform properties in the RVFW as used in the parameter estimation, the midwall layer was assigned a larger stiffness compared to the endo- and epicardial layers. Specifically, the parameter c for *endo*, *mid*, and *epi* layers were chosen such that

$$(V_{RVFW})^{(-1)} \sum_{L = \text{endo}, \text{mid}, \text{epi}} Vol(\Omega^L) c^L = c, \quad (2)$$

where the value of c is the uniform stiffness of the RVFW estimated from the inverse model, V_{RVFW} is the total volume of the RVFW, and $Vol(\Omega^L)$ is the volume of each layer. The effect of this parametrization of the RVFW on the changes in organ-level RV behavior was studied.

2.7.3. Functional Extent of the RV—A long-standing question of whether functional extent of the RV includes part of the interventricular septum becomes particularly important when one studies the pathological adaptation of the RV [14]. Here, using Laplace–Dirichlet boundary-value problems, we modified the control and PAH RHMs such that the RV includes part of septal region. For each heart, we developed two additional biventricular models with extended RVs (Fig. 3), one with moderate and one with high RV extension. We used these models to examine the effects of the RV's extent on organ-level parameter estimation and made comparisons with the case of respective original RHMs with standard RV (i.e. RV not including any part of septum; see Fig. 1A).

3. Results

3.1. Adaptation of Pressure-Volume Loops

Significant changes were observed in the function and dimensions of both RV and LV from control to PAH (Fig. 4A). The P–V loop in the RV dramatically shifted to the right,

indicating a significant RV enlargement during the development of PAH, while it nearly preserved the stroke volume (SV). The ED and end-systolic (ES) pressures in the RV increased from 3.1 ± 0.5 and 23.9 ± 1.1 mmHg to 4.5 ± 0.6 ($p = 0.03$) and 44.6 ± 2.3 mmHg ($p < 0.01$), respectively ($n = 4$ for each group.) Increase in the RV overall contractility, measured by ES elastance (Ees), was noticeable (Fig. 4(a)). Interestingly, RV isovolumetric contraction in the PAH heart showed an opposite trend compared to that of the control heart by increasing volume while relaxing. The P–V loop in the LV showed a significant reduction in the SV, largely due to a decrease in the ED volume. A marked septal bowing towards to the LV was observed (Fig. 1B), leading to a smaller ED volume of the LV. The ES pressure was slightly smaller in the PAH heart, indicating a compromised systemic vascular resistance. The simultaneous fits of the RHMs to the respective P–V loop measurements of the RV and LV were excellent for both control and PAH hearts (Fig. 4A), with $r^2 > 0.98$.

Significant alterations were observed in the anatomy of the RV and the RVFW in the PAH heart (Table 1). A distinct change in the RVFW geometry from the control to PAH heart was the increase in the epi- and endocardial surfaces, stemming from the lengthening in the circumferential direction. This lengthening appeared to have a transmural variation with a small and significant amounts in epi- and endocardial regions, respectively. The total volume and average thickness of the RVFW showed minimal differences between the two states.

3.2. Material Parameters

A large increase in the overall passive stiffness of the RVFW myocardium was observed (nearly a three-fold increase in c), while the stiffness of LV only slightly increased (Table 2). Our pilot simulations indicated such an increase is necessary to capture both passive inflation and active contraction behaviors of the RV in the PAH heart. The full-cycle magnitude of the T_{Ca}^{+2} showed a significant increase in the peak value for the RVFW, while it slightly decreased for the LV myocardium (Fig. 4B).

3.3. Adaptation of Fiber Orientation

The transmural variation of the average fiber orientation across the RVFW thickness for the control heart had a consistent trend with previous histological studies [2]; the average fiber orientation at the endocardium was the closest to the longitudinal direction (i.e. apex-to-base direction, see Fig. 2(b)) and exhibited a circumferential rotation as moving towards the epicardium (see Fig. 5). The orientation distribution was also similar to the bi-layer representation of the normal rat RVFW architecture revealed previously in DT-MRI studies [15]. The fiber orientation for the PAH case showed much less variation across the RVFW thickness with a preferred alignment of fibers at nearly 45° from the longitudinal direction. The comparisons between control and PAH cases indicate that the fibers underwent a re-orientation towards the longitudinal direction (see Fig. 5), again, consistent with the previous histological studies using a PAB rat model for PAH [2, 5]. The amount of average reorientation was nearly uniform across the three layers of the RVFW, consistent with our histological analysis for the PAB model (see Fig. 4a in Ref. [5]).

