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Mechanics, Mechanobiology, and Modeling of Human Abdominal Aorta and Aneurysms

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Abstract

Biomechanical factors play fundamental roles in the natural history of abdominal aortic aneurysms (AAAs) and their responses to treatment. Advances during the past two decades have increased our understanding of the mechanics and biology of the human abdominal aorta and AAAs, yet there remains a pressing need for considerable new data and resulting patient-specific computational models that can better describe the current status of a lesion and better predict the evolution of lesion geometry, composition, and material properties and thereby improve interventional planning. In this paper, we briefly review data on the structure and function of the human abdominal aorta and aneurysmal wall, past models of the mechanics, and recent growth and remodeling models. We conclude by identifying open problems that we hope will motivate studies to improve our computational modeling and thus general understanding of AAAs.

Keywords

wall stress; growth; remodeling; finite elements; hemodynamics

INTRODUCTION

Abdominal aortic aneurysms (AAAs) are focal, asymmetric dilatations of the infrarenal aortic wall. These lesions rupture when intramural mechanical stress exceeds strength and they are increasingly responsible for morbidity and mortality in our aging society. Wall stress is dictated by the evolving geometry, wall properties, and hemodynamic loads/perivascular boundary conditions, but clinical estimates of rupture potential, and thus interventional planning, continue to be based primarily on geometry. That is, intervention is typically advocated if the maximum diameter of the lesion reaches 5.0 cm in women or 5.5 cm in men, or if the maximal diameter increases more than 0.5 to 1 cm in one year (Lederle et al., 2002; Hans et al., 2005; Grootenboer et al., 2009). Yet, many smaller lesions rupture (e.g., 13% of those less than 5 cm) while larger lesions may not rupture over long periods

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(e.g., 54% of those over 7 cm) – see Vorp (2007). There is clearly a need for increased understanding (cf. Wassef et al., 2007).

Although wall stress has been shown to predict rupture better than does maximum diameter (Fillinger et al., 2002; 2007), we must develop computational models that exploit our increasing understanding of the underlying mechanobiology and pathophysiology. That is, most models have employed classical continuum mechanics and have only used advances in medical imaging to define patient-specific lesion geometries. Without accounting for the biochemo-mechanics, such models cannot be expected to predict either the time course of enlargement or the likelihood of rupture. The goal of this paper is to review our current understanding of AAA mechanics and mechanobiology and to identify specific needs for improving patient-specific modeling.

BACKGROUND

Risk Factors

Primary risk factors associated with AAAs are male gender, aging, cigarette smoking, and hypertension, but other factors can include atherosclerosis, prior surgery (e.g., lower limb amputation), spinal cord injury, and genetics (Choke et al., 2005; Sakalihasan et al., 2005). Noting that amputation and spinal cord injury alter the hemodynamics within the infrarenal aorta and tend to increase the incidence of AAAs suggests further the importance of the mechanics and mechanobiology (Dua and Dalman, 2010).

Reasons for gender-related differences remain unclear, but older (over 65) men are ~6× more likely than older women to have an AAA while older women having an AAA are ~3–4× more likely to experience a rupture (Grootenboer et al., 2009). There is a similar dearth of information on the effects of cigarette smoking on the aortic wall (Enevoldsen et al., 2011), yet smoking is perhaps the most potent controllable risk factor (increasing risk up to 7×). Like aging (Table 1), hypertension tends to increase the caliber and stiffness of the aorta (O'Rourke and Hashimoto, 2007; Lakatta et al., 2009). It is thus important to remember when modeling AAAs that these lesions typically arise from aged vessels in the presence of co-morbidities that alter wall properties and thereby can affect subsequent aneurysmal dilatation (Watton et al., 2009a; Wilson et al., 2011). See Humphrey (2002) and Holzapfel and Ogden (2010a) for reviews of constitutive relations for arterial behavior in health and disease.

Abdominal Aorta

AAAs occur primarily in the infrarenal aorta, which is delimited by the renal arteries and the aorto-iliac bifurcation. The normal human infrarenal aorta is approximately 12 cm long, 2 cm in diameter, and 0.2 cm in thickness (Table 2). Because the renal arteries take ~19% of total cardiac output (cf. 13% by cerebral arteries and 4% by coronary arteries; Milnor, 1990), volumetric blood flow is less in the infrarenal than in the suprarenal aorta – this explains, in part, its smaller diameter and thinner wall (cf Collins et al., 2011). Hemodynamic studies suggest that the infrarenal aorta experiences reversed flow (and thus oscillatory wall shear stress), which may contribute to its susceptibility to aneurysmal dilatation (Amirbekian et al., 2009). Classified as an elastic artery, the young healthy infrarenal aorta consists of a thin intima, layered media containing abundant smooth muscle cells, proteoglycans, and collagen organized within ~30 concentric elastic lamellae, and collagen-rich adventitia. The lower number of elastic lamellae than expected of a vessel of its size may also contribute its susceptibility to aneurysmal dilatation (Wolinsky and Glagov, 1969). Likely because of perivascular support from the spine and adjacent tissue, the normal aorta is thinner along its posterior aspect than its anterior aspect. Nevertheless, cyclic wall

strain is greater along the anterior surface, which, along with the presence of the posterior support, may contribute further to the susceptibility of the antero-lateral surface to dilatation (Goergen et al., 2007).

