Estimated in Vivo Postnatal Surface Growth Patterns of the Ovine Main Pulmonary Artery and Ascending Aorta

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Delineating the normal postnatal development of the pulmonary artery (PA) and ascending aorta (AA) can inform our understanding of congenital abnormalities, as well as pulmonary and systolic hypertension. We thus conducted the following study to delineate the PA and AA postnatal growth deformation characteristics in an ovine model. MR images were obtained from endoluminal surfaces of 11 animals whose ages ranged from 1.5 months/15.3 kg mass (very young) to 12 months/56.6 kg mass (adult). A bicubic Hermite finite element surface representation was developed for the each artery from each animal. Under the assumption that the relative locations of surface points were retained during growth, the individual animal surface fits were subsequently used to develop a method to estimate the time-evolving local effective surface growth (relative to the youngest measured animal) in the end-diastolic state. Results indicated that the spatial and temporal surface growth deformation patterns of both arteries, especially in the circumferential direction, were heterogeneous, leading to an increase in taper and increase in cross-sectional ellipticity of the PA. The longitudinal PA growth stretch of a large segment on the posterior wall reached 2.57 ± 0.078 (mean $\pm$ SD) at the adult stage. In contrast, the longitudinal growth of the AA was smaller and more uniform (1.80 ± 0.047). Interestingly, a region of the medial wall of both arteries where both arteries are in contact showed smaller circumferential growth stretches—specifically 1.12 ± 0.012 in the PA and 1.43 ± 0.071 in the AA at the adult stage. Overall, our results indicated that contact between the PA and AA resulted in increasing spatial heterogeneity in postnatal growth, with the PA demonstrating the greatest changes. Parametric studies using simplified geometric models of curved arteries during growth suggest that heterogeneous effective surface growth deformations must occur to account for the changes in measured arterial shapes during the postnatal growth period. This result suggests that these first results are a reasonable first-approximation to the actual effective growth patterns. Moreover, this study clearly underscores how functional growth of the PA and AA during postnatal maturation involves complex, local adaptations in tissue formation. Moreover, the present results will help to lay the basis for functional replacement by defining critical geometric metrics. [DOI: 10.1115/1.4024619]

Introduction

The normal development of the pulmonary artery (PA) can be greatly affected in many congenital heart defects, often leading to pulmonary hypertension if left untreated [1,2]. Congenital abnormalities of these arteries often necessitate surgical repair or the use of a valved conduit replacement [3–5], requiring multiple reinterventions due to regurgitation or failure of the prosthetic conduit [6]. In recent years, there has been a growing interest in the development of a living autologous tissue graft that could address the critical need for growing substitutes in the repair of congenital cardiovascular defects [7–9]. Regardless of the particulars of the therapeutic approach, the detailed growth characteristics of the native artery are required to establish the baseline dimensional changes post-implantation. Moreover, delineating the normal arterial growth patterns has implications for the timing and nature of surgical repair [3,10]. The geometries of the PA and ascending aorta (AA) are also important indicators of pulmonary and systolic hypertension [11], such as the ratio of diameters of

the PA to the AA is an important measure of pulmonary hypertension in younger adults [12].

During the prenatal period, a state of physiologic pulmonary hypertension exists due to the equalization of pressures by the patent ductus arteriosus, resulting in similar wall thickness of the AA and the PA. After birth, as the ductus arteriosus closes, the pulmonary arterial pressure decreases. After the first year of life, thickness of the PA is normally less than half that of the adjacent ascending aorta, although the diameters of the two great arteries remain the same relative to one another [13]. During homeostatic conditions, the total pulmonary and systemic blood flows are essentially identical. In spite of their comparable blood flow rate, the anatomic characteristics of these two segments of the cardiovascular system differ substantially [14].

The significance of postnatal remodeling in the geometry of the great arteries (mainly for the aorta) has been previously identified and basic dimensional changes during the postnatal growth period reported [15,16]. An understanding of the dynamic processes of developmental growth in arteries requires a detailed description of the temporal and spatial patterns of geometrical changes. However, the full postnatal surface growth deformation of these arteries has yet to be established. Moreover, despite their close mechanical association throughout life, the effects of the AA and PA physical interactions on their respective geometries during the

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normal postnatal remodeling period remain unknown. In a recent study using basic geometric characterization approach, we demonstrated that the PA did not undergo a strictly affine scaling during normal postnatal growth [17], but rather demonstrated heterogeneous growth patterns. Specifically, it was shown that the PA becomes increasingly tapered with maturation along with an increase in the cross-sectional ellipticity, with quite different growth patterns in the AA. These preliminary results suggested that during postnatal development each artery is possibly guided by local physical interactions resulting in heterogeneous growth patterns.

These considerations point towards a need for a basic understanding of the driving process of the growth trends in the PA and AA. In the kinematics of finite growth, the effects of growth are represented by the transformation of the stress-free state using a multiplicative decomposition of the total deformation gradient $\mathbf{F}$ into an elastic $\mathbf{F}_e$ and a growth $\mathbf{F}_g$ component, so that $\mathbf{F} = \mathbf{F}_e \mathbf{F}_g$ [18]. However, no such information currently exists for the postnatal development of the PA and AA. Moreover, the undertaking of detailed investigations to determine $\mathbf{F}_g$ and $\mathbf{F}_e$ need to be preceded by studies to establish basic patterns to see if such studies are fully warranted and to guide the experimental designs. Our goal was to shed light on the specific effective growth deformation patterns in these arteries during postnatal development.

