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Hyperelastic remodeling in the intrauterine growth restricted (IUGR) carotid artery in the near-term fetus

R. Blair Dodson^a, Paul J. Rozance^b, Esther Reina-Romo^c, Virginia L. Ferguson^{a,d,1}, and Kendall S. Hunter^{e,*}

^aDepartment of Mechanical Engineering, University of Colorado, Boulder, CO 80309, USA

^bDepartment of Pediatrics, University of Colorado School of Medicine, Aurora, CO 80045, USA

^cDepartment of Mechanical Engineering, University of Seville, 41092 Seville, Spain

^dDepartment of Obstetrics and Gynecology, University of Colorado at Denver Anschutz Medical Campus, Aurora, CO 80045, USA

^eDepartment of Bioengineering, University of Colorado at Denver Anschutz Medical Campus, Aurora, CO 80045, USA

Abstract

A constitutive model for a fiber reinforced hyperelastic material was applied to understand arterial fiber remodeling in a sheep model of Intrauterine Growth Restriction (IUGR). IUGR is associated altered hemodynamics characterized by increased resistance to blood flow in the placenta and elevated fetal arterial pressure and pulsatility. The constitutive model describes the collagen contribution to the mechanics within the arterial wall in both control and IUGR carotid artery through defining the material modulus and the orientation of the microstructure. A sheep model of placental insufficiency induced IUGR (PI-IUGR) was created by exposure of the pregnant ewe to elevated ambient temperatures. Experimental data was collected using pressure–diameter measurements to measure passive compliance in control and PI-IUGR carotid arteries. The constitutive model was optimized to fit the experimental data predicting the material parameters. Specifically, the collagen fiber predicted angle (γ) in the control artery was 49.9° from the circumferential axis while the PI-IUGR was 16.6° with a 23.5% increase in fiber orientation (κ). Quantitative assessment of collagen fiber orientation in secondary harmonic generation images confirmed the shift in orientation between the two groups. Together these suggest vascular remodeling of the ECM fiber orientation plays a major role in arterial stiffening in the PI-IUGR near-term fetal sheep.

Keywords

Fetal programming; Extracellular matrix; Vascular remodeling; Collagen; Mechanics

*Corresponding author. Tel.: +1 303 724 4197; fax: +1 303 724 5800. reuben.dodson@ucdenver.edu (R.B. Dodson), kendall.hunter@ucdenver.edu (K.S. Hunter)..

¹Both are senior authors on this paper.

Conflict of interest statement

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1. Introduction

Hypertension reduces arterial compliance, introducing health problems such as increased overall hydraulic impedance and cardiac workload (London et al., 2001; Mahmud and Feely, 2004; Safar, 2003; Shadwick, 1999). Altered hemodynamics has also been shown to contribute to altered growth and vascular remodeling, with increased blood flow or blood pressure increasing vascular stiffness and geometry (Eberth et al., 2010; Cardamone et al., 2010; Hu et al., 2008). Recent studies of both systemic and pulmonary hypertension demonstrate that both organ resistance and vascular compliance are critical factors in the progression of cardiovascular diseases (CVD) (Blacher et al., 1999; Et-Taouil et al., 2003; Kobs and Chesler, 2006; Laurent et al., 2001), with Intrauterine growth restriction (IUGR) infants showing a higher incidence of CVD in adulthood (Barker, 1995; Louey and Thornburg, 2005; Thornburg, 2005).

IUGR is a common complication of pregnancy that is associated with hypertension and abnormal blood flow in a fetal sheep model (Galan et al., 2005). Changes in circulation and the associated intrinsic hemodynamic forces created by placental insufficiency induced IUGR (PI-IUGR) (Galan et al., 2005) during critical periods of gestation may influence the formation of the vessels, creating stiffer, less compliant arteries (Dodson et al., in press). While IUGR human umbilical arteries have been shown significantly stiffer than controls (Burkhardt et al., 2009), the mechanisms are still poorly understood. Structural remodeling in response to hypertension is believed in part to be due to fiber alignment.

Arterial compliance mechanics depend largely on the passive extracellular matrix (ECM) constituents: elastin and collagen. The arterial wall is a complex composite structure that remodels in response to hemodynamic stresses, which change with growth and development. Initial insight into structural organization of the ECM in adult human arteries was described by Canham et al. (1989), Finlay et al. (1995), Finlay et al. (1998). Gasser et al. developed a structural continuum constitutive model of arterial layers to integrate tissue structure and function to mechanical loading (Gasser et al., 2006). Studies in normal pregnancy have described vascular ECM in aortic development (Kelleher et al., 2004), the contributions of vascular ECM to arterial mechanics in development (Wagenseil and Mecham, 2009), and the role of elastic fiber contribution to mechanical function (Carta et al., 2009), but no constitutive characterization of the developing artery in health and disease exists. However, measurements alone are insufficient to link fiber orientation and mechanics. Constitutive equations can provide deeper insight into the physiological and pathological load carrying mechanisms within the artery elucidating structural changes that occur in response to hypertension.

