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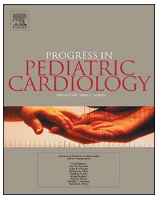

Evaluation of pulmonary artery wall properties in congenital heart disease patients using cardiac magnetic resonance

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ABSTRACT

Congenital heart disease patients (CHD) with complex right heart disease are often left with residual lesions that result in right ventricular (RV)-pulmonary artery (PA) dysfunction post surgery. The appropriate timing of re-intervention to correct these lesions is difficult to determine due to lack of suitable quantifiable diagnostic techniques. The PA wall (material) properties characterize the mechanical behavior of the PAs and thus, contribute significantly to the RV-PA function. Therefore, the arterial wall properties of the main PA (MPA), left PA (LPA), and right PA (RPA) of three CHD subjects with normal RV-PA function and anatomy were quantified using retrospective pressure-diameter data as input to a constitutive (material) model. Intra-vessel (MPA *vs* branched PAs) and inter-subject variability was observed in the wall properties and consequently, the arterial wall compliance and stress-stretch characteristics. The LPA was least compliant in comparison to the MPA and RPA. Also, the circumferential and axial stress in the PAs increased with the subject's age. Therefore, monitoring the wall properties of the individual PAs may provide valuable longitudinal (time-dependent) information on disease progression of CHD patients.

1. Introduction

Pediatric patients with congenital heart disease (CHD) experience critical ventricular-vascular abnormalities leading to a high risk of morbidity and mortality. Specifically, patients with complex right heart lesions account for 25% to 30% of the total number of CHD cases [1,2]. Common surgical intervention procedures for right heart lesions include the placement of native patches, artificial valves, and right ventricle-pulmonary artery (RV-PA) homografts and conduits. Although the surgical outcomes are excellent, patients encounter post-operative sequelae *i.e.* residual lesions such as pulmonary regurgitation due to an incompetent pulmonary valve, RV outflow tract obstruction, and PA stenosis [3–5]. These residual lesions result in varying degrees of functional and anatomical derangement of the RV and PAs as the patients age. Consequently, a remodeling of the internal structure of the RV-PA wall takes place, which causes progressive RV and PA dilatation. Over time, this dilatation can induce irreversible RV myocardial contractile dysfunction, RV hypertrophy, arrhythmias, and even sudden death [3–5].

The imaging modalities, cardiac magnetic resonance (CMR) and Doppler echocardiography, are considered as current gold standards for obtaining functional and anatomical information of post-operative RV-PA dysfunction. These modalities are also supplemented by cardiac catheterization for accurately obtaining functional (pressure) data. Although the early post-operative mortality rate has been reduced with recent advances in diagnostic and treatment measures, the mortality rate during the later years still remains high [6]. Therefore, the pathophysiology of the RV and PAs has to be carefully monitored throughout the patient's lifetime in order to accurately determine the time of re-intervention. RV volume- and pressure-based hemodynamic diagnostic endpoints are commonly used in conjunction with guidelines for clinical cut-off values [7,8], for monitoring the post-operative RV-PA status and disease progression in a clinical setting. However, due to the complexity of post-operative symptoms, it is sometimes challenging to accurately assess the disease progression with these endpoints.

Recent studies have proposed energy-based diagnostic endpoints for monitoring the RV-PA hemodynamics and determining the timing of re-intervention [9–11]. Furthermore, analytical, computational fluid dynamics, and 4D MRI techniques have been used to augment the evaluation of PA hemodynamics and energy-based endpoints [9,12–21].

Considering the coupled nature of the RV-PA wall mechanics and hemodynamics, it is important to account for the mechanical behavior of the PA wall in addition to the hemodynamics in the longitudinal (time-related) assessment of CHD patients. More importantly, the PA

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geometry and morphology, which governs its wall mechanics, has been known to play a significant role in post-operative RV dilatation and afterload [22].

The mechanics of the PA wall are known to be complex – the PA tissue displays deformation-, direction-, and time-dependent properties. In other words, the PA wall exhibits a nonlinear, anisotropic, and viscoelastic behavior. The PA wall mechanics including compliance and stress-stretch characteristics can be evaluated using the PA wall (material) properties. Considering the geometrical dissimilarities between the different branches of the pulmonary vasculature (for example, main, left, and right PA), the main and branched PAs may have distinct wall properties. Therefore, monitoring the wall properties of the individual PAs may provide valuable longitudinal (time-dependent) information (*e.g.* diagnostic endpoint) on disease progression of CHD patients. For example, the wall properties of the PAs could be used as inputs to patient-specific computational and analytical models to accurately simulate compliant PA hemodynamics.

Multiple *in vivo* and *ex vivo* studies have focused on evaluating the wall microstructure and pressure-strain modulus of either the main PA (MPA) or one of the branches (left PA (LPA) or right PA (RPA)) of CHD patients [22–30]. Furthermore, constitutive modeling has been used in conjunction with *in vivo* and *ex vivo* test data to characterize the complex wall properties of animal PAs [31–34]. However, application of such modeling techniques for characterizing the PAs of CHD patients has been limited by the lack of experimental data for human tissue. Using an *in vivo*-based methodology proposed for constitutive modeling of human arteries [35], our group [36] characterized and delineated the material properties of only the LPA of an abnormal and normal CHD subject. However, the evaluation and delineation of wall properties of each of the PAs for normal and abnormal subjects are lacking.

