SB^{3}C2016
Summer Biomechanics, Bioengineering and Biotransport Conference
June 29 –July 2, National Harbor, MD, USA

COMPUTATIONAL ANALYSIS OF RIGHT-VENTRICULAR FIBER DISTRIBUTION AS A COMPENSATORY MECHANISM DURING PRESSURE OVERLOAD

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INTRODUCTION

Right ventricular failure (RVF) is a deadly deterioration of pump function that can occur in range of etiologies including congenial hearth disease, pulmonary hypertension and indirect pressure-overload from cardiomyopathy [1]. Although research focusing on elucidating progression of left ventricular (LV) failure is plentiful, current knowledge concerning the failing and recovering right ventricle (RV) is limited and insufficient for systematic development of effective treatments [2]. Characterizing patterns of failure and adaptation using preclinical and computational research are important tools for bridging this knowledge gap and for designing and testing of treatments that could have significant impact.

RVF due to pressure overload has been shown to reduce diastolic function associated to hypertrophy and interstitial collagen deposition (in fibrosis). These changes are conceptualized as compensatory mechanisms for limiting the magnitude of internal wall stresses via tissue stiffening [3]. Understanding the effects of structural remodeling in terms of fiber orientation is more difficult, but also of interest, because it relates not only to passive tissue stiffening, but also because fiber orientation has been shown to be a significant contributor to systolic organ function [4].

As in the LV, myocytes in the RV align in fibers following a helical structure quantified in terms of elevation angles with respect to the circumferential direction tangent to the ventricular wall [5]. In the healthy epicardium, the angles are mostly negative resulting in left-handed fiber helices, and the opposite is true in the endocardium. Angles in the mid-myocardium vary from positive to negative almost linearly i.e., the transmural rate of change in helical elevation angles can be approximated by a constant helical angle slope (HAS).

There is some inconsistency on reports regarding hypertension-induced HAS variations due to surgically induced RV pressure overload (RVPO) in animals studies, and there is little information on the precise mechanical consequences of such variation [6], [7]. Therefore, in the present study, we hypothesized that HAS variations caused by surgically induced pressure overload may be associated with a systolic structural compensatory mechanism.

METHODS

Subject-specific biomechanical simulations were constructed to interpret the effect of transmural fiber orientation (quantified by HAS) on cardiac function under elevated RV afterload. To this end, subject-specific finite-element (FE) models (n=3) were constructed from 3D images of the ventricular myocardium at early diastole obtained via multislice CINE MRI. The models were used to generate simulated predictions of RV function quantified by per ejection fraction (RVEF) under 4 conditions depending on RV afterload (normal or RVPO), and transmural fiber orientation (baseline or longitudinally aligned) for a total of 12 simulations. Significance in RVEF was calculated using parried t-tests with a p-value of 0.01

Geometry, structural variation, and intraventricular pressure information was obtained from a group of New Zealand white rabbits (2.0-2.5 kg) including controls (n=3), and RVF (n=6) due to pressure overload obtained via pulmonary artery banding. Band tightness was increased until RV end systolic pressure reached a minimum of 25 mmHg, and maintained until evidence of RVF was observed [8]. Images information was produced using a Bruker Biospec 7T imaging instrument. CINE-MRI was performed *in vivo* in the control group, and DT-MRI was performed *ex vivo in* controls and RVF. All animal protocols were subject to established guidelines and approved by supervisory offices at the University of Utah (protocol #13- 02010).

Pressure boundary conditions were based on interventricular catheter measurements of control animals for normal RV afterload,

and banded animals for RVPO, which was simulated as an increase of 20% on systolic pressure. The RVF group was divided in two groups according to wall thickness, which was interpreted as compensation to increased afterload. In the uncompensated group (n=3), 3D high-resolution DT-MRI scans in the RV wall yielded a quasi-linear variation from -60° in the endocardium to 60° in the epicardium (HAS = *120*°). The compensated group, had a 30% steeper HAS, which was modeled as a longitudinally aligned fiber distribution ranging from -75° to 75°.

The first set of simulations (normal pressure, and baseline fiber orientation) were used to optimize material parameters in a transversely isotropic Fung-type hyperelastic strain energy function so that predicted RVEF matched experimental measurements per CINE MRI observations at systole and diastole. Once optimized, all parameters other than those under study were held constant. A typical FE model and additional boundary conditions and material distribution appear in Figure 1. All simulations were performed using the FEBio Software Suite [9].