3.4. Alterations in Transmural Wall Stress

The distributions of the average longitudinal and circumferential stresses (denoted by T_{ll} and T_{cc} , respectively) across the RVFW were compared for the control and PAH heart models (Fig. 6). The stress distribution exhibited stronger variation across the RVFW for the PAH RHM while the stress distribution across the control RHM was essentially uniform. The circumferential stress was nearly restored to the corresponding homeostatic values while the longitudinal stress remained much higher (in magnitude) than the respective stress in the control RHM. The stress alteration was stronger at the midwall region for both longitudinal and circumferential stresses. These observations were consistent with our previous findings on the changes in the (full-thickness) average wall stress in response to PAH using a Laplace model [5].

3.5. In-Silico Experiments

3.5.1. Pressure Overload in Normal Heart—The simulation of the control heart model subjected to the ventricular pressures recorded from the PAH heart was performed to investigate the exclusive effect of an elevated pressure on the active behavior of the normal RVFW (Fig. 7A). The estimated values of T_{Ca}^{+2} in the RVFW and LV were compared to the corresponding values for the case of control and PAH RHM simulations (Fig. 7B; the results in the left and right figures are extracted from Figs. 4B). The alteration in the peak value of T_{Ca}^{+2} in the RVFW of the control RHM, when subjected to an elevated pressure, was much less pronounced compared to the increase for the case of the PAH RHM. In contrast, the estimated range of T_{Ca}^{+2} values for the LV in the control RHM with elevated pressure remained approximately the same as that in the PAH RHM.

3.5.2. Transmural Adaptations of RVFW Properties—The sensitivity of the RV function to the transmural adaptation of contractility and stiffness in the RVFW of the control and PAH RHMs was examined for two cases: (i) $c^{(mid)} = 2c^{(endo)}$, (ii) $c^{(mid)} = 2.5c^{(endo)}$, with the condition of $c^{(epi)} = c^{(endo)}$. The forward simulations of RHMs with layered RVFW were carried out to generate new PV loops (Fig. 8). The results are shown only for the case of transmural adaptation in the passive stiffness while the contractility remained uniform in the entire RVFW. A transmural variation in the RVFW stiffness with pronounced changes in the midwall region improved the RV ejection fraction (RVEF) such that a more contrast between the midwall region and the rest of RVFW led to a stronger improvement in the RVEF. The improvement in the RVEF resulted from a considerable increase in the ED volume while the ES volume remained relatively unchanged. On the other hand, assigning transmurally-varying properties to the RVFW had virtually no effect on the LV function. The result for similar transmural changes, applied concurrently to contractility and stiffness of the RVFW, indicated no changes in the RV and LV P-V loops for either above-mentioned cases of (i) and (ii). (Results are not shown here for brevity.)

3.5.3. Extended RV—The contractility parameter T_{Ca}^{+2} was estimated for the control and PAH RHMs for three cases of standard, moderately extended, and highly extended RV, approximately included about 0%, 20%, and 40% of septal volume, respectively (see Fig. 3; two latter cases are referred to as Ext. RV1 and Ext. RV 2.) No significant differences were detected between the corresponding properties estimated for the control heart with standard

and extended RVs (Fig. 9(a-b)). However, for the PAH RHMs, the estimated T_{Ca}^{+2} for the RV exhibited moderate and significant increase (10% and 45% in the peak value, respectively), compared to that of the case of standard RV, while the estimated T_{Ca}^{+2} for the LV showed slight decrease (5% and 15% in the peak value, respectively), compared to the corresponding value for the case of standard RV.