The relationship between stress and strain in hyperelastic materials is best described through micro-structurally driven strain energy functions. The aim of this work is to use a microstructurally driven constitutive model, based upon previous work by Gasser et al. (2006), to understand the role of fiber remodeling in systemic vessel stiffening for control and IUGR arteries. This study will test the hypothesis that changes in the IUGR carotid artery fiber orientation and structure due to vascular remodeling contribute to increased systemic arterial stiffness.

2. Methods

2.1. Experimental

Pregnant Columbia-Rambouillet ewes were studied at the Perinatal Research Center (PRC) at the University of Colorado at Denver Anschutz Medical Campus and approved by the Institutional Animal Care and Use Committee. The PRC is accredited by the National

Institutes of Health, the United States Department of Agriculture, and the American Association for Accreditation of Laboratory Animal Care. The Placental Insufficiency and IUGR model (PI-IUGR) was created as previously described (Barry and Anthony, 2008; Barry et al., 2008; Rozance et al., 2009; Rozance et al., 2009). Briefly, PI-IUGR was created by exposure of pregnant ewes to elevated ambient temperatures (40°C for 12 h; 35°C for 12 h) for ~80 days (35–112 days gestational age, dGA; term=148 dGA). Control ewes were housed in a normothermic environment for the duration of the study.

Ewes and the fetuses were euthanized using pentobarbital sodium (2 ml, approximately 250 mg/kg). The fetal common right and left carotid arteries were dissected from the base of the carotid branch to the base of the skull (CON $n=10$, PI-IUGR $n=8$). Arteries were stored in calcium-free phosphate buffered saline (PBS) at 4 °C and tested between 24–72 h after necropsy. The passive mechanics, or static mechanics, and ECM of the arteries remained constant for up to three days (Stemper et al., 2007; Garcia-Herrera et al., 2012).

Arteries were tested on previously described groups of near-term control sheep 134 ± 1 dGA weighing 3.32 ± 0.18 kg with a placental weight of 465 ± 46 g and PI-IUGR sheep 133 ± 1 dGA with significantly reduced fetal weight ($P<0.05$) of 2.13 ± 0.17 kg and significantly reduced placental weight ($P<0.05$) of 226 ± 17 g (Dodson et al., in press). Briefly, the left or right artery was selected at random. Arteries were tested for passive compliance on a custom arteriography chamber that stretched the artery axially, pressurized and imaged for diameter. The vessels were statically pressurized with calcium-free PBS solution using a Cole–Parmer Masterflex pump (Vernon Hills, IL) from 5 mmHg and 10–200 mmHg in 10 mmHg increments, held to allow stress relaxation and imaged for diameter. Vessels were tested across prescribed axial stretches of 1.0, 1.1, 1.2, 1.3 and 1.4 mm/mm, where stretch is defined as current length divided by initial length. Each loading configuration was matched with time, pressure data and the outer diameter was measured optically. Following mechanical testing, arterial segments were examined histologically as described below.

Three representative test samples of control and PI-IUGR carotid arteries were processed for imaging. Test samples were fixed using 10% neutral buffered formalin, ethanol dehydrated, and rehydrated using PBS. Samples were dissected and oriented for imaging in the circumferential-axial plane then imaged using second harmonic generation (SHG) to visualize collagen and elastin content. The SHG imaging system consisted of a Zeiss LSM 510 instrument (Carl Zeiss Inc.; Germany) equipped with a tunable pulsed two-photon infrared laser (Chameleon from Coherent Inc.; Santa Clara, CA) and external non-descanned PMT detectors. Arterial samples were excited with 800 nm via a water immersion objective 40x, 1.4NA Plan-Apochromat (Carl Zeiss Inc.; Germany). The response signal was split using a dichroic mirror, 425 DCLP (Chroma Technologies; Rockingham VT). Collagen fluorescence was measured using a narrow band pass filter HQ400/20 m-2p (Chroma Technologies; Rockingham, VT). Images were quantified for collagen fiber orientation and dispersion using a previously validated custom written ImageJ analysis macro OrientationJ (Rezakhaniha et al., 2012). An effective fiber angle was determined through a weighted mean and dispersion through the standard deviation from the mean.