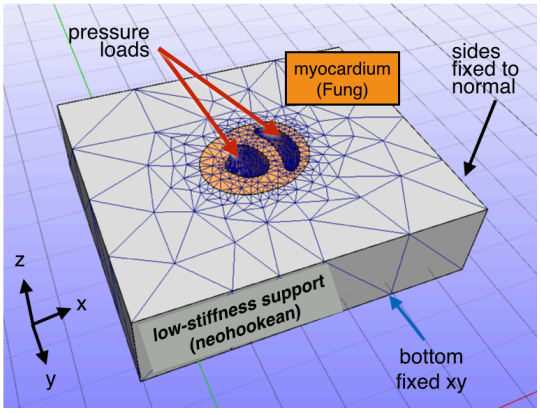

Figure 1: Finite element model of ventricular myocardium. Each subject-specific model (n=3) was modeled in 4 different conditions depending on RV systolic afterload and fiber orientation.

RESULTS

A typical FE model at different stages of the cardiac cycle was illustrated in Figure 2. As expected, end diastole results in dilated chambers, and active contraction results in diminished intraventricular volume development of torsion. Normal pressurization and fiber orientation resulted in volume predictions within 5% of those measured using CINE-MRI *in vivo*. Simulated RVEF calculations for normal and elevated pressure using with baseline or longitudinally aligned fiber are tabulated in Table 1. In RV pressure overload, with other parameters held constant, an increase in helical angle slope (by 30%, which is the high range of DT MRI observations) results in an improvement in ejection fraction of approximately 35%. This gain did not occur in the absence of pressure overload, which remained in the order of 3%.

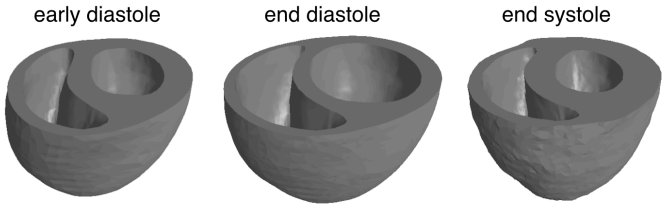

Figure 2: Representative simulation results under normal systolic pressure and baseline fiber orientation.

Table 1: Simulated RV ejection fraction for normal and elevated systolic pressure with or without fiber structure compensation (via HAS increase).

Pressure	*Normal*	*RVPO*
baseline (HAS = 120°)	0.36 ± 0.04	0.20 ± 0.06
longitudinally aligned (+30% HAS)	0.37 ± 0.04	0.27 ± 0.05
difference	*2%*	*35%**

Numerical values are expressed as mean ± (SD). * p =0.01

DISCUSSION

The numerical results show a clear functional consequence associated with structural changes. Increasing transmural helical slope, by an amount similar to that observed in the DT-MRI analysis, results in a remarkable improvement in RVEF under pressure overload. The same increase in HAS was not accompanied by significant changes in RVEF under normal conditions. This result suggests that longitudinal alignment may be particularly beneficial to recover ejection fraction in the presence of pressure overload, and it is consistent with previous studies where longitudinal alignment has been observed as one of the consequences of RVPO [6].

Further, even though all the animals in the RVF group showed clear signs of failure, DT-MRI showed that differences in HAS were observable on hypertrophic RVF hearts, and not on non-hypertrophic RVF, which may explain why previous DT-MRI studies did not report a change [7]. However, due to the relatively low number of animals, the results cannot be uniquely attributed to a biological mechanism without considering fixation or specimen preparation error as a possible disqualifier on the experimental result.

Nevertheless, this study offers numerical evidence that longitudinal fiber alignment could be a compensatory mechanism associated to systolic organ function. Further, mathematical modeling, CINE and diffusion tensor MRI could differentiate between compensated and decompensated forms of RV failure, as limitations associated with non-invasive measurement of fiber orientation can be mitigated by application of in vivo imaging in the sort future.

ACKNOWLEDGEMENTS

Thanks to the Small Animal Imaging Facility, and the Musculoskeletal Research Laboratories at the University of Utah.

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