By dry weight, the normal infrarenal aorta consists of ~40% collagen, 25% elastin, 20% vascular smooth muscle, and 15% ground substance (Table 2; He & Roach, 1994). Residual stresses, which are associated with marked three-dimensional deformations best quantified in terms of stretch and curvature (Holzapfel et al., 2007), and axial pre-stresses, which associate with significant axial pre-stretches (Humphrey et al., 2009), arise during development and are important determinants of wall mechanics; both change with aging and aneurysmal dilatation and must be accounted for in computational models. Although such modeling can be difficult for geometries other than cylindrical (cf. Humphrey, 2002), rule-of-mixture models may allow these stresses to be included naturally (Cardamone et al., 2009). Possible thickening and stiffening of the intima with age or disease, eventually occupying 20% or more of the infrarenal aortic wall (Holzapfel et al., 2007; Schriefl et al., 2011), likely contributes to observed changes in residual and axial pre-stresses.

Pathophysiology

An AAA is typically defined by a 1.5 or more fold increase in diameter or simply a diameter greater than 3 cm. Expansion rates have been estimated from 0.1 to 0.8 cm/year, initially slower, then faster as the lesion enlarges (Brady et al., 2004; Choke et al., 2005). If left untreated, many AAAs continue to enlarge until they rupture (Fillinger et al., 2004), which has an associated mortality of 65 to 90% (Sakalihasan et al., 2005; Shimizu et al., 2006). It appears that loss of elastic fibers and possibly smooth muscle initiates the dilatation, turnover of collagen promotes enlargement, and local weakening of collagen by proteases leads to rupture. In particular, AAAs may have up to 90% less elastin than normal, much of which is fragmented, and concomitantly few smooth muscle cells (Table 2; Carmo et al., 2002). The significantly attenuated media appears to be compensated structurally by a thickened, fibrotic adventitia, though the role of the collagenous intima merits attention as well. Although the amount of intramural collagen in an AAA may not differ significantly from that in the non-aneurysmal aorta, there may be different degrees of undulation, realignment toward the circumferential direction, increased cross-linking, and varying distributions along the length of the lesion (Menashi et al., 1987; Carmo et al., 2002), all of which could alter distensibility to a degree that is evident clinically (Tables 1 and 2).

About 75% of AAAs have an associated intraluminal thrombus (Wang et al., 2002), yet its role in the natural history remains unclear. Stenbaek et al. (2000) claimed that rupture of a AAA correlates with the rate of growth of the thrombus, Kazi et al. (2003) reported that the portion of the AAA that is covered with a thrombus is thinner (with less elastin and smooth muscle, but more T- and B-cells), and Tong et al. (2011) suggested that an older thrombus contributes to the increasing anisotropy and decreasing strength of the aneurysmal wall. In contrast, Fillinger et al. (2004) and Hans et al. (2005) suggested that the thickness of the thrombus does not correlate with rupture when based on matched diameters of the AAAs. Nevertheless, a thrombus may stress-shield the aortic wall and thereby reduce intramural stress, it displaces the endothelium, it is a barrier to the diffusion of oxygen and nutrients from the blood stream to the inner (avascular) wall, it sequesters leukocytes and platelets that produce proteases, cytokines, and growth factors, and it influences local levels of plasmin, which in turn activate latent MMPs (Wang et al., 2002; Rizas et al., 2009). Indeed, it is increasingly recognized that inflammatory responses play key roles in AAAs (Thompson, 2005; Shimizu et al., 2006). Hence, potential biochemomechanical roles of thrombus in evolving AAAs must be understood and modeled better. For more on overall lesion pathophysiology, see Alexander (2004), Choke et al. (2005), Sakalihasan et al. (2005), Thompson (2005), and Shimizu et al. (2006).