2.2. Theoretical framework

The arterial wall was modeled in the commercial finite element program Abaqus (6.10) as single layer fiber reinforced hyperelastic material (Gasser et al., 2006; Holzapfel et al., 2000). This model assumes ideal elastic behavior throughout the test with an isotropic ground matrix and symmetric fiber arrangement and orientation. Isochoric (isovolumetric) deformation was assumed with incompressibility and homogeneous vessel composition such that samples from different locations in the artery will have the same collagen and elastin

content and similar mechanical behavior. The appropriate strain energy function is also assumed to be:

$$\widehat{\Psi} = \widehat{\Psi}_{Isotropic} + \widehat{\Psi}_{Orthotropic} \quad (1)$$

in which the first function $\widehat{\Psi}_{Isotropic}$ describes the ground substance and elastin dominant portion of the vessel low load response, while the second function, $\widehat{\Psi}_{Orthotropic}$, accounts for collagen fiber orientation and engagement at higher loads with an exponential increase in material stiffness at high strains as collagen recruitment takes over the load response. Forms of the strain energy functions are based on neo-Hookean and Fung models respectively.

The first term of Eq. (1), $\widehat{\Psi}_{Isotropic}$, is a function of the first invariant of the right Cauchy–Green, $\mathbf{C}$, tensor and is based on the neo-Hookean model that is often employed in describing the behavior of isotropic rubber-like materials. In two dimensions this term becomes

$$\widehat{\Psi}_{Isotropic} = \frac{c}{2}(\widehat{I}_1 - 3), \quad \widehat{I}_1 = \lambda_z^2 + \lambda_\theta^2 + \frac{1}{\lambda_z^2 \lambda_\theta^2} \quad (2)$$

where I_1 is the first invariant, c is a fitting constant, and λ_θ , and λ_z are the stretches in the circumferential and axial directions respectively. Definition of the first invariant derives from the assumption that arterial soft tissue is isochoric, so that the material preserves volume under deformation: $\lambda_{VOL} = 1 = \lambda_r \lambda_\theta \lambda_z$, where λ_r is the radial stretch. This strain energy function involves a single parameter and provides a mathematically simple model for the isotropic non-linear deformation behavior of rubber-like materials. The constant c is related to the shear modulus of the tissue.

The second term Eq. (1), $\widehat{\Psi}_{Orthotropic}$, describes the exponential increase in load as collagen engagement begins, and the strain energy function is appropriately in exponential form

$$\widehat{\Psi}_{Orthotropic} = \frac{k_1}{k_2} \{ \exp[k_2 (\kappa \widehat{I}_1 + (1 - 3\kappa) \widehat{I}_4 - 1)] - 1 \}, \quad \widehat{I}_4 = \lambda_z^2 \sin^2 \gamma + \lambda_\theta^2 \cos^2 \gamma \quad (3)$$

in which the constant k_1 is a stress-like parameter, k_2 is dimensionless, κ describes the fiber dispersion ($\kappa = 0$ fibers ideally aligned, $\kappa = 1/3$ fibers isotropically distributed), and the collagen fiber angle, γ . The invariant I_4 characterizes the constitutive response of the fibers to mechanical loading.

2.3. Boundary conditions

The inflation of the thin-walled tube with a thickness (H) and mean-radius (R) was considered across the experimentally prescribed axial stretches with no applied axial load and for an internal pressure, p_i , with the associated boundary conditions in the axial and circumferential directions (Fig. 1) (Gasser et al., 2006)

$$f_z = \lambda_z \frac{\partial \widehat{\Psi}}{\partial \lambda_z} - \frac{\lambda_z (\lambda_\theta R - (H/2\lambda_\theta \lambda_z))^2}{2HR} p_i = 0, \quad f_\theta = \lambda_\theta \frac{\partial \widehat{\Psi}}{\partial \lambda_\theta} - \left(\frac{\lambda_\theta^2 \lambda_z R}{H} - \frac{1}{2} p_i \right) = 0, \quad (4)$$

where f_z and f_θ denote the axial and circumferential functions. Eq. (4) define a system of nonlinear equations that can be solved numerically for a prescribed internal pressure p_i .

2.4. Numerical fit

Fitting the material model to experimental data was achieved by optimizing the correspondence between model predicted behavior and experimental behavior provided

from the above mentioned pressure–diameter tests, by minimizing the stress-based nonlinear error function

$$f_{error} = \sum_{i=1}^n [w_1 f_z^2 + w_2 f_\theta^2] \quad (5)$$

where n is the number of experimental data points and the weighting factors are w_1 and w_2 . Minimization was performed using the `fminsearch` procedure in Matlab 7.9 (The Mathworks, Natick, MA) across a continuous spectrum of circumferential stretches and at five discrete axial stretches, corresponding to the available experimental data. Constitutive parameters were found for across all sets of data minimizing the error function.