Methods

Imaging, Segmentation, and Registration. The methodology for obtaining the 3D in vivo arterial geometry data using an ovine model has been previously presented [17]. Briefly, the in vivo end-diastolic magnetic resonance images (MRI) of both arteries' endoluminal surfaces in eleven different animals (Ovis aries, subspecies Dorset) weighing between 15.3 to 56.6 kg, of ages 1.5 (the earliest time point used for ovine heart valve implants [19]) to 12 months (full adulthood), were obtained. Imaging was performed with a 1.5 T MRI scanner (Philips Achieva, Best, the Netherlands) and a 5-channel cardiac radio frequency surface coil. After localizing images, breath-hold ECG-gated steady-state free precession sequences of thorax were obtained in long and short-axis ventricu-

lar planes, and in the long and short-axis planes to the pulmonary valve. A three-dimensional isotropic data set (with resolution of $1.5 \times 1.5 \times 1.5$ mm sections, reconstructed to $0.78 \times 0.78 \times 0.78$ mm) was acquired at end-expiration and end-diastole. The segmentation masks of MR images of the PA and AA endoluminal surfaces were acquired using the semiautomated shells and spheres method [20]. The algorithm also generated a set of paired boundary and local center locations [20]. The local center points helped define the centerline paths used in registering PAs as well as to develop an appropriate curvilinear coordinate system to carry out the deformation analysis. In the present work, the PA was defined from the pulmonary sinotubular junction (STJ) to the pulmonary bifurcation point (BFN), and the AA from the aortic STJ to the BFN-intersecting plane of the AA. The section of each artery so defined was utilized as the region of interest (ROI) (Fig. 1).

While semiautomated nonrigid 3D registration methods that can deform one image to match the template image by defining a spatial transformation exist [21], the inherent variations of the PA and AA surface geometries precluded their use. The AA and PA datasets were therefore registered separately through the following global affine transformation sequence. The affine registration of the PA was defined from three significant features: the centerline path, and the left and right pulmonary arteries at the BFN (Fig. 1(a)). The AA registration was based on the main side branch and the two coronary arteries at the sinuses of Valsalva (Fig. 1(a)), which formed three prominent anatomical landmarks. The AA and PA of the youngest animal (1.5 month-old, 15.3 kg in mass) were chosen as the referential templates to define registration. Each segmentation image was aligned to the corresponding template using the following two-step registration procedure. An automated intensity-based registration was first used to align the images, and then the images were manually transformed to improve alignment of the aforementioned features. The automated registration was performed within a standard registration framework consisting of a cost function, optimizer, transform, and interpolator. In this framework, a cost function was computed between the two images to measure similarity; the optimizer iteratively adjusted the parameters of a transform to improve the cost function, and the interpolator applied image transforms to calculate sub-voxel values. In this study, a multiresolution global

Fig. 1 (a) 3D rendered anatomical positions of the ascending aorta (AA) and pulmonary trunk (PT), shown in the anterior view (Top), with the medial aspect outlined as a dashed square, and in the posterior view (Bottom). (b) and (c) illustrate nonregistered images of the oldest adult pulmonary artery (PA) and AA (Top), and registered to their corresponding templates of youngest animal (Bottom). Note that the main side branch coming off of AA in ovine branches off to brachiocephalic, left common carotid and left subclavian arteries at a more distal point.

Fig. 2 (a) The common center axis of the PA along with individual center axes points (black) from multiple time points (scaled), with the Frenet frame and global Cartesian coordinate systems. Note the high degree of consistency between the centerline paths from the animals studied. Also shown in (b) are the AA and PA center axes from two perspectives to demonstrate larger tortuosity of PA compared to AA. (c) A schematic surface parameterization and deformation showing the base vectors in the reference to the end-diastolic loaded state of the youngest animal (15 kg) and those of current or 'deformed' geometry and the fitted centerline (CL).

optimization method [22] with a correlation ratio cost function was used to determine the affine transformation variables of 3D rotation and scaling with the nearest neighbor interpolation, appropriate for binary data, used to apply the transform.

The AA registration was manually refined by aligning the segments of coronary arteries proximal to sinuses of Valsalva and the main side branch with those of the template (Fig. 1(c)). To develop the PA centerline paths, the surface and local center points were aligned with the X₃ axis (Fig. 2(a)), and the cylindrical polar coordinates of local center points computed. The centerline path of each PA was defined using fourth and second order polynomials to interpolate the radial and angle coordinates of local center points as a function of the X₃ coordinate, respectively. The 3D curvilinear feature of the centerline paths allowed refining PAs' registration and defining optimal scaling factors (Fig. 1(b)). The AA and PA registered surface renderings were displayed together and each surface data set was re-cropped according to the aforementioned boundary definitions (Fig. 1(b) and 1(c)).

General Surface Fitting Considerations. Due to practical considerations, the imaging data was acquired from animals at different ages, so no direct physical marker information was available. Thus, for the present study we assumed that the *relative* circumferential and longitudinal locations of surface points were locally preserved throughout postnatal growth. This assumption was based on our observations that the overall shape of both arteries appeared to

be remarkably well preserved (see "Registration" results below). The 3D coordinates of arterial surfaces points were fit to an in-surface coordinate space using piece-wise cubic order polynomial finite-element shape functions. The resulting surfaces were fit to a contiguous time based node fitting functions to estimate the effective growth deformation field. Specific steps are given in the following.

Surface Parameterization. A toroidal coordinate system was defined to allow use of the linear least-squares fitting method for developing surface models of the PA and AA, where only a single coordinate was fitted [23], and resulted in a relatively uniform distribution of data points in the in-surface coordinate plane [24]. The local coordinate of each surface point was determined by finding its orthogonal projection on the centerline path using the gradient-based unconstrained optimization routine of backtracking line search, implemented in Mathcad (Parametric Technology Corporation, MA, USA).