4. Discussion

In this work, we have presented, to our knowledge, the first study using a computational model of the rat heart to examine the *transmural* adaptation of the RVFW with respect to its organ-level response to PAH. Using our anatomically and structurally image-based biventricular RHMs, we sought to test our hypothesis that the deviation of the in-vivo wall stress from homeostatic values in the RVFW plays a crucial role in fiber-level remodeling of the wall. Our analysis revealed a strong correlation between the transmural reorientation of the fibers and the restoration of pertinent components of the in-vivo wall stress. As a common advantage of image-based computational heart models, the RHM provided us an in-silico platform to investigate questions that are generally very difficult to answer with experiments alone. Two questions of interest in this work were: (1) what are the independent effects of an elevated pressure on RVFW function, and (2) what is the functional extent of the RV/RVFW, especially with respect to the septum. Discussion of specific results is given in the following.

4.1. Adaptations of Heart Active and Passive Behaviors

Our RHM predicted a three-fold increase in the passive stiffness of the RVFW. This is consistent with the increase in the diastolic stiffness, measured by ED elastance (Eed), observed in both clinical studies of PAH patients [7, 16, 17] and animal studies with MCT-injected [18] as well as pulmonary artery-banded (PAB) models [2, 4]. The amount of increase in the passive stiffness of RVFW, predicted by our RHM, falls within the reported increases [2, 16–18] in the Eed from control to PAH subjects that range from two to eight folds. This stiffening has been attributed to multiple mechanisms including hypertrophy, collagen fibrosis and intrinsic stiffening of cardiomyocytes in the RVFW. In our recent study [5] of PAB models of PAH, we used our fiber-specific constitutive modeling to quantify the contribution of these mechanisms and found that the a major portion of passive stiffening of hypertensive RVFW specimens is likely due to synthesis of new and significantly less undulated collagen fibers. Large increases in the collagen content of the RVFW have also been reported for MCT models of PAH [19] as we hypothesized to be a major cause for the passive stiffening of the RVFW in this study. Interestingly, in the latter report, noticeable increases in collagen content of LVFW and septum have also been observed in the MCT specimens which could explain the modest increase in the LV passive stiffness predicted by our model. The mechanisms behind the fibrosis in the LV of PAH hearts are the subject of ongoing research, but a potential RV-LV interdependency mechanism is the underfilling of the LV at advanced stages of the PAH [20, 21] that leads to the atrophy of cardiac myocytes and consequently the fibrosis.

Our prediction of about a six-fold increase in the peak value of T_{Ca}^{+2} (characterizing the continuum-level contractile force generation capacity of the myocardium) was consistent with the previous clinical and animal studies, reporting an increase in the RV contractility from P-V loop metrics such as Ees and the maximal dp/dt [16, 18]. The increase in Ees is a well-recognized compensatory mechanism of the RV in the early stage of the PAH to avoid the dilation of the RV and remain coupled with the vascular load [20, 22]. In fact, in response to pressure overload, the RV first exhausts its capacity to increase the contractility of RVFW myofilaments, which could go up to five to six folds, before it succumbs to a rapid dilation to maintain the cardiac output. On the other hand, our model predicted a slight decrease in the peak value of the LV contractility for the PAH RHM which is consistent with the possible myocytes apoptosis in the underused LV[23, 24] as a results of septal bowing and RV prolonged contraction [20, 25]. (We observed an average of 15 ms increase in the RV cardiac cycle duration with a normal cardiac cycle taking 225 ms.)

Furthermore, it is important to clarify that the parameter T_{Ca}^{+2} characterizes the active tension generated *per unit volume* at the resting length. This means that an increase in volume (such as hypertrophy) was already accounted for in the PAH anatomy, and changes in T_{Ca}^{+2} are chiefly due to *intrinsic* changes in the behavior of fiber ensembles once it is scaled by any change in the fiber density (see [2] for the analysis of density for the case of PAB specimens). That said, we emphasize that our RHMs were based on a phenomenological description of myocardium where collagen and myofibers contributions are not differentiated, and the estimates of the quantitative changes in T_{Ca}^{+2} and stiffness should be interpreted with this limitation.