A goodness of fit test was performed to assess the degree of agreement between the experimental data and the constitutive model. The F distribution (F) was measured based upon the value of the residual sum of the squares ($Res\ SS$) of the considered constitutive model for the individual experimental data points (y_i) and the residual points ($\hat{y}_i$) and defined

$$F = \frac{\sqrt{ResSS/(n-q)}}{RegSS} = \frac{\sqrt{\sum_{i=1}^n (y_i - \hat{y}_i)^2 / (n-q)}}{RegSS} \quad (6)$$

where n is the number of considered data points, q is the number of parameters of Ψ , and $n-q$ is the number of degrees of freedom. The regression sum of the squares ($Reg\ SS$) is the sum of all the wall stresses for each data point divided by the number of all data points.

3. Results

3.1. Constitutive model and microstructure

The constitutive parameters c , k_1 , k_2 , γ and κ based upon the macroscopic mechanical response are summarized in Table 1 for both control and PI-IUGR arteries. The PI-IUGR artery shows increased isotropic and anisotropic contribution to the overall stiffening of the artery compared to the control artery. Experimental data (points) with the constitutive model fit (line) for axial stretches of 1.0, 1.2 and 1.4 are shown in Fig. 2. The F distribution was 2.53 for the control arteries and 5.61 for the PI-IUGR arteries, which suggested constitutive model parameters were statistically significant ($P < 0.05$). The predicted fiber angle values, γ , as described by the mechanics seem to be in relatively good agreement with the SHG image analysis with values of $42.2^\circ \pm 11.2^\circ$ (mean $\pm$ standard error of the mean) for control arteries and $19.2^\circ \pm 7.5^\circ$ for the PI-IUGR arteries (Fig. 3). The dispersion of collagen fibers from SHG images was 0.286 and 0.193 for control and PI-IUGR arteries respectively with collagen fibers more aligned in the PI-IUGR arteries. Observed qualitative differences in the bundling of the collagen fibers were noted in the PI-IUGR arteries with PI-IUGR arteries being more fibrillar driving the mechanics compared to the sheets of collagen in the control arteries.

3.2. Biomechanical behavior

The control artery model exhibits a maximum von Mises stress of 52.3 kPa (Fig. 4) and increases 24.9% as pressure increases to previously shown mean blood pressure, 50.2 mmHg in this sheep model of PI-IUGR (Galan et al., 2005). Constitutive remodeling works to reduce arterial wall stress by 27.8%, while geometric changes may accommodate relatively increased blood flow to the brain in PI-IUGR increase stress by 69.7%. Therefore,

while increased pressure and geometry contribute to increased wall stress, constitutive remodeling through fiber orientation, γ , and fiber dispersion, κ , reduce arterial wall stress.

The softer compliance of the control arteries allows similar inner diameters for both arteries at the respective mean blood pressures (Fig. 5). However, as inflation pressures increase the control arteries distend much more, storing more strain energy and creating a larger volume, an increase of 100% in the control versus the PI-IUGR at 200 mm Hg. Finally, mean fiber orientation (Fig. 6), which changes to respond to stress, displays less response over a theoretical cardiac cycle in the in PI-IUGR configuration.

4. Discussion

4.1. Major Findings

This study supports the hypothesis that changes in collagen fiber orientation is responsible for vascular stiffening in the PI-IUGR fetal sheep in response to hemodynamic alterations. Both macroscopic mechanics and microscopic analysis show angle (γ) and dispersion (κ) reorientation of collagen fibers, leads to the stiffening of the carotid artery. Collagen fibers in the PI-IUGR fetus align preferentially and are more fixed in the circumferential direction to accommodate the increased blood pressure as well as altered geometry that accommodates flow. The model predicts that constitutive remodeling occurs in response to increased blood pressure and geometric growth to reduce arterial wall stress in PI-IUGR while reducing overall compliance of the artery.