Common Centerline Path Generation. In order to define all the corresponding surfaces with respect to one coordinate system, a common centerline path was developed. The common centerline path of all PA surfaces was simply developed by interpolating the radial and angle coordinates of individual centerline paths as a function of X₃ coordinate using second and fourth order polynomial functions, respectively, (Fig. 2(a)). The common

centerline path of AA surfaces was defined by applying the same order of polynomial interpolations to all the local center points together.

Coordinate Transformation. Once the parameterization of surface points was complete, the local Cartesian coordinate was defined at each of the projection points on the centerline path based on the Frenet frame (Fig. 2(a)) [25]. This coordinate transformation is represented by

$$\mathbf{r}(\theta, x_3) = \mathbf{x}(\theta, x_3) = \mathbf{Q}(s) \cdot \mathbf{x}'(\theta, s) + \mathbf{y}(x_3) \quad (1)$$

where s is the length along center axis path, $\mathbf{x}'$ is the local coordinate of the surface point in the current configuration, with its projected centerline path point $\mathbf{y}$, and $\mathbf{Q}$ is the local 3D rotation matrix (Appendix A).

Surface Fit Methodology. A finite element based surface fit was developed to model the arterial surface geometry using 2D finite element interpolation functions derived from the tensor product of 1D cubic Hermite element formulation to enforce C^1 continuity [23]. The bicubic Hermite finite element has four functions defined at each node: the radial coordinate and its partial first and cross derivatives with respect to local isoparametric coordinates ξ and η (which correspond to the θ and s in Fig. 2). Thus, the radial coordinate of an internal surface point P is computed by summing the product of 16 terms

$$\rho_P = \psi_i^{jk}(\xi, \eta) \rho_i^{jk} \quad (2)$$

where ρ_i^{jk} is the vector of nodal variables, subscript $i = 1, 4$ denotes the node number, and subscripts $j, k = 0, 1$ denote the order of derivatives with respect to ξ and η , respectively.

Finite Element Grid Size. The very high density of data points from MR images greatly exceeded the minimum requirement of 16 data points per element (with 16 nodal variables). However, the accurate reconstruction of the 3D surface in the toroidal coordinate system through the finite element interpolation scheme required determination of the appropriate mesh resolution for capturing the prominent features while simultaneously smoothing the noise inherent in MR imaging and the segmentation processes. To this end, we developed the following approach to determine the optimal number of elements required to accurately represent the endoluminal surface geometries. The mesh resolution was determined based on the oldest PA geometry due to its more complex 3D shape compared to the AA. The in-plane dimensions of the smallest feature of interest among all PA surfaces was resolved to be 6 mm and 7 mm in s and θ directions, respectively. A finite element surface fit with relatively dense grid size of 8 by 8 elements, that captured the features having twice as high of the spatial frequency as that of the smallest feature of interest, was initially generated. The surface fit was sampled at quarter size of the smallest targeted feature in θ and s directions. A 2D FFT analysis was performed on the surface fit data using MATLAB (The MathWorks Inc. MA, USA). The numbers of elements in θ and s directions were reduced iteratively until the 2D FFT power spectrum of the surface fit indicated significant smoothing of the determined spatial noise.

2D Effective Surface Deformation. As stated earlier, we are concerned with estimating the total surface growth in the loaded end-diastolic state, using an effective deformation gradient tensor $\mathbf{F}_{\text{eff}}$ as the descriptor referenced to the youngest animal (of 15.3 kg mass). We utilized a convective coordinate system under the assumption that deformations occur such that the coordinate locations (i.e. θ, s) for any surface point undergo minimal changes

during maturation (Fig. 2(c)). Starting with the endoluminal surfaces in the polar toroidal coordinate, base vectors were defined as

$$\mathbf{G}_\alpha = \frac{\partial \mathbf{R}}{\partial \Theta^\alpha}, \quad \mathbf{g}_\alpha = \frac{\partial \mathbf{r}}{\partial \Theta^\alpha} \quad (3)$$

where $\alpha = 1, 2$ and $(\Theta^1, \Theta^2) = (\theta, s)$, $\mathbf{G}_\alpha$, and $\mathbf{g}_\alpha$ are the referential and current base vectors (determined for each time point), respectively (Fig. 2(c)). Note that the base vectors are not necessarily orthogonal nor of unit magnitude [26]. The resulting strain tensor was determined using [26]

$$\varepsilon_{\alpha\beta} = \frac{1}{2} (g_{\alpha\beta} - G_{\alpha\beta}) \quad (4)$$

where $g_{\alpha\beta} = \mathbf{g}_\alpha \cdot \mathbf{g}_\beta$ and $G_{\alpha\beta} = \mathbf{G}_\alpha \cdot \mathbf{G}_\beta$. Since we are interested in an effective strain tensor expressed in current configuration, we defined the $\varepsilon_{\alpha\beta}$ as an effective Almansi strain tensor $\varepsilon_{\alpha\beta}$, so that the corresponding effective growth-induced stretches along the coordinate lines were determined using

$$\lambda_\alpha = \frac{1}{\sqrt{1 - 2 \frac{\varepsilon_{\alpha\alpha}}{g_{\alpha\alpha}}}} \quad (5)$$

where the repeated indices do not imply summation. The measure of shear during growth was defined as

$$\gamma = \cos^{-1}(\hat{\mathbf{u}}_\theta \cdot \hat{\mathbf{u}}_s) - \cos^{-1}(\hat{\mathbf{U}}_\theta \cdot \hat{\mathbf{U}}_s) \quad (6)$$

where $\hat{\mathbf{u}}_\theta = \mathbf{g}_\theta / |\mathbf{g}_\theta|$, $\hat{\mathbf{u}}_s = \mathbf{g}_s / |\mathbf{g}_s|$ and $\hat{\mathbf{U}}_\theta$ and $\hat{\mathbf{U}}_s$ are the corresponding unit base vectors in the reference configuration (here, again, defined as the youngest animal end-diastolic state). Since it was shown that the mass of the animals highly correlated with their age and was known more exactly, mass was used to identify the growth stage throughout the study [17]. The subsequent growth rates $\dot{\lambda}_\alpha$ (in units of kg^{-1}) were obtained by computing the instantaneous slope of the growth stretch ratio curves as a function of mass, at each unit mass interval from 15 kg to 60 kg.