MECHANICS

Three basic types of information are needed to solve any problem in continuum mechanics: geometry, material properties, and applied loads/boundary conditions. Advances in medical imaging, particularly CT and MRI, provide exquisite information on overall patient-specific geometries, yet limitations in spatial resolution continue to hamper estimates of wall thickness that are fundamental to computing wall stress. Applied loads arise primarily from three sources: the hemodynamic loads that act on the luminal surface, the perivascular tissue that acts on the outer surface, and an inherent pre-stretch that stresses the aorta axially. Whereas hemodynamic loads (i.e., components of the traction vector normal and tangential to the lumen) can be estimated from computational studies (see below), perivascular effects remain difficult to assess (Moireau et al., 2011). In vivo residual and axial pre-stresses (cf. Stålhand and Klarbring, 2005) and material properties (Zeinali-Davarani et al., 2011b) are similarly difficult to assess on a patient-specific basis, particularly when seeking to include changes due to aging, co-morbidities, and the evolution of the lesion.

Mechanical Properties

Despite universal recognition of the importance of wall mechanics in the natural history of AAAs (e.g., Humphrey, 2002; Alexander, 2004; Vorp, 2007), there have been few detailed studies of the mechanical properties. Early studies focused on gross measures of structural stiffness (Table 1), which are useful for clinical correlations but not biomechanical analyses. The most complete data on both the (biaxial) mechanical behavior of aging aorta and AAAs comes from vande Geest et al. (2004, 2006a); see Ferruzzi et al. (2011) for quantification of these data using a single nonlinear constitutive relation and Haskett et al. (2011) for comparisons to other aortic locations. Nevertheless, we must account better for the different compositions and properties of the intima, media, and adventitia within the aorta (Holzapfel, 2006) and how they contribute to lesion enlargement. There have also been limited studies on the mechanical properties of intraluminal thrombus, the most complete of which include vande Geest et al. (2006b) and Tong et al. (2011).

Computational Fluid Dynamics (CFD) and Fluid-Solid-Interactions (FSI)

Many studies have used CFD to estimate wall shear stress in AAAs based on rigid wall models and with incomplete outlet boundary conditions (cf. Lasheras, 2007). Because of the central importance of the mechanobiology of the wall, however, there is also a need in many cases to compute pulsatile blood pressure and associated changes in wall strain. Hence, FSI studies based on appropriate inlet and outlet boundary conditions are more useful (Humphrey and Taylor, 2008). There have been but a few FSI studies of AAAs (see, e.g., Wolters et al., 2005; Scotti et al., 2008; Rissland et al., 2009, and references therein), all of which remain limited by simplifying assumptions (e.g., isotropy and uniform thickness of the wall and outlet conditions that compromise estimates of propagating pressure waves).

Finite Element Analyses (FEA)

Stress analyses have appropriately improved from early estimates based on Laplace's equation, axisymmetric membrane solutions, and linear elastic FEA such that most studies now use geometrically and materially nonlinear FEA (cf. Table 3). Moreover, many other inappropriate assumptions (e.g., idealized geometries, isotropic properties, and stress-free diastolic reference configurations; see Rodríguez et al. (2008) for a comparative study of some assumptions) have given way to more sophisticated studies, which can include the presence of calcifications and/or an intraluminal thrombus (e.g., Li et al., 2008; Gasser et al., 2010; Georgakarakos et al., 2010; Maier et al., 2010a, 2010b; and references therein). Nonetheless, most studies continue to assume an isotropic constitutive behavior, often as reported by Raghavan and Vorp (2000), despite clear data to the contrary (vande Geest et

al., 2006a). Moreover, nearly all prior studies assumed uniform wall thicknes[1] and all prior studies assumed material homogeneity, both of which are unlikely based on available mechanical and histological data (e.g., Raghavan et al., 2006) and growth and remodeling computations (e.g., Wilson et al., 2011). There is clearly a need for improved computational modeling.

Many investigators have used (and continue to use) the von Mises stress to assess the maximum stress in an AAA (cf. Table 3; Vorp, 2007). This scalar metric is useful in classical engineering analyses of yielding due to excessive shear stresses, but data on aortic tissue suggest that maximum normal stress, not shear, likely governs failure (e.g., Mohan and Melvin, 1983) and results for aneurysms appear similar (cf. Fillinger et al., 2002; Raghavan et al., 2006, 2011). Moreover, whereas many reports suggest that aortic and aneurysmal tissue fail at normal stresses on the order of 1 MPa (Table 3), FEA suggest that aneurysms likely rupture at stresses of 450 kPa (Fillinger et al. 2002) or lower. This possibility reminds us that it is likely a locally compromised portion of the aneurysmal wall that ruptures. Indeed, highly localized weakening may result in “blisters” on AAAs that are particularly vulnerable to rupture (Faggioli et al., 1994; Raghavan et al., 2006). There is, therefore, a need to understand better both the mechanobiology, particularly the role of mechanics in proteolytic activity (e.g., MMP production, activation, and action on stressed matrix fibers), and the effects of multiaxial states of stress on aortic and aneurysmal failure (e.g., human abdominal aortic dissection properties are anisotropic (Sommer et al., 2010), but there is a need for better models)..