4.2. Clinical relevance and scope within literature

This work aims to characterize fetal carotid arterial development at the near-term fetal time point, in addition to changes in their structure and mechanics due to the maternal disease of IUGR. Epidemiologic results strongly support the idea of gestation being a highly sensitive developmental period with IUGR adversely affecting lifelong cardiovascular health (Barker, 1995; Louey and Thornburg, 2005; Thornburg, 2005; Eriksson et al., 1999; Meyer and Zhang, 2007; Nilsson et al., 2008; Norman, 2008; Ojeda et al., 2008; Ong, 2002; Robillard and Segar, 2006; Rueda-Clausen et al., 2008). The major proteins contributing to arterial compliance, collagen and elastin, are synthesized most rapidly during the fetal period (Wagenseil and Mecham, 2009; Wells et al., 1999) and appear to be altered in the PI-IUGR sheep model. Others have shown arterial mechanics characterized throughout the lifespan of sheep (Wells et al., 1999; Wells and Walter, 2010; Wells et al., 1998; Wells et al., 1998) and mice (Wagenseil and Mecham, 2009; Carta et al., 2009) demonstrating changes in ECM constituents and mechanics relationships in normal development. Elastin insufficiency models of genetic diseases in developing mice are characterized by an increased incidence of cardiovascular disease with increased blood pressures and arterial stiffness (Shifren et al., 2008; Wagenseil et al., 2009; Wagenseil et al., 2005) showing arterial mechanics to be an important component throughout development and aging. Additionally, recent studies of physiologic diseases of pregnancy have shown reduced elastin content in aorta of the hypoxic sheep fetus (Thompson et al., 2011) and decreased elastin content with increased stiffness in adulthood of the PI-IUGR guinea pig (Thompson et al., 2011). Decreased elastin content of the systemic arteries is postulated to be the mechanism linking cardiovascular disease in adulthood to human IUGR (Nilsson et al., 2008; Norman, 2008; Martyn and Greenwald, 1997; Martyn and Greenwald, 2001; Rondo et al., 2008). However, a definitive IUGR effect on fetal arterial mechanics has never been shown. Our work demonstrates the important role of *in utero* stress on arterial development in the PI-IUGR model. PI-IUGR sheep showed collagen reorientation and the noted fibrillation an ECM component shown to alter the passive pressure/diameter relation at higher pressure and induce a progressive stiffening of the arterial wall (Garcia-Herrera et al., 2012). Our work shows that collagen

organization is also altered in the near-term sheep fetus, contributing to increased stiffness and playing an important role along with changes in elastin (Dodson et al., in press).

The mechanics of stiffening in the PI-IUGR carotid artery is driven by increased collagen content (Dodson et al., in press) and its remodeling of the orientation in the adventitia. Remodeling appears to preferentially align fiber dispersion in the circumferential direction, decreasing the stretch at which collagen engagement begins to carry load, thereby stiffening arterial walls while reducing wall stress and compliance. Furthermore, remodeled collagen may disrupt the elastin and collagen content of systemic vessels disturbing development during neonatal and adolescent life as pressures and flows increase. Vascular stiffening has been shown to be a predictor of the progression of CVD (London et al., 2001; Mahmud and Feely, 2004; Safar, 2003; Shadwick, 1999) and may be an important factor in increasing the risk factor of CVD over the life of an IUGR infant. This study provides a first glimpse into the reduced hyperelastic function driven by micro-structurally driven circumferentially oriented collagen.

4.3. Limitations

Several limitations in our model must be acknowledged. First, the arterial wall was modeled as a single fiber reinforced hyperelastic layer while an artery is known to have three distinct layers (intima, media and adventitia). The media in the PI-IUGR artery was shown to have altered elastin content than that of the control. Elastin remodeling was experimentally shown to contribute very little to the mechanisms controlling the arterial stiffening (Dodson et al., in press). We were interested in quantifying the change in the observed adventitial collagen in PI-IUGR with a large majority of the mechanics being driven by the adventitial layer. The model chosen was robust enough to account for both isotropic and anisotropic changes in all the layers as a composite, modeling the elastin dominated isotropic media and the collagen dominated anisotropic adventitia. Finally, the artery was modeled through static, biaxial *in vitro* pressure and diameter measurements though the cardiovascular system is dynamic *in vivo*. However, the biaxial *in vitro* tests are well documented in the literature for characterizing the passive constitutive properties of arteries (Gasser et al., 2006; Wagenseil and Mecham, 2009; Holzapfel et al., 2000; Wagenseil et al., 2009; Humphrey, 2002).

4.4. Future work

Time course models characterizing vascular mechanics in altered pulsatility (Eberth et al., 2010; Cardamone et al., 2010; Hu et al., 2008) and pulmonary hypertension (Kobs, 2004) exist, but none exists for a model of IUGR. This work represents a first step in understanding vascular mechanics in the critical and complicated fetal developmental period. Additional studies are needed to understand the growth and development trajectory for the PI-IUGR sheep. Micro-structural driven models should be developed accounting for growth and development in individual layer responses as well as for elastin and collagen content contributions during growth and development. Such a constitutive model has the ability to aid our clinical understanding of the relationship between vessel stiffening and altered blood flow characteristics in growth and development.

5. Conclusions

While IUGR infants exhibit a higher incidence of CVD as adults, clinical studies have not been able to elucidate the role of the increased stress in the intrauterine environment on the altered physiology. This study suggests that the altered collagen fiber orientation in PI-IUGR leads to altered biomechanics, which would lead to altered hemodynamics. These results also support the hypothesis that IUGR plays an important role in the increased onset of adult CVD (Barker, 1995; Louey and Thornburg, 2005; Thornburg, 2005).