Time Interpolated Growth. To gain better insight into major trends in spatiotemporal relationships, continuous surface deformation maps of the growing PA and AA were generated as follows. The 3D surface shapes were approximated as a function of time (again using the animal mass value) by interpolating the four nodal surface fit variables. The radial coordinates were found to follow a linear behavior, whereas the remaining nodal variables were approximated using a second order polynomial. The scaling factors, obtained from registration, were interpolated linearly as a function of mass. The interpolated shape of each artery at 15 kg was used as the referential geometry to obtain the spatiotemporal surface growth deformation map up to 60 kg using Eqs. (1)–(5). This approach also had the advantage of developing an interpolated referential configuration that avoided issues with individual specimen variations. Net results are presented as mean $\pm$ SD.

Results

Affine Registration. The scaled gross shapes of the PAs and AAs of the entire growth series closely matched with that of the 15.3 kg template (Figs. 1(b) and 1(c)). The agreement of the center axis registration in particular provided additional evidence that the overall shape of the arteries were preserved during the growth period. Moreover, the mass and scaling factor values correlated linearly ($r^2 = 0.85$ with RMS error = 0.065 in PA and $r^2 = 0.91$ with RMS error = 0.022 in AA), with every 10 kg increase in mass resulting in an increase of 0.2 in scale (unitless) in both the

PA and AA size. The fourth and second order polynomial regressions of radial and angle coordinates very accurately approximated the coordinates of combined PAs centerline paths, further validating the accuracy of the registration method (RMS error = 0.46 mm and 3.90 deg of radial and angle fits, respectively). The resulting AA common centerline path provided an accurate representation of the combined local center coordinates with angle coordinates of local center points staying relatively constant along the X_3 coordinate (RMS error = 2.43 mm and 2.46 deg for radial and angle fits, respectively). The PA and AA segments of the centerline paths were calculated to be 24.01 mm and 27.06 mm long, respectively.

Geometry. The results from the 2D FFT analysis on different mesh densities indicated that the optimal number of equally spaced element in θ and s was a grid of 4×3 , respectively. For the sake of computational efficiency the data density was reduced by 50% to approximately 80 points per element. The 12 bicubic Hermite element mesh provided an excellent representation of the endoluminal surface geometries (PA RMS error = 0.60 ± 0.10 mm, AA RMS error = 0.50 ± 0.04 mm). The interpolated arterial shapes with respect to animal mass provided a faithful representation of spatiotemporal geometric changes in both the PA (RMS error = 0.80 ± 0.033 mm for radial coordinates, RMS error = 0.28 ± 0.11 mm and 1.61 ± 0.22 for first derivatives in θ and s directions, respectively, and RMS error = 1.70 ± 0.88 mm for cross partial derivatives) and the AA (RMS

error = 0.64 ± 0.034 mm for radial coordinates, RMS error = 0.33 ± 0.11 mm and 2.23 ± 0.26 for first derivatives in θ and s directions, respectively, and RMS error = 2.20 ± 1.25 mm for cross partial derivatives).

Overall Growth Patterns. With the improved approaches developed herein compared to our previous study [17], we determined the change in orientation of the cross-sections along each artery relative to that of the STJ sections (i.e. the twist) using principal component analysis. We noted that the orientation of the PA was largely maintained in the youngest (15 kg) and oldest animals (60 kg), whereas the AA lost most of the observed twist (Fig. 3(a)). Interestingly, while it was again found that both arteries became increasingly tapered during postnatal development, the PA taper increased from 0.86 (i.e. nearly straight) to 0.67 (highly tapered) while the AA taper increased only from 0.74 to 0.62 (Fig. 3(b)). Another important difference between the arteries was the pronounced change in cross-sectional ellipticity in the PA with age, including increased changes along its length (Fig. 3(c)). In contrast, the AA exhibited both lower ellipticity (i.e. was more circular) and exhibited very little change with age (Fig. 3(d)).

Estimated Local Effective Surface Deformation Patterns. The effective growth shear strains were small both in the PA ($\gamma = 1.17 \pm 3.50$ deg) and the AA ($\gamma = -0.37 \pm 1.40$ deg). Thus,

Fig. 3 Basic geometric information of the growing AA and PA. (a) Orientation of cross-section major axes along the center axis coordinate s (as an index of twist), showing while that of the PA remained mostly unaltered, the AA reduced with growth. **(b)** Alteration in arterial taper with growth, as measured by the ratio of cross-sectional areas of BFN or end-ROI to the STJ, was substantially more prominent in the PA than AA. **(c)** Cross-sectional ellipticity of the PA increased substantially with growth (left), whereas in the AA it was relatively maintained (right). These simple measures underscore the geometric complexities of great vessel growth during the post-natal period.

Fig. 4 Time-interpolated circumferential growth stretches on medial/posterior walls of PA (*top*) and AA (*bottom*). Both arteries demonstrated highly heterogeneous distributions, likely due to mutual mechanical interactions. Note in particular the effect of impingement on the PA medial wall by the AA, which resulted in reduced local deformations.

Fig. 5 Time-interpolated circumferential growth stretch on anterior and lateral walls of PA (*top*) and AA (*bottom*). Overall, this aspect of both vessels experienced more homogenous growth, with the PA of slightly higher heterogeneity.

the principal directions of growth deformation coincided closely with the circumferential and longitudinal axes. This result indicates that the PA and AA grow almost exclusively along the circumferential and longitudinal directions. Therefore, we report the effective growth stretches only along the arterial axes. The following surface deformation results are based on interpolated surface geometries and stated differences in deformation values were all statistically significant with $p < 0.05$.