4.2. The independent effect of a pressure overload

The comparisons of the results for the contractility parameter between the three cases, namely, the control RHM with normal pressure, the control RHM with PAH ventricular pressures, and the PAH RHM, provided important insights into how much of the contractility enhancement in an advanced-stage PAH heart is exclusively due to the pressure overload. Our results suggested that the normal heart could accommodate an immediately-developed pressure overload and preserve its RVEF with only a moderate enhancement in T_{Ca}^{+2} compared to a post-PAH heart that would need a significant increase in RVFW contractility. This result implies that a considerable portion of advanced-stage, and perhaps early-stage, remodeling events in response to PAH consist of maladaptive changes that intensifies the need for a stronger contractility in the RV to cope with the pressure overload. These changes involve alterations in the geometry of RV, and fibrotic processes and fiber re-orientation in the RVFW. The RHMs have the potential to guide the decoupling of the adaptive and maladaptive parts of these alterations that could significantly enhance our understanding of the RV adaptation to PAH.

4.3. Is Wall Stress Driving the Fiber-Level Remodeling?

Although it is generally known that the elevation of the wall stress in the hypertensive RVFW triggers wall remodeling via a hypertrophic response, the details of correlations between accurate wall stress alterations and fiber-level remodeling events remain largely unknown. Our recent study on using an approximate (Laplace) model to calculate the *full-*

thickness average wall stress [5] was the first report on correlation between the partial restoration of the wall stress and the re-orientation of the fibers for an end-stage PAH model. Motivated by this observation, in this work, we used the organ-level FE simulation to investigate this correlation in the transmural level. Consistently, our result suggested that normalization of the circumferential stress—in the ES configuration—plays an important role in the re-orientation of the fibers towards the apex-to-base direction across the RVFW. (Note that the stress along the fiber direction is, on average, the largest stress component at peak systole.) On the other hand, an important question concerns the concurrent role of the wall stress in specific anatomical alterations of the RVFW, in particular lengthening and flattening of the RVFW in the circumferential and longitudinal direction, respectively (as seen in Fig. 1B). This question certainly needs further investigation, but one plausible link between the fiber and anatomical remodeling events is that the RVFW lengthening undermines the dominant contractile capability of RVFW in the circumferential direction, and the longitudinal re-orientation of the fibers appears to be an attempt to improve the RV longitudinal mode of contraction.

4.4. Effects of Transmural Adaptations of RVFW on Cardiac Function

Our model predicted that the transmural remodeling, where the changes in the passive stiffness are concentrated in the midwall region, results in an increase in the ED volume while it does not affect the ES volume. This organ-level manifestation effectively works as increasing the preload in the RV at constant afterload and inotropy leading to an increase in the RV stroke volume and, consequently, to the RVEF. This observation could be linked to the clinical understanding of the RV dilation during PAH. More specifically, it is clinically believed that [26, 27] the end-diastolic RV chamber dilation progresses when contractility enhancements from wall thickening can not further maintain the cardiac performance (in particular, RVEF) under sustained pressure overload. Indeed, our model predictions suggest that the transmural changes of the stiffness with concentrations in the midwall could serve as one tissue-level remodeling mechanism to facilitate the RV dilation, that eventually leads to the decoupling of the RV output from atrial load [20, 28, 29]. Although the lengthening of myocytes could still be a primary mechanism behind the RV dilation in advanced PAH (as is the case in volume overload studies [30, 31]), the transmural adaptations of RVFW fiber-level properties may serve as another mechanism behind the dilation. On the other hand, our model predicted that the transmural remodeling of the RVFW did not influence the LV volume at all.