As a first step, the aim of this pilot study was to apply the *in vivo*-based methodology to characterize the wall properties of individual PAs of CHD subjects having a normal right heart. Therefore, in this retrospective human study, the arterial wall properties of the MPA, LPA, and RPA of CHD subjects with normal RV-PA function and anatomy were quantified using pressure-diameter data as input to a constitutive (material) model. Subsequently, the wall properties were used to evaluate the mechanical behavior *i.e.* compliance and stress-stretch characteristics of the PA wall. A primary comparison of the wall properties and characteristics has been made between the MPA and branched PAs (LPA and RPA) of a specific subject (intra-vessel variability). In addition, comparisons have also been made for a specific PA of different subjects (inter-subject variability). Due to the retrospective nature of this study, a limited and small patient population was used to characterize the intra-vessel and inter-subject variability in the wall properties of the PAs. This may limit the clinical relevance of this study and hence, a future prospective study will be necessary for validating these study findings. However, the findings, reported in the *Results* section can be useful in determining a larger sample size for the prospective study.

2. Methods

First, details of the human subjects considered for this study are provided, followed by a description of the clinical procedure for acquiring the *in vivo* pressure and diameter data. Lastly, the material model including the constitutive governing equations and the optimization algorithm is described.

2.1. Study Population

Clinical data from three CHD subjects ($n = 3$) was used for conducting this retrospective human study. The data was obtained in a de-identified form from the Cincinnati Children's Hospital Medical Center (CCHMC) under the approval of the Institutional Review Board (IRB). All three subjects (subject N1: age = 13 years, body surface area (BSA) = 1.57 m^2; subject N2: age = 19 years, BSA = 2.06 m^2; subject N3: age = 25 years, BSA = 1.8 m^2) had a normal RV-PA physiology including a normal RV outflow tract, native MPA and branched PAs (LPA and RPA), and a normal pulmonary valve function. However, subjects N1 and N2 had an abnormality in the left heart – subject N1 was diagnosed with a coarctation of the aorta while subject N2 was observed to have sub aortic stenosis. Subject N3 was brought in to CCHMC for clinical diagnosis due to the occurrence of unexplained syncope. Cardiac catheterization and cardiac magnetic resonance (CMR) imaging were conducted as routine clinical procedures for all three subjects. Catheterization and CMR data of the MPAs of all the three subjects was available. On the other hand, data of the branched PAs was limited – catheterization and CMR was conducted on the LPAs of subjects N1 and N2 while catheterization and CMR was conducted on the RPA of only subject N2.

2.2. Data Acquisition

CMR was performed using a 3.0 Tesla MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands) at the Heart Institute of CCHMC. A representative CMR image of the longitudinal view of the MPA, LPA, and RPA, taken in the short-axis plane of the heart, is shown in Fig. 1. Two-dimensional (2D) cine CMR images were obtained at 30 time-points over a single cardiac pulse at planes oriented perpendicular to the MPA, LPA, and RPA as indicated by the red dashed lines in Fig. 1. Details of the CMR imaging sequence, used to acquire data for an individual vessel (MPA, LPA, RPA) of a specific subject are provided in Table 1. The length of each acquisition was 1–2 min depending on the field of view and heart rate. Further, each acquisition was conducted using a combined breath holding (cine structural imaging) and free breathing (phase contrast) protocol.

Fig. 2 shows typical CMR images of the MPA (Fig. 2a) and a branched PA (LPA, Fig. 2b), obtained at different phases of the cardiac cycle. The images in the left pane represent the anatomy and flow magnitude at systole while the images in the right pane represent the anatomy and flow magnitude at diastole. In order to obtain anatomic information of the arteries, contours (marked in red in Fig. 2) were created along the artery wall using a thresholding scheme, based on image pixel intensity (QFlow, Medis medical imaging systems). The area enclosed within the red contour represented the cross-sectional area of the artery. Subsequently, the diameter (hydraulic) of the PAs was evaluated from the areas. Using this method, the diameters of the PAs were computed at 30 time-points over the cycle for all the three subjects.

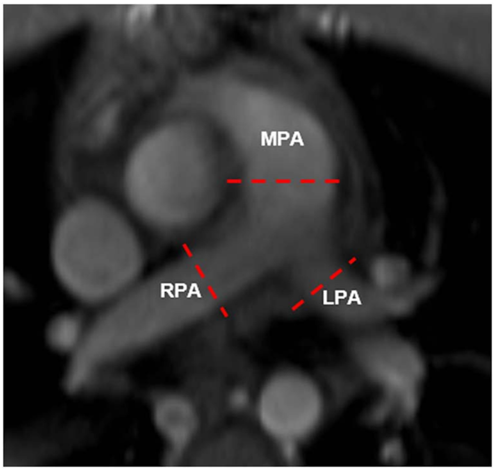

Fig. 1. A representative two-dimensional magnetic resonance image showing a longitudinal view of the pulmonary arteries. The image shows the main pulmonary artery (MPA), left pulmonary artery (LPA), and right pulmonary artery (RPA) captured in a plane perpendicular to the long axis of the human body. The red dashed lines represent cut planes at which cross-sectional magnetic resonance images of the arteries were taken.