Presenting the results for circumferential growth λ_θ first, we noted that most of the medial wall of the PA grew very little

circumferentially compared to other regions ($\lambda_\theta = 1.12 \pm 0.012$), while the corresponding segment of the AA medial wall was not as substantially inhibited ($\lambda_\theta = 1.43 \pm 0.071$) (Figs. 4 and 8(a) and 8(b)). The circumferential growth of the PA lateral wall considerably decreased towards the BFN (from 1.69 ± 0.11 to 1.28 ± 0.067 , Figs. 5 and 8(b)). A similar, but less pronounced, trend was observed on the PA anterior wall, where towards the BFN, the λ_θ values dropped from a mean of 1.70 ± 0.066 to 1.48 ± 0.035 (Figs. 5 and 8(b)). The average circumferential growth was significantly larger on the PA posterior wall compared

Fig. 6 Time-interpolated longitudinal growth stretch of posterior and a segment of medial walls of PA (*top*) were significantly larger, due to a larger curvature, than that of the posterior wall of AA (*bottom*)

to the other three walls, and the pattern was relatively less heterogeneous (1.73 ± 0.056 , Figs. 4 and 8(b)).

The largest circumferential growth in the AA occurred on a large segment of its posterior wall with λ_θ of 2.019 ± 0.047 (Figs. 4 and 8(b)). The λ_θ growth patterns did not significantly change on most of the lateral wall of the AA (1.66 ± 0.056 , Figs. 5 and 8(b)). On the anterior wall of the AA, where the main side branch was located, circumferential growth appreciably changed, with

the region located right after the side branch undergoing significantly smaller growth (1.28 ± 0.029) compared to the rest of that aspect (1.47 ± 0.067 , Figs. 5 and 8(b)).

In contrast, the longitudinal growth λ_s was more homogenous compared to the circumferential growth (Figs. 6 and 7). The posterior wall and to a lesser extent medial wall and a portion of the lateral wall of the PA showed larger longitudinal growth (2.50 ± 0.10) compared to most of the anterior wall (1.99 ± 0.094 ,

Fig. 7 (a) Time-interpolated longitudinal growth stretch of anterior walls of PA (*top*) and AA (*bottom*), showing relatively uniformly changed with age with larger values in the PA at the 60 kg growth stage due to its larger curvature than AA. (b) Longitudinal growth stretch profiles shown along four walls of PA (*left*) and AA (*right*)

Fig. 8 (a) Stretch profiles at the adult stage (60 kg) of the PA and AA taken from paths along four wall locations along the length of each artery. (b) Circumferential growth stretch profiles of medial (M), lateral (L), anterior (A) and posterior (P) walls of the PA and AA. Note: In a small region after AA main side branch, towards which is oriented, slower circumferential growth rate was measured. (c) Corresponding longitudinal growth stretch profiles. Overall, these results underscored the pronounced variation in longitudinal growth stretch for the PA and circumferential growth stretch for both the AA and PA.

Figs. 6 and 7 and 8(c)). For most part, the longitudinal growth of the AA was relatively smaller and less heterogeneous with a mean of 1.80 ± 0.023 (Figs. 6 and 7 and 8(c)).

As a means to represent effective regional growth, we determined regional areal growth stretch as $\Delta = \lambda_\theta \lambda_s$, since the shear deformations were small. Overall, the PA lateral wall consistently had relatively smaller Δ , starting about 30% away from BFN ($\Delta = 2.77 \pm 0.18$) compared to the rest of that wall ($\Delta = 3.72 \pm 0.13$). The medial wall had on average the smallest growth ($\Delta = 2.88 \pm 0.28$). The posterior wall grew the most (4.19 ± 0.22) with anterior wall having the next largest growth ($\Delta = 3.31 \pm 0.26$). The areal stretch of the AA was on average similar in magnitude to those of the PA. The areal stretch of the AA exhibited only moderate heterogeneity (for the medial and anterior walls $\Delta = 2.72 \pm 0.21$ and 2.51 ± 0.22 , respectively). The change in surface area was larger on the lateral wall of the AA ($\Delta = 3.03 \pm 0.12$) with the posterior wall growing the most ($\Delta = 3.44 \pm 0.29$).

Growth Rates. The growth rates were computed in the STJ, middle regions (MRN) and the BFN region of the PA or end-ROI region of the AA on all four aspects of each artery (Fig. 8(a), Table 1). Both circumferential and longitudinal growth rates increased with age as compared at four different growth stages from youngest to oldest time points (except λ_s of the AA was constant up to 35 kg growth stage). For the most part, λ_θ of the PA was small up to about the 35 kg growth stage (about four months of age) and increased approximately linearly thereafter. However, the AA λ_θ was relatively more linear with smaller change in growth rates. The circumferential growth rate on the ‘contact’ segment of the medial region of the PA was substantially smaller than that of the corresponding segment of the AA medial wall.

Discussion

General Trends. In this first study of the spatial and temporal postnatal growth deformation patterns of the AA and PA during the postnatal development, we determined that temporal growth patterns were relatively consistent during the developmental

period. The spatial heterogeneity became progressively increased with growth, with the circumferential direction demonstrating a larger degree of spatial variation than longitudinal growth (Figs. 4–8). The region of the medial PA wall in contact with AA had the smallest estimated circumferential growth at the 12-month postnatal (adult) stage. A large segment of the AA medial wall and part of its posterior wall, which is proximal to the end-ROI (where the PA wraps around the AA), showed about 40–70% smaller circumferential growth. The lack of significant growth on the sections of both arteries, where they are associated with each other, implies that both mutually impose radial constraints. The circumferential growth rate on the AA medial wall in the PA-coupling region was about four times as fast as that of the corresponding region on the PA medial wall. Therefore, the constraint imposed by the AA on the PA had a substantially larger inhibiting effect on the PA circumferential growth than vice versa.