4.5. What constitutes the functional extent of the RV?

Inaccurate identification of the RV contractile extent may lead to an overor underestimation of the RV function in normal physiology and pathophysiology of the heart. RV free wall is traditionally known to drive the contraction in the RV, while the LV free wall and septum constitute the functional part of the LV. Our biventricular model provided a platform to perturb such a division and examine its effect on the estimation of the RV function. We found that although the extension of the functional part of the RV to include regions of the septum does not notably affect the estimation of the RV function in a normal heart, an accurate estimation of the changes in the RV contractile force (expressed by T_{Ca}^{+2}) in a PAH heart is highly dependent on the definition of the RV region. In particular, our RHM results

suggested that the limitation of the RV contractile part to the RVFW may lead to an underestimation and overestimation of the adaption in the RV and LV contractile forces, respectively. This finding may indicate an adaptation in the functional role of interventricular septum in advanced stages of PAH such that the physiological contractile motion of septum change to contribute to the contraction in the RV [32].

5. Limitations

Overall, the heart remodeling events predicted herein were qualitatively consistent with the clinical observations and extensive small animal studies for PAH, however, the values of the estimated parameters could have been somewhat impacted by the limitations and approximations in our computational RHM. Here, we assumed that myocardium is contracting in synchrony throughout each ventricle during the cardiac cycle. Given the collected data available to us, this assumption was sufficient to obtain preliminary estimates on tissue-level adaptation of material properties and average wall stress, however, we plan to implement a fully coupled electromechanical model of the heart to further investigate the changes in the contractile pattern of the RV during PAH. Our parameter estimation for the passive stiffness of the PAH heart was also limited to use the ED data from the P-V measurements. In the future, we plan to improve the estimation of passive properties by using biaxial mechanical testing of viable myocardial specimens of preferably the same animal (used to build the RHM). This procedure will also help to better fine-tune the estimation of the active properties using the P-V data. Finally, the MCT animal model used this work, although is regarded as a well-established model of PAH [33], is known to cause an inflammatory response in the pulmonary vasculature and the RV, separate from the effects of pressure overload. Although the significance of such confounding effects in the RV remodeling is the subject of ongoing research ([34]), they certainly limit the translation of our animal based-study findings to the case of PAH in humans.

6. Conclusions

In this work, we developed a detailed computational rat heart model of pulmonary arterial hypertension and used the model to explore the role of wall stress on the transmural fiber-level remodeling mechanisms, and their manifestation in the organ-level behavior. We found from the transmural analysis of DT-MRI data, collected from the MCT model, that fiber-level remodeling were dominated in the longitudinal direction, consistent with our previous histological studies of the RVFW specimens of the PAB rat model. Consistently, our biventricular model predicted that the longitudinal stress is *not restored* and remains higher in the midwall region. Several numerical experiments provided new insights on the RV's function and its adaptation to PAH. We found that the changes in the RV geometry and the RVFW stiffness, induced by pressure overload, have a larger impact on alterations of RVFW contractility than that of pressure overload alone. Our model further revealed that a better understanding of how the septal region adapts in response to PAH will have a significant impact on the accurate estimation of the RV's changes in stiffness and contractility. In conclusion, the insights provided in this study lay the foundation for developing an organ-level, structure-based growth and remodeling model that can simulate the experimentally-observed multiscale remodeling of the heart in response to PAH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

7. Acknowledgments

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Figure 1:

A. The separation of the meshed biventricular RHM into two regions: (i) RV which includes only the RVFW, and (ii) LV including the LVFW and the interventricular septum. The same method was applied to separate the regions for control and PAH hearts. **B.** The endocardial surfaces of the control and PAH hearts. (left) Right-ventricular surfaces, showing the RV significant dilation during PAH. (right) Left-ventricular surfaces, indicating a marked septal bowing toward the LV for the case of PAH heart.

Figure 2:

(a) Registration of the fiber orientation distribution, calculated from the DTMRI scans, to the meshed geometry. The vectors identify the local preferred fiber direction at the centroid of every element. (b) The local coordinate system used in this work. The local coordinates were used to calculate the mechanical stress components in each element. The transmural fiber orientation, represented by angle θ , was measured with respect to the local circumferential direction (positive anticlockwise). (c) Separation of the RVFW to three layers, labeled as *endo*, *mid*, and *epi* layers with equal volumes at end diastole. (d) The central region of the RVFW (shown in hatch) used for the calculation of the average stresses and fiber orientation in each layer. All the figures correspond to the RVFW of the control RHM.