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References

- Barker D. Intrauterine programming of adult disease. *Molecular Medicine Today*. 1995; 1:418–423. [PubMed: 9415190]
- Barry JS, Anthony RV. The pregnant sheep as a model for human pregnancy. *Theriogenology*. 2008; 69:55–67. [PubMed: 17976713]
- Barry JS, Rozance PJ, Anthony RV. An animal model of placental insufficiency-induced intrauterine growth restriction. *Seminars in Perinatology*. 2008; 32:225–230. [PubMed: 18482626]
- Blacher J, Guerin AP, Pannier B. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation*. 1999; 99((18)):2434–2439. [PubMed: 10318666]
- Burkhardt T, Matter C, Lohmann C, et al. Decreased umbilical artery compliance and IGF-I plasma levels in infants with intrauterine growth restriction—implications for fetal programming of hypertension. *Placenta*. 2009; 30:136–141. [PubMed: 19070892]
- Canham P, Finlay H, Dixon J, Boughner D, Chen A. Measurements from light and polarised light microscopy of human coronary arteries fixed at distending pressure. *Cardiovascular Research*. 1989; 23:973. [PubMed: 2611805]
- Cardamone L, Valentin A, Eberth JF, Humphrey JD. Modelling carotid artery adaptations to dynamic alterations in pressure and flow over the cardiac cycle. *Mathematical Medicine and Biology*. 2010; 27:343–371.
- Carta L, Wagenseil J, Knutsen R, et al. Discrete contributions of elastic fiber components to arterial development and mechanical compliance. *Arteriosclerosis, thrombosis, and vascular biology*. 2009; 29:2083–2089.
- Dodson, R.; Rozance, P.; Fleenor, B., et al. Pediatric Research. Increased stiffness and extracellular matrix reorganization in intrauterine growth restricted (IUGR) fetal sheep. <http://dx.doi.org/10.1038/pr.2012.156>, in press.
- Eberth JF, Popovic N, Gresham VC, Wilson E, Humphrey JD. Time course of carotid artery growth and remodeling in response to altered pulsatility. *American Journal of Physiology—Heart and Circulatory Physiology*. 2010; 299:H1875–H1883. [PubMed: 20852047]
- Eriksson J, Forsen T, Tuomilehto J, Winter P, Osmond C, Barker D. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *British Medical Journal*. 1999; 318:427–431. [PubMed: 9974455]
- Et-Taouil K, Safar M, Plante GE. Mechanisms and consequences of large artery rigidity. *Canadian Journal of Physiology and Pharmacology*. 2003; 3:205–211. [PubMed: 12733819]
- Finlay H, McCullough L, Canham P. Three-dimensional collagen organization of human brain arteries at different transmural pressures. *Journal of Vascular Research*. 1995; 32:301–312. [PubMed: 7578798]
- Finlay H, Whittaker P, Canham P. Collagen organization in the branching region of human brain arteries. *Stroke*. 1998; 29:1595–1601. [PubMed: 9707199]
- Galan H, Anthony R, Rigano S, et al. Fetal hypertension and abnormal Doppler velocimetry in an ovine model of intrauterine growth restriction. *American Journal of Obstetrics and Gynecology*. 2005; 192:272–279. [PubMed: 15672036]
- Garcia-Herrera CM, Atienza JM, Rojo FJ, et al. Mechanical behaviour and rupture of normal and pathological human ascending aortic wall. *Medical and Biological Engineering and Computing*. 2012
- Garcia-Herrera CM, Celentano DJ, Cruchaga MA. Bending and pressurisation test of the human aortic arch: experiments, modelling and simulation of a patient-specific case. *Computer Methods in Biomechanics and Biomedical Engineering*. 2012