The lateral wall and anterior walls of the PA showed, respectively, the next highest degrees of spatial heterogeneity. The region proximal to the BFN of the PA lateral wall, that coincides with the anatomical position of the auricle of the left atrium, had an average circumferential growth comparable to that of the medial wall of the PA and grew about a quarter as fast as the rest of that wall. On the anterior wall of the PA, we speculate that the decrease of at least 20% in circumferential growth stretch values in the vicinity of the BFN is due to the connections to Ligamentum Arteriosum in that region.

In a study by Huang et al. [27], increasing taper in the AA of mice during the postnatal growth stage was reported. The aforementioned constraints proximal to the BFN on the lateral and anterior walls of the PA probably have resulted in slower circumferential growth compared to more distal regions, and explain the increase in PA taper towards the BFN with age. The presence of the main side branch between the STJ and the end-ROI regions in the AA is the cause of its greater taper compared to the PA (Figs. 1 and 3). The radial impingement of the PA on the posterior wall of the AA proximal to the end-ROI limits growth in that region and leads to an increase in axial taper as the rest of the posterior wall of the artery is considerably less constrained to grow.

Table 1 The circumferential and longitudinal growth rates in PA and AA computed after about 35 kg growth stage in four circumferential and three longitudinal regions

Circumferential growth rate (reported as mean $\pm$ SD in %/kg)						
Artery	Axial region	Circumferential region				Mean
		Medial	Posterior	Lateral	Anterior	
PA	STJ	1.5 $\pm$ 0.5	2.3 $\pm$ 0.7	2.4 $\pm$ 1.3	1.9 $\pm$ 0.6	2.0 $\pm$ 0.8
	MRN	0.48 $\pm$ 0.12	3.0 $\pm$ 1.1	1.1 $\pm$ 0.5	1.9 $\pm$ 0.6	1.6 $\pm$ 0.6
	BFN	0.24 $\pm$ 0.03	1.9 $\pm$ 0.6	0.48 $\pm$ 0.13	0.83 $\pm$ 0.16	0.9 $\pm$ 0.2
AA	STJ	1.6 $\pm$ 0.06	2.7 $\pm$ 0.7	1.3 $\pm$ 0.2	1.5 $\pm$ 0.5	1.8 $\pm$ 0.4
	MRN	1.1 $\pm$ 0.05	2.9 $\pm$ 0.8	1.7 $\pm$ 0.3	0.50 $\pm$ 0.25	1.6 $\pm$ 0.4
	End-ROI	1.5 $\pm$ 0.2	2.1 $\pm$ 0.5	1.1 $\pm$ 0.02	1.0 $\pm$ 0.1	1.4 $\pm$ 0.2
Longitudinal growth rate (reported as mean $\pm$ SD in %/kg)						
Artery	Axial region	Circumferential region				
		Medial	Posterior	Lateral	Anterior	
PA	STJ	2.9 $\pm$ 0.7	3.3 $\pm$ 1.0	3.3 $\pm$ 0.7	3.4 $\pm$ 0.9	
	MRN	4.6 $\pm$ 1.1	4.2 $\pm$ 0.9	3.6 $\pm$ 0.9	2.3 $\pm$ 0.6	
	BFN	2.9 $\pm$ 0.7	3.5 $\pm$ 0.9	2.8 $\pm$ 0.7	2.2 $\pm$ 0.6	
	Mean	3.5 $\pm$ 0.8	3.7 $\pm$ 0.9	3.2 $\pm$ 0.8	2.6 $\pm$ 0.7	
AA	STJ	1.7 $\pm$ 0.4	2.5 $\pm$ 0.7	1.5 $\pm$ 0.7	1.7 $\pm$ 0.4	
	MRN	1.9 $\pm$ 0.4	2.1 $\pm$ 0.4	2.3 $\pm$ 0.6	1.6 $\pm$ 0.4	
	End-ROI	1.9 $\pm$ 0.4	1.9 $\pm$ 0.4	1.4 $\pm$ 0.7	2.1 $\pm$ 0.4	
	Mean	1.8 $\pm$ 0.4	2.2 $\pm$ 0.5	1.7 $\pm$ 0.7	1.8 $\pm$ 0.4	

The circumferential growth patterns of the rest of the AA appeared to be also guided by the presence of surrounding tissue impingements. On anterior wall of the AA due to the slanted orientation of the main side branch towards the end-ROI, the region located after the main branch showed an average of about 18% less growth than other areas of that wall (Figs. 5 and 8(b)), resulting in the circumferential growth rate slowing down by a factor of about two and a half. Compared to the posterior wall, the relatively slower growth on the large axial region on the anterior wall extending to the lateral wall appears to be caused by the constraints imposed by the superior vena cava and the left brachiocephalic vessel.

The considerably larger λ_s of the PA posterior wall as compared to the anterior wall (Fig. 8(c)) was mainly due to its axial curvature in presence of larger longitudinal than circumferential surface growth and essentially unchanged tortuosity of the centerline path during the whole growth period [17]. That is, in order to maintain the axial curvature, the posterior PA wall had to grow faster than the anterior wall. This is consistent with a previous report that the larger curvature is associated with larger growth deformation [28]. The relatively smaller and significantly more uniform longitudinal growth in the AA is due to the absence of comparable axial curvature to the PA (Fig. 2(b) and 8(c)). The even larger λ_s on the PA medial wall was a result of the concaved shape of the vessel in that region due to mechanical coupling with the AA.