Figure 3:

The inclusion of part of interventricular septum in the RV region of the PAH RHM. (a) Standard definition for the LV where it includes the LVFW and the entire septum. In this case, RV only includes the RVFW. (b) The RV region includes about 20% of the septal volume. (c) The RV region includes about 40% of the septal volume.

Figure 4:

A. Comparisons of pressure-volume (P-V) loops for the control and PAH RHMs. (left) Right-ventricular loops. (right) Left-ventricular loops. The markers and lines correspond to experimental data and fitted simulations, respectively. **B.** The estimated values of the active parameter $T_{\text{Ca}^{+2}}$ as a function of time for the Control and PAH hearts. Homogeneous values were simultaneously estimated for the (left) RV and (right) LV regions in each heart.

Figure 5:

Transmural distribution of the fiber orientation in the central region of the endo, mid, and epi layers (shown in Fig. 2(c-d)). **A.** Transmural distribution of the average fiber orientation angle, relative to the short-axis plane (Fig. 2(b)), for the control and PAH hearts. Color represents position across the thickness of the RVFW. **B.** 3-D representation of the fiber orientation distribution in the central regions of the endo, mid, and epi layers (These regions are identified in Fig. 2(c-d)).

Figure 6:

Transmural distribution of the wall stress at peak systole. **A.** Transmural distribution of the average wall stress across the RVFW thickness in the control and PAH RHMs. The average longitudinal and circumferential components (refer to Fig. 2(b)) of the Cauchy (true) stress were calculated for the three endo, mid and epi layers. **B.** Variation of the local wall stress along the fiber direction (denoted by T_{ff}) at multiple cross sections of the control and PAH biventricular RHMs. Note that the contrast between the RVFW and LV stress values is reversed in the PAH model compared to that of the control.

Figure 7:

The effect of a pressure overload on the active behavior of the control heart. **A.** The generated P-V loops in the RV and LV. The loops in the left and right figures are extracted from Figs. 4A. The loops in the middle figure are generated by prescribing the PAH pressure in the control model. **B.** The active parameter $T_{\text{Ca}^{+2}}$ estimated for the RV and LV regions as a function of time for the case of the (left) control RHM with normal pressure, (middle) control RHM with elevated pressure (i.e. the ventricular pressures recorded in the post-PAH state), and (right) PAH RHM.

Figure 8:

The effect of transmural variation in the passive stiffness of the RVFW on the PV loops in the PAH RHM. Numerical experiments 1 and 2 correspond to $c^{(mid)} = 2c^{(endo)}$ and $c^{(mid)} = 2.5c^{(endo)}$, respectively. (left) The right-ventricular loop. (right) The left ventricular loop. The transmural distribution of the properties with pronounced stiffness in the midwall region resulted in a marked increase in the RV end-diastolic and stroke volumes. The P-V loops of the left ventricle remained unchanged.

Figure 9:

The effect of variation in the definition of the right ventricular region on the estimation of the contractility parameter $T_{Ca^{+2}}$. The estimated values of $T_{Ca^{+2}}$ are shown for (a-b) control and (c-d) PAH hearts for three cases (see Fig. 3): RV region includes (i) only the RVFW, (ii) RVFW and 20% of the septum, (iii) RVFW and 40% of the septum.

Table 1:

Selected dimensional measurements from the control and PAH biventricular models.

Measure	Control	PAH
RV EDV (μL)	40.67	78.86
RV ESV (μL)	22.25	56.11
RV SV (μL)	18.42	22.75
RVFW Volume (μL)	6.96	6.47
RVFW Endo Area (mm^2)	46.21	67.12
RVFW Epi Area (mm^2)	92.23	96.65
RVFW Ave Thickness (mm)	1.01	0.98
RVFW Circ Length (Base)(mm)	9.85	12.25

Table 2:

List of estimated passive properties of the RV and LV regions for the control and PAH RHMs.

	RVFW		LV	
	α	$c(\text{kPa})$	α	$c(\text{kPa})$
Control	2.07	0.43	2.07	0.52
PAH	2.26	1.35	2.26	0.61