Nevertheless, vande Geest et al. (2006c) introduced a phenomenological “rupture potential index” (*RPI*) based primarily on correlations from surgical and pathological data. Briefly, they suggest that the *RPI* can be defined as the ratio of either the von Mises stress or maximum principal stress to the ultimate stress, which in turn was estimated by

$$\sigma_{ULT}(kPa)=719-379(\sqrt{ILT}-0.81)-156(NORD-2.46)-213(HIST)+193(SEX) \quad (1)$$

where $ILT \in [0,3.6\text{cm}]$ is the local intraluminal thrombus thickness, $NORD \in [1.06,3.9]$ is a normalized diameter, $HIST = 0.5$ if a first degree relative had an AAA and $= -0.5$ otherwise, and $SEX = 0.5$ if male and $= -0.5$ if female. See Maier et al. (2010a) for further discussion.

MECHANOBIOLOGY

Simply put, mechanobiology is the study of biological responses by cells to mechanical stimuli. There are three fundamental processes in mechanobiology: transduction (sensing of a mechanical stimulus), transcription (selecting appropriate information from the genetic code to govern the response), and translation (converting genetic information into the 3-D structure of functional biomolecules), which often result in the altered production of a protein or glycoprotein (including structural proteins, growth factors, proteases, or cytokines) or a change in cell status (proliferation, migration, differentiation, or apoptosis).

Cellular Responses

All three primary cell types of the aortic wall (endothelial, smooth muscle, and fibroblast) are exquisitely sensitive to their mechanical environment and so too many allied cells (e.g., monocyte/macrophages and platelets). Endothelial cells are highly responsive to wall shear

[1]Maier et al. (2011) presented FEA results at Rotterdam in April 2011 that suggested that accounting for regional variations in material properties and especially thickness results in more uniform predictions of lesion stresses in patient-specific models of AAAs, consistent with expectations for mechanobiological responses.

stress, but they are also responsive to cyclic stretching. Smooth muscle cells are highly responsive to cyclic wall stretch/stress, but they are also responsive to transmural interstitial flow (Shi and Tarbell, 2011). Fibroblasts are similarly sensitive to cyclic stretch/stress. See Humphrey (2008) for a review and references. In addition to direct effects, these cells can be affected by mechano-regulated paracrine effects, as, for example, endothelial derived vasoactive molecules can affect smooth muscle or fibroblast activity. There is, therefore, a need to quantify the fluid mechanics, solid mechanics, and biotransport/reaction kinetics that define the in vivo chemomechanical environment to which these cells are exposed and how these stimuli change during initiation, enlargement, and rupture of an AAA. Of particular note, the presence of an intraluminal thrombus locally eliminates wall shear stress effects on endothelial cells, thus disrupting this normal mechanobiological pathway.

Matrix Remodeling

Elastin is produced primarily during development and it normally has a long half-life (~40 years in humans; Arribas et al., 2006). Yet, arterial elastin becomes fragmented and degraded during aging and hypertension, and especially so during the development of an AAA (cf. He and Roach, 1994). Potentially reparative elastogenesis appears to be ineffective (Alexander, 2004), consistent with reports of little elastin in AAAs (Table 2). Because collagen is so stiff when straight (less than 10% extensibility), loss of elastin and smooth muscle must be accompanied by a continued turnover of collagen during the enlargement of an AAA. In particular, the remnant adventitia appears to experience a stress-induced thickening via the deposition of new collagen that reinforces the wall (Freestone et al., 1995); this altered turnover is probably a response to the altered mechanics, not just a consequence of altered genetics (Zarins et al., 1988). Whereas turnover of collagen (Baaijens et al., 2010) is likely a protective response to the loss of elastin and smooth muscle, localized imbalances between synthesis and degradation may be responsible in large part for eventual rupture (Humphrey, 2002; Sakalihasan et al., 2005).

Elastin and collagen are degraded primarily by matrix metalloproteinases (MMPs), which in AAAs include (Alexander, 2004): MMP-1 (interstitial collagenase, acting on fibrillar collagens), MMP-2 (gelatinase A, acting primarily on elastin and denatured collagen), MMP-9 (gelatinase B, acting primarily on collagen IV), and MMP-3 (stromelysin-1, acting primarily on elastin). Although produced in a latent form and counteracted by tissue inhibitors of matrix metalloproteinases (TIMPS), MMPs are activated by plasmin, trypsin, cathepsins, MT-MMPs, oxygen radicals, etc., and are significantly up-regulated in AAAs compared to normal aorta. MMP-9 is produced primarily by inflammatory cells (e.g., macrophages and B-cells) that invade from adventitial vasa vasorum or an atherosclerotic intima; MMP-9 is often found in smaller lesions, but is thought to play a role in the continued enlargement of AAAs. MMP-2 is produced primarily by medial smooth muscle cells, perhaps associated with the increased apoptosis. MMP-1 is found primarily in ruptured AAAs, but it is likely active in evolving lesions.