A Simplified Geometric Model Interpretation. In the present work, we relied on the evident geometric self-similarity of the arteries over the growth period. To more clearly demonstrate how these observed geometrical phenomena must manifest themselves, we performed the following parametric study. A tapered cylindrical and two toroid phantoms with key dimensions taken from the PA measurements [29] were generated (Fig. 9). The toroidal formulae were modified to incorporate the mean ellipticity and taper measurements for each PA growth stage, with centerline path tortuosity maintained with growth (Appendix B). For the tapered cylindrical phantom, heterogeneous change in λ_θ with growth is clearly evident (Fig. 8). In contrast, the presence of curvature in

the circular cross-section torus phantom produced heterogeneous λ_s patterns. When both effects were combined in the tapered elliptical toroid, which most closely represented PA geometry, the resulting phantom demonstrated both heterogeneous growth deformation patterns as observed in the PA. Thus, *any toroidal shell structure with an ellipsoidal cross-section intrinsically requires heterogeneous regional surface growth patterns to match delineated shape characteristics over the measured growth period* (Fig. 8).

Physiological Functional Implications. Knowledge of arterial growth kinematics can shed light on mechanisms guiding development which can set the stage for the onset of a degenerative disease [30]. As an example, it has been determined that during normal embryogenesis, the Truncus Arteriosus begins to split and form into the anterior PA and the posterior aorta [10]. Possibly due to their common embryologic origin from a single outflow tract and their close association, there are disease conditions that originate in one artery and eventually affect both arteries [31,32]. This provided an additional reason to characterize the growth deformation of both the AA and PA to quantify the effect of mechanical connection of these two arteries.

The existence of and changes in geometric features such as curvature and cross-sectional torsion can also result in hemodynamic conditions leading to disease localization [33,34]. Additionally, due to the correlation between vessel geometry and its microstructure, the change in morphology of the artery as it grows will result in changes in its mechanical properties [35–37]. Furthermore, the data on surface growth deformation patterns allows computation of changes in stress distribution, which is an important measure of the onset of disease and an indicator of predisposition to a variety of vascular pathologies.

Finally, understanding normal arterial morphogenesis can yield unique insight into the mechanisms of vascular adaptations and their important physiological factors. There is probably a dynamic interplay between arterial growth kinematics, pulsatile blood flow, and arterial hemodynamics. The existence of taper in the AA has been recognized as a physiological adaptation allowing for the optimization of pulsatile flow and favorable wave reflective properties

Elliptical Tapered Cylinder

Circular Toroid

Elliptical Tapered Toroid

Fig. 9 Geometric parametric studies using a tapered cylinder and two toroid phantoms, with key dimensions taken from the PA measurements. For the tapered cylindrical phantom, heterogeneous change in λ_θ with growth is clearly evident. In contrast, the presence of curvature in the circular cross-section toroid phantom produced heterogeneous λ_s patterns. When both effects were combined in the tapered elliptical toroid, (which geometrically most closely represented PA geometry), the resulting phantom demonstrated both heterogeneous growth deformation patterns as estimated in the PA in vivo.

that are inherent to the design of the conduit arteries [38]. The arterial taper enables connecting segments of the cardiovascular system that have different wave propagation or input impedance properties in order to decrease blood flow fluctuations [39]. As reported by Wells et al. [40] the viscoelasticity of the aortic wall decreases during postnatal development as measured by a drop in wave attenuation coefficient from juvenile to adult ovine. The increase in taper, therefore, may be compensating for this decline in arterial dampening that would lead to a decrease in attenuation of the flow rate amplitude. We also note that according to Melbin et al. [41], due to the lower flexure rigidity relative to the in-plane stiffness of elastic arteries, ellipticity results in an initial deformation with constant perimeter via pure bending at the onset of systole, resulting in an almost circular cross-sectional geometry.

Implications to Tissue Engineering and Cellular Level Growth Mechanisms. Overall, the geometric information detailed in this study is required to establish the baseline for achieving functional equivalence in engineered tissue replacements. Hoerstrup et al. [8], for example, reported the basic dimensional changes in the tissue engineered PA replacements. They

reported a maximum increase of 45% in length of the tissue-engineered ovine PA constructs within the 100-week postoperative period while our results indicated an increase of at least 200% in native PA length ($\lambda_s = 2.0$) within about a ten month postnatal maturation period. They stated that mean internal diameter increased by about 30% between 20 and 100 weeks; however, based on our results, the PA grew by about 40% in circumference after 20 weeks (circumferential growth stretch: from 1.1 to 1.5). Clearly, growth metrics have not been yet fully achieved when compared to native arteries. We furthermore maintain that these and future results can guide the development of repair techniques of both arteries in congenital abnormalities and restoring the normal pulsatile arterial behavior.

Interestingly, relatively little is known about the exact regulatory mechanisms underlying the biology of organ size determination [42]. In one model of early postnatal life, the simultaneous upregulation of multiple specific growth-promoting genes results in periods of rapid growth [43]. Growth causes negative feedback and subsequent down-regulation of these growth-promoting genes. As a result, growth slows, and an organism's growth rate eventually approaches zero. Finkelstein et al. [44] concluded that there exists an extensive genetic program occurring during postnatal life.

Alternatively, in the large conduit arteries, vascular cells are thought to transduce cyclic strain, caused by pulsatile blood flow, into signaling cascades which result in cell hypertrophy, hyperplasia, and extracellular matrix synthesis [45–48]. Although these mechanisms of remodeling and growth have been proposed, the specific signals that determine the rate of vascular remodeling (either in normal postnatal development or with congenital defects) have not yet been defined. Ultimately, finding links between molecular mechanisms of growth and the geometry of large vessels holds promise for patients with congenital heart disease because hemodynamics are dictated by vascular geometry [49].