- Gasser T, Ogden R, Holzapfel G. Hyperelastic modelling of arterial layers with distributed collagen fibre orientations. *Journal of the Royal Society Interface*. 2006; 3:15.
- Holzapfel G, Gasser T, Ogden R. A new constitutive framework for arterial wall mechanics and a comparative study of material models. *Journal of Elasticity*. 2000; 61:1–48.
- Hu JJ, Ambrus A, Fossum TW, Miller MW, Humphrey JD, Wilson E. Time courses of growth and remodeling of porcine aortic media during hypertension: a quantitative immunohistochemical examination. *Journal of Histochemistry and Cytochemistry*. 2008; 56:359–370. [PubMed: 18071063]
- Humphrey, JD. *Cardiovascular Solid Mechanics: Cells, Tissues, and Organs*. Springer; 2002.
- Kelleher CM, McLean SE, Mecham R. Vascular extracellular matrix and aortic development. *Current Topics in Developmental Biology*. 2004
- Kobs R. Linked mechanical and biological aspects of remodeling in mouse pulmonary arteries with hypoxia-induced hypertension. *American Journal of Physiology: Heart and Circulatory Physiology*. 2004; 288:H1209–H1217. [PubMed: 15528223]
- Kobs R, Chesler N. The mechanobiology of pulmonary vascular remodeling in the congenital absence of eNOS. *Biomechanics and Modeling in Mechanobiology*. 2006; 5:217–225. [PubMed: 16520964]
- Laurent S, Boutouyrie P, Asmar R, Gautier I. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension*. 2001
- London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. *Hypertension*. 2001; 38:434–438. [PubMed: 11566918]
- Louey S, Thornburg KL. The prenatal environment and later cardiovascular disease. *Early Human Development*. 2005; 81:745–751. [PubMed: 16137844]
- Mahmud A, Feely J. Review: Arterial stiffness and the renin–angiotensin–aldosterone system. *Journal of Renin–Angiotensin–Aldosterone System*. 2004
- Martyn CN, Greenwald SE. Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. *Lancet*. 1997; 350:953–955. [PubMed: 9314885]
- Martyn CN, Greenwald SE. A hypothesis about a mechanism for the programming of blood pressure and vascular disease in early life. *Clinical and Experimental Pharmacology and Physiology*. 2001; 28:948–951. [PubMed: 11703403]
- Meyer K, Zhang L. Fetal programming of cardiac function and disease. *Reproductive Sciences*. 2007; 14:209. [PubMed: 17636233]
- Nilsson P, Lurbe E, Laurent S. The early life origins of vascular ageing and cardiovascular risk: the EVA syndrome. *Journal of Hypertension*. 2008; 26:1049. [PubMed: 18475139]
- Norman M. Low birth weight and the developing vascular tree: a systematic review. *Acta Paediatrica*. 2008; 97:1165–1172. [PubMed: 18554273]
- Ojeda N, Grigore D, Alexander B. Intrauterine growth restriction: fetal programming of hypertension and kidney disease. *Advances in Chronic Kidney Disease*. 2008; 15:101. [PubMed: 18334233]
- Ong K. Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults. *Best Practice and Research Clinical Endocrinology and Metabolism*. 2002; 16:191–207. [PubMed: 12064888]
- Rezakhaniha R, Ajianniotis A, Schrauwen JT, et al. Experimental investigation of collagen waviness and orientation in the arterial adventitia using confocal laser scanning microscopy. *Biomechanics and Modeling in Mechanobiology*. 2012; 11:461–473. [PubMed: 21744269]
- Robillard J, Segar J. Influence of early life events on health and diseases. *Transactions of the American Clinical and Climatological Association*. 2006; 117:313. [PubMed: 18528483]
- Rondo PHC, Lemos JO, Pereira JA, Oliveira JM, Innocente LR. Relationship between birthweight and arterial elasticity in childhood. *Clinical Science*. 2008; 115:317–326. [PubMed: 18393941]
- Rozance PJ, Limesand SW, Barry JS, Brown LD, Hay WW. Glucose replacement to euglycemia causes hypoxia, acidosis, and decreased insulin secretion in fetal sheep with intrauterine growth restriction. *Pediatric Research*. 2009; 65:72–78. [PubMed: 18704001]