MODELING DISEASE PROGRESSION

Despite tremendous advances in modeling (CFD, FSI, and FEA), we must move from computational “snap-shots” during aneurysmal development (i.e., focusing on a mechanical state) to studies focusing on dynamic mechanobiological processes that encompass the time course of lesion growth and remodeling (G&R). By growth, we mean a change in mass; by remodeling, we mean a change in structure. Because remodeling can occur via removal and replacement of material, not just reorganization, G&R are often inextricably linked and one should seek a theoretical framework that encompasses both (Humphrey and Rajagopal, 2002).

There are currently two basic approaches for modeling growth and/or remodeling of soft biological tissues[2]. In 1994, K. Rodríguez and colleagues built upon a 1981 paper by R. Skalak and proposed a theory of "kinematic growth". This approach has been embraced, extended, and employed to study various classes of vascular adaptation (e.g., Rachev et al., 1998; Taber, 1998; Kuhl et al., 2007). Although mathematically convenient, this approach focuses on consequences of growth, not cell-mediated mechanisms by which G&R occur (i.e., production and removal of individual structural constituents). For this reason, it may be difficult to use this approach to model disease processes wherein outcomes are less predictable. In contrast, although he never proposed a specific approach, Y.C. Fung suggested in 1995 the need for mass-stress based relations for growth. In 1999, J. Humphrey built on this idea and recommended the use of rule-of-mixture relations for the stress response that incorporate evolving mass fractions for individual constituents. This "constrained mixture" approach was generalized by Humphrey and Rajagopal (2002) and has led to diverse applications (cf. Kroon and Holzapfel, 2009; Valentín et al., 2009; Watton et al., 2009b), including models of AAAs.

Although a few papers have included computations of the G&R of AAAs as illustrative examples of new frameworks (e.g., Kuhl et al., 2007; Machyshyn et al., 2010; Schmid et al., 2010), we focus here on detailed studies of AAAs (Watton et al., 2004; 2009a; Sheidaei et al., 2011; Wilson et al., 2011; Zeinali-Davarani et al., 2011a). These papers necessarily focused first on conceptual issues and thus thin-walled geometries in the absence of intraluminal thrombus and atherosclerosis. They each employed the basic concept of an evolving constrained mixture and thus assumed rule-of-mixtures expressions for stored energy that include contributions by elastin, fibrillar collagen, and smooth muscle or ground substance (proteoglycans). Moreover, they enforced classical linear momentum balance, assuming quasi-static motions in the absence of gravity, using finite element methods. Finally, they assumed that aneurysmal dilatation initiates via a focal loss of elastin and continues due to expected mechanobiological responses by the resident cells that result primarily in the turnover of collagen. The primary differences in these papers thus relate to the choice of constitutive relations for the G&R.

Watton et al. (2004, 2009a) focused on two classes of G&R relations: one for changes in a "collagen density variable" n^c and one for the evolution of reference configurations for the collagen, which was prescribed via a relation for the overall evolving stretch λ^R at which undulated collagen fibers become straight (i.e., Recruited) and begin to carry load. These two evolution equations were written[3]

$$\frac{\partial n_J^c}{\partial s}=\frac{\beta}{2}\left((\lambda_J^c)^2-(\lambda_a^c)^2\right),\qquad \frac{\partial \lambda_J^R}{\partial s}=\frac{\alpha}{2}\left((\lambda_J^c)^2-(\lambda_a^c)^2\right),\qquad J=M(\text{media}),A(\text{adventitia}) \tag{2}$$

where β and α are kinetic (gain-type) parameters, λ_a^c is the (homeostatic) stretch at which newly deposited collagen is assumed to be "attached" to extant matrix; s is G&R time, which spans larger intervals than cardiac cycle time. The evolution equation for collagen density reflects responses by fibroblasts to changes in matrix stretch that alter the synthesis of collagen and the production of proteinases that degrade the collagen. Evolution of the recruitment stretch was motivated by this observation that collagen fibers turnover continually but are incorporated within extant matrix in a stretched state; the parameter α is thus associated with the half-life of the collagen. Updated values of n^c enter the equilibrium solution via the prescribed stored-energy function (which includes a neo-Hookean response