Limitations and Accuracy of the Current Approach. Since the animals used in the present work were sacrificed at varying times for nonrelated studies, the same individual animals could not be imaged for the entirety of the study. However, we found that the growth trends in both arteries for all animals were consistent. We thus had to make the assumption that the relative spatial locations with respect to in-surface coordinates were maintained (i.e. radially directed growth) within the growth period. This assumption was supported by the registration results (Figs. 1 and 2), especially the similarity in shapes of the scaled centerline paths over the entire growth period (Fig. 2(a)), which demonstrated that the overall arterial shape was maintained. This included the maintenance of the orientations of the PA bifurcation and sinuses of Valsalva (Figs. 1(b) and 1(c)). We also noted that the circumferential location of AA-induced indentation on medial PA wall was preserved. This was evidenced using positional measurements at three different cross-sectional locations along the PA surfaces, using the centerline path, over the growth period (Table 2).

Also relevant are the findings of our recent study wherein we performed thickness, mechanical behavior, and detailed structural analyses on the PA arterial tissues [50]. Interestingly, we observed no changes in thickness or significant differences in the arterial wall circumferential stiffness from the juvenile to adult stages. This suggests that our arterial dimensions in the end-diastolic state [17] cannot be attributed to changes in elastic behavior, i.e., the medial wall did not become circumferentially stiffer with growth, so the smaller measured λ_θ in that region is only attributable to lack of surface growth.

It should be noted here that our approach is not a model per se, but rather a means to estimate the effective surface growth as a form of deformation from a set of successive, co-registered 3D surface reconstructions. The only assumptions made with respect to our kinematic analysis is that the arterial surfaces only grow in-plane, and that the relative position of material points in the *scaled* (θ, s) coordinate remains constant.

Interestingly, our parametric studies using simulated toroidal shapes (Fig. 9) suggest that our initial results are a reasonable first-approximation to the actual effective growth patterns. For example, the longitudinal effective growth stretch λ_s on the inner curvature was about 1.29 in both the PA (Fig. 6, top-right image) and the

toroidal phantom with ellipsoidal cross-section (Fig. 8, bottom right image). Similarly, λ_θ at the STJ was found to vary from 1.3 to 1.8 for the oldest animal (Fig. 4, top right image) and 1.54 to 1.74 for the toroidal phantom (Fig. 9, center bottom image).

Summary. Overall, our results indicated that the spatial and temporal surface growth deformation patterns of both arteries were heterogeneous, including an increase in taper in both arteries and increase in cross-sectional ellipticity of the PA. Contact between the PA and AA resulted in increasing spatial heterogeneity in postnatal growth, with the PA demonstrating the greatest changes. Parametric studies using simplified geometric models of curved arteries during growth suggest that heterogeneous effective surface growth deformations must occur to account for the changes in measured arterial shapes during the postnatal growth period. Results of this study clearly underscore and extend our earlier observations that functional growth of the PA and AA during postnatal maturation involves complex geometric adaptations. Moreover, they help to lay the basis for functional duplication for repair and replacement by defining critical geometric metrics. How this process is biologically regulated remains a major question for both native and engineered tissue PA replacements.

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Appendix A: Coordinate Transformation

The local coordinate of the surface point, $\mathbf{x}'$, with its projected centerline path point, $\mathbf{y}$, and $\mathbf{Q}$ are the 3D rotation matrix defined by local Frenet frame as

$$\begin{aligned}\mathbf{x}' &= \begin{bmatrix} \rho(\theta, s) \cos(\theta) \\ \rho(\theta, s) \sin(\theta) \\ 0 \end{bmatrix} \\ \mathbf{y} &= \begin{bmatrix} R(x_3) \cos(\Theta(x_3)) \\ R(x_3) \sin(\Theta(x_3)) \\ x_3 \end{bmatrix} \\ \mathbf{Q}(s) &= \begin{bmatrix} n_1(s) & b_1(s) & t_1(s) \\ n_2(s) & b_2(s) & t_2(s) \\ n_3(s) & b_3(s) & t_3(s) \end{bmatrix}\end{aligned}\quad (\text{A1})$$

where ρ is the radial coordinate defined as a function of circumferential location, θ , and length along the centerline path given by

$$s(x_3) = \int_0^{x_3} \sqrt{\left(\frac{dy_1}{dx_3}\right)^2 + \left(\frac{dy_2}{dx_3}\right)^2 + 1} \cdot dx_3 \quad (\text{A2})$$

Appendix B: Modified Torus

Equation of torus in cylindrical polar coordinates is given by

$$\begin{aligned}X_1 &= r_{\text{maj}} \cos(\theta) \\ X_2 &= (r_{\text{min}} \sin(\theta) + R) \cos(\phi) \\ X_3 &= (r_{\text{min}} \sin(\theta) + R) \sin(\phi)\end{aligned}\quad (\text{B1})$$

where θ and ϕ define circumferential and centerline path coordinate; R is the radius of the torus centerline and

$$r_{\text{min}}(\phi) = r_{\text{STJ}} + (\sqrt{\text{taper}} - 1) \cdot r_{\text{STJ}} \cdot \frac{R \cdot \phi}{L} \quad (\text{B2})$$

Table 2 Location of the AA induced indentation on medial PA wall with growth as measured in three different cross-sections of PA surfaces along centerline path at 15 kg, 30 kg, 40 kg, 50 kg, and 60 kg time points. The reported angular location values were taken at the center of the span and were accurate to within approximately ± 3 deg and varied in circumferential position by the same amount. Interestingly, they did not undergo changes with growth.

Distance of cross-sections from STJ, s	Location θ (deg)	Angular span (deg)
30%	175	38
60%	167	37
90%	145	25

where L is the length of centerline, $r_{\text{maj}} = \text{ecc} \times r_{\text{min}}$ with ecc being the mean cross-sectional ellipticity.

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