- Rozance PJ, Crispo MM, Barry JS, et al. Prolonged maternal amino acid infusion in late-gestation pregnant sheep increases fetal amino acid oxidation. *American Journal Of Physiology—Endocrinology and Metabolism*. 2009; 297:E638–E646. [PubMed: 19602583]
- Rueda-Clausen C, Morton J, Davidge S. Effects of hypoxia-induced intrauterine growth restriction on cardiopulmonary structure and function during adulthood. *Cardiovascular Research*. 2008; 81:713–722. [PubMed: 19088083]
- Safar M. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation*. 2003; 107:2864–2869. [PubMed: 12796414]
- Shadwick R. Mechanical design in arteries. *Journal of Experimental Biology*. 1999; 202:3305–3313. [PubMed: 10562513]
- Shifren A, Durmowicz A, Knutsen R, Faury G, Mecham R. Elastin insufficiency predisposes to elevated pulmonary circulatory pressures through changes in elastic artery structure. *Journal of Applied Physiology*. 2008; 105:1610–1619. [PubMed: 18772328]
- Stemper B, Yoganandan N, Stineman M, Gennarelli T, Baisden J, Pintar F. Mechanics of fresh, refrigerated, and frozen arterial tissue. *Journal of Surgical Research*. 2007; 139:236–242. [PubMed: 17303171]
- Thompson JA, Richardson BS, Gagnon R, Regnault TRH. Chronic intrauterine hypoxia interferes with aortic development in the late gestation ovine fetus. *Journal of Physiology London*. 2011; 589:3319–3332. [PubMed: 21540340]
- Thompson JA, Gros R, Richardson BS, Piorkowska K, Regnault TR. Central stiffening in adulthood linked to aberrant aortic remodeling under suboptimal intrauterine conditions. *American Journal of Physiology: Regulatory Integrative Comparative Physiology*. 2011; 301:R1731–R1737.
- Thornburg K. Fetal roots of cardiac disease. *Heart*. 2005; 91:867–868. [PubMed: 15958348]
- Wagenseil J, Ciliberto C, Knutsen R, Levy M, Kovacs A, Mecham R. Reduced vessel elasticity alters cardiovascular structure and function in newborn mice. *Circulation Research*. 2009; 104:1217–1224. [PubMed: 19372465]
- Wagenseil JE, Mecham R. Vascular extracellular matrix and arterial mechanics. *Physiological Reviews*. 2009
- Wagenseil JE, Nerurkar NL, Knutsen RH, Okamoto RJ, Li DY, Mecham RP. Effects of elastin haploinsufficiency on the mechanical behavior of mouse arteries. *American Journal of Physiology Heart and Circulatory Physiology*. 2005; 289:H1209–H1217. [PubMed: 15863465]
- Wells S, Walter E. Changes in the mechanical properties and residual strain of elastic tissue in the developing fetal aorta. *Annals of Biomedical Engineering*. 2010; 38:345–356. [PubMed: 19859808]
- Wells SM, Langille B, Adamson S. In vivo and in vitro mechanical properties of the sheep thoracic aorta in the perinatal period and adulthood. *American Journal Of Physiology-Heart and Circulatory Physiology*. 1998; 274:H1749–H1760.
- Wells SM, Adamson S, Langille B, Lee JM. Thermomechanical analysis of collagen crosslinking in the developing ovine thoracic aorta. *Biorheology*. 1998; 35:399–414. [PubMed: 10656049]
- Wells SM, Langille B, Lee JM, Adamson S. Determinants of mechanical properties in the developing ovine thoracic aorta. *American Journal Of Physiology-Heart and Circulatory Physiology*. 1999; 277:H1385–H1391.

Fig. 1. Carotid artery modeled as an inflation of a single fiber reinforced thinwalled tube based upon previous work of Gasser et al. (2006). Orientations of the collagen fibers are described by a mean orientation, γ , and the fiber dispersion, κ .

Fig. 2. Experimental data for control (●) and PI-IUGR (○) with experimental fit for control (solid line) and PI-IUGR (dashed line) at axial stretches of 1.0 (a), 1.2 (b) and 1.4 (c).

Fig. 3.

Experimental Second Harmonic Generation (SHG) image measurements showed a fiber angle (γ) $42.2^\circ \pm 11.2^\circ$ and dispersion (κ) of 0.286 for control arteries and a fiber angle (γ) $19.2^\circ \pm 7.5^\circ$ and dispersion (κ) of 0.193 for the PI-IUGR arteries matching predicted values. Images qualitatively showed control arteries formed collagen sheets while IUGR arteries formed collagen bundles.

Fig. 4.

Von Mises stresses were determined for the control carotid artery at physiologic mean blood pressure of 44.5 mmHg (a). The control artery was modeled at IUGR physiologic blood pressure of 50.2 mmHg (b) increasing the wall stress. Altering the wall constitutive model reduced stress (c) while an increase in geometry increases stress (d). The PI-IUGR artery (e) is remodeling to reduce increased stresses due to increased pressure and geometry.

Fig. 5. At physiologic pressures of 44.5 mmHg for the control carotid artery (a) and 50.2 mmHg for the PI-IUGR artery (b) the morphology has a similar inner diameter. As pressures increase to 200 mmHg, the control artery (c) show larger displacement, or compliance, and morphology than the PI-IUGR artery (d).

Fig. 6.

The initial fiber orientations for control carotid artery is 49.9° and the PI-IUGR artery of 16.6° . The control artery (a) and the PI-IUGR artery (b) are stretched to physiologic length (20%). After the axial stretch is applied, the control artery (c) and the PI-IUGR artery (d) inflated to physiologic mean blood pressures of 44.5 mmHg and 50.2 mmHg respectively. The fiber angle change (e) for the fiber orientation in the control (●) and PI-IUGR (○) arteries. The PI-IUGR arteries show a less responsive, more fixed, fiber orientation when introduced to stress.

Table 1

Data fit coefficients using the anisotropic hyperelastic model of the carotid artery in control and IUGR near-term fetuses.

Group	c (kPa)	k_1 (kPa)	k_2	γ (Deg.)	κ
CON	3.85	26.7	3.52	49.9	0.289
IUGR	5.56	22.4	9.11	16.6	0.221