[2]Some studies combine these two approaches, as, for example, Alford et al. (2008) and Machyshyn et al. (2010).
[3]Some notational changes were introduced for purposes of internal consistency and increased clarity.

for both elastin and ground substance and an exponential response for collagen fibers) whereas updated values of λ^R (initial value of 1.19) similarly enter the stored energy via the strains experienced by the collagen. Notice that evolution ceases when the stretch experienced by all families of collagen equals the homeostatic (or attachment) value, which was assumed to be 1.09. Similar to formulations by Rachev and Taber, this G&R framework is rate-based with the evolution equations depending on strains not stresses. A subtle but important difference from kinematic growth formulations, however, is that the evolution equations are expressed relative to natural configurations of individual constituents and thus can model cell-mediated mechanisms of G&R. Finally, albeit employed so far for only cerebral aneurysms, Watton et al. (2009b) have extended their G&R framework to include fluid-solid-growth (FSG) modeling (cf. Figueroa et al., 2009).

In contrast, Zeinali-Davarani et al. (2011a), Sheidaei et al. (2011), and Wilson et al. (2011) employed integral-based G&R formulations wherein the strain-energy function for the wall is given by $w = \Sigma w^k$ for all G&R times s. Despite some differences in implementation, these papers were all motivated by the earlier study of Baek et al. (2006), wherein

$$w^k(s)=\frac{M^k(0)}{\rho(s)}Q^k(s)W^k\left(\lambda^k_{n(0)}(s)\right)+\int_0^s\frac{m^k(\tau)}{\rho(s)}q^k(s-\tau)W^k\left(\lambda^k_{n(\tau)}(s)\right)d\tau. \tag{3}$$

This equation reveals the three classes of constitutive relations that are needed for each of the k constituents: individual strain-energy functions W^k, rates of mass density production $m^k > 0$, and survival functions $Q^k \in [0,1]$ and $q^k \in [0,1]$ that account for the half-lives of cells and matrix. Note, too, that M^k are apparent mass densities defined per surface area and $\lambda^k_{n(\tau)}$ are stretch ratios defined relative to evolving natural configurations defined at the time of deposition $\tau \in [0, s]$. Similar to Watton and colleagues, Baek and colleagues assumed neo-Hookean and exponential forms for the strain energies for elastin and collagen, respectively. Moreover, the evolution equations have been assumed to have forms similar to

$$m^k(\tau)=m^k_B\left(1+K^k_\sigma\Delta\sigma^k\right),\qquad q^k(s-\tau)=\exp\left(-\int_\tau^s K^k_d(\tilde{\tau})d\tilde{\tau}\right), \tag{4}$$

where m^k_B are basal values for production, K^k_σ are stress-mediated (gain-type) G&R parameters, $\Delta\sigma^k$ represent a normalized difference between a scalar metric of the Cauchy stress and an associated homeostatic (target) value, and K^k_σ are degradation parameters that reflect half-lives of individual constituents, which may depend on the state of tension in that constituent or the stress-induced production of proteolytic biomolecules. Hence, when measures of stress/tension equal homeostatic values, production and removal (first order decay) return to basal values and enable “tissue maintenance” provided the applied loads remain the same. The linear dependence of mass production on increased stress is consistent with the earliest such description of this phenomenon (Wolinsky, 1970), though this relation needs to be refined based on more complete data (cf. Humphrey, 2008). An advantage of constrained mixture models is that loosely coupled reaction-diffusion equations can also be used to quantify evolving concentrations of effector molecules (vasoactive, mitogenic, proteolytic, inflammatory), which in turn can be incorporated directly within refined constitutive equations for cell or matrix turnover (equations 4).

Motivated by Figueroa et al. (2009), Sheidaei et al. (2011) similarly used a loosely coupled approach to inform a G&R code for aneurysmal dilatation with information on the evolving hemodynamics. Because of the very different time scales associated with G&R (weeks to years) and the cardiac cycle (approximately one second), loosely coupled approaches are

both appropriate and recommended. In concluding this section, we note that two other papers have addressed G&R of AAAs. Helderman et al. (2008) described the behavior of the aneurysmal wall using isotropic linear elasticity and prescribed changes in the associated Young's modulus (reduced over time to weaken the wall) to model enlargement. These assumptions are not appropriate based on available data (including stiffening and changing material symmetries) and do not address the mechanisms by which a lesion evolves (i.e., turnover of cells and matrix in evolving configurations). Volokh and Vorp (2008) modeled the enlargement of a spherical AAA via evolution equations for wall density and two material parameters found in a nonlinear isotropic model for the wall. Although simple mathematically, this phenomenological approach similarly does not allow increasing data on the mechanobiology to be included naturally. This paper also emphasized the importance of embedding failure criteria within G&R models, which is important and has not received appropriate attention heretofore (cf. Wilson et al., 2011).

In summary, because of the lack of longitudinal data on AAAs or associated well accepted hypotheses on aneurysmal dilatation, it is not possible to validate current G&R models of AAAs. For this reason, AAA models have been motivated by models of vascular adaptations (in response to altered blood flow, pressure, and axial stretch as well as chemical insults and aging; see Valentín et al., 2009). There is a need, however, to determine whether G&R relations that hold for modest adaptations similarly hold in pathological situations, as, for example, whether the so-called attachment/deposition stretch remains the same during lesion enlargement and similarly whether mechanical properties of collagen fibers remain the same during turnover.

CLOSURE

Summary

Often characterized by "atherosclerosis at the luminal aspect, a thinned fibrous, acellular media, and a thickened adventitia with a variable inflammatory infiltrate" (Freestone et al., 1995), ruptured AAAs are expected to become increasingly problematic in our aging society. The two primary methods of treatment are (a) open surgical repair by replacing the diseased segment with a synthetic arterial graft and (b) endovascular repair by deploying a stent-graft to separate the thrombus and aneurysmal wall from hemodynamic loads. Particularly provocative is the observation that some endovascularly treated AAAs regress, with decreases in size up to 8% (Bertges et al., 2003). Given that an AAA actively grows and remodels during most of its natural history, this observation suggests that particular chemomechanical loads could render such G&R favorable. It is hoped that computational tools will one day help determine how interventions could be designed to exploit underlying biochemomechanical processes to promote regression or repair, but at the minimum to provide increased predictive capability for designing interventions.

Other Aneurysms

In addition to abdominal lesions, aneurysms occur in the ascending and descending thoracic aorta (Elefteriades and Farkas, 2010) and the intracranial circulation (Humphrey and Taylor, 2008). Although the etiology differs amongst these three primary types of aneurysms (abdominal, thoracic, and intracranial), similarities exist and one should be familiar with advances in all three areas of study. In particular, it appears that (mechanical) damage to or (chemical) degradation of elastic fibers and loss of smooth muscle function is a common early contributor to the formation or expansion of all aneurysms and both remodeling of collagen (i.e., turnover) and inflammation likely play fundamental roles in dictating rates of enlargement as well as the potential for rupture.

Of Mice and Men

Notwithstanding the substantial clinical data base available, there continues to be a lack of longitudinal data on the evolution of lesion geometry, gene expression, composition, mechanical properties, and hemodynamics. In particular, there is little information on early events because patients typically present only after the lesion has expanded considerably. Hence, despite their inherent limitations, animal models will remain as important complements to human studies. Amongst others, mouse models (cf. Daughtery and Cassis, 2004; Collins et al., 2011) are expected to play increasingly greater roles in our learning process. Indeed, whereas some investigators ignore mouse models because of differences between the structure of and hemodynamics within the mouse and human aorta as well as differences in the location and time course of the development of aneurysms and dissections in mice and men, inherent differences may be able to be exploited to provide yet a greater level of overall understanding.

Open Problems

Related to the fundamental importance of both biomechanics and mechanobiology to the natural history of AAAs, we suggest that the most pressing overall need is development of computational models that can predict the evolving wall stress and strength of AAAs based on clinically available patient-specific data. Such models must be informed by new data and understanding, hence we must:

- Determine why males are more susceptible to developing AAAs and yet females have a higher risk of rupture. Animal models suggest that differences may depend more on the roles of androgens than estrogen (Henriques et al., 2004), yet more data are needed to provide general insight.
- Elucidate the mechanobiology of adventitial fibroblasts, which because of the loss of smooth muscle cells may be responsible for most remodeling of the evolving wall. Moreover, we must determine if mechano-sensitive responses by vascular cells are similar in health and disease or if target values of stress/stretch or other metrics are reset.
- Investigate the mechanobiology of MMPs, including roles of mechanical stress in dictating their production, activation, and effectiveness in degrading stressed matrix.
- Quantify the time course of thrombus development and maturation, particularly related to structural stratification of the clot and release of proteolytic molecules that may influence highly localized weakening of the aneurysmal wall.
- Identify appropriate (representative) metrics of stress for characterizing the multi-dimensional state of stress locally and for governing cell and matrix turnover. In particular, the former could help identify new failure criteria, preferably in terms of failure properties of remnant elastin and remodeled collagen, especially under the influence of proteolytic activity. Without appropriate failure criteria, G&R models will remain incapable of addressing the fundamental issue of rupture-potential.
- Investigate and model transmural distributions of collagen, including evolving mass fractions, orientations, fiber diameters, and cross-linking, and how they change with disease progression. Similarly, we must quantify changes in smooth muscle phenotype and density, and how chemomechanical responses by smooth muscle affect the stress distribution in AAAs.
- Determine how patient-specific co-morbidities (cigarette smoking, atherosclerosis, hypertension, diabetes, prior injury or surgery) affect the both the hemodynamics

and wall stiffness. In particular, our computational models must account for the biological state of the artery from which the AAA arises (Wilson et al., 2011).

In other words, there is a pressing need to advance and then exploit our understanding of the underlying mechanobiology and pathobiology so that we can move patient-specific modeling well beyond focusing on lesion geometry alone. That is, by moving from phenomenological to structurally motivated constitutive relations for G&R (the simplest of which are rule-of-mixture relations), computational modeling has great promise to contribute to the move our field towards personalized medicine wherein interventional planning will be based on an understanding of the biological status of the lesion, not just overall lesion size. We hope that this brief review will stimulate experimental and computational research that will contribute to this long-term goal.

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Table 1

Clinical data showing effects of aging on the abdominal aorta. Noting that aneurysms develop in aged, diseased aorta, these effects likely influence greatly any subsequent response to injury or insult that leads to the development of an aneurysm. It appears that the Diameter Strain was defined as $(d_s - d_d)/d_d$ where d denotes luminal diameter and indices s and d denote systolic and diastolic. The metric of stiffness is the so-called in vivo pressure-strain modulus: $(P_s - P_d)d_d/(d_s - d_d)$, where P is luminal pressure

Mean Age (Years)	Heart Rate	Systolic Pressure	Diastolic Pressure	Systolic Diameter	Diastolic Diameter	Diameter Strain	Stiffness (kPa)
25/25	62	117	70	17.0	15.6	0.094	69/40
46/--	62	134	79	18.0	17.4	0.056	144 /
60/55	61	133	80	20.2	19.5	0.030	220/104
71/71	62	143	77	21.1	20.6	0.028	337/140

Note: Age (years) and pressure – strain modulus (i.e., stiffness in kPa) are taken from two reports: Länne et al. (1992)/MacSweeney et al. (1992). All other data are from Länne et al. (1992). Note, too, that MacSweeney et al. report a stiffness of 313 kPa for AAAs, which is not very different for the stiffness reported by Länne et al. for the oldest group of aortas. Heart Rate in bpm, Pressure in mmHg, and Diameter in mm.

Table 2

Comparison of basic data for the normal thoracic and infrarenal abdominal aorta as well as AAAs. The thoracic data are included for purposes of comparison only

	Thoracic Aorta	Infrarenal Aorta	AAA	References
In Vivo Luminal Diameter (cm)	1.6 – 1.7	1.2 – 1.5	>3	Vorp (2007) Zarins et al. (2001)
In Vivo Wall Thickness (mm)	1.6 – 1.7	1.4 – 1.5	1.7	Zarins et al. (2001) Raghavan et al. (2006)
% Intima/Media/Adventitia	6/76/18	20/47/33	-	Iliopoulos et al. (2009) Holzapfel et al. (2007)
# Elastic Lamellae[+]	64 – 72	17 – 34	0	Wolinsky (1970) Zarins et al. (2001)
GAGs (%)	-	18	32	He and Roach (1994)
Smooth Muscle (%)	-	23	2	He and Roach (1994)
Elastic Fibers (%)	22 – 33	23 – 30	2	He and Roach (1994) Cattell et al. (1996)
Collagen (%)	18 – 31	36 – 45	64 – 84	He and Roach (1994) Menashi et al. (1987) Cattell et al. (1996)
Collagen I/III	-	73/27	74/26	Menashi et al. (1987)
Axial Prestretch	1.2	1.1 – 1.3	-	Holzapfel et al. (2010)
Circ Failure Stress (MPa)	-	-	0.5 – 0.8	Vallabhaneni et al. (2004) Di Martino et al. (2006)
Axial Failure Stress (MPa)	-	-	1.5	Raghavan et al. (2006)
Circ Failure Stretch	-	1.5 (1-D) 1.25 (2-D)	1.5	Mohan & Melvin (1983) Di Martino et al. (2006)
Axial Failure Stretch	-	1.5 (1-D) 1.25 (2-D)	1.3	Vallabhaneni et al. (2004)

[+]The number of elastic lamellae varies around the circumference, with fewer lamellae on the posterior side closest the support of the spine (e.g., ~20 on the posterior and 35 on the anterior surfaces of the abdominal aorta). By 1-D and 2-D in failure stretches, it is meant uniaxial and equibiaxial stretching, respectively. Finally, it is important to note that dimensions are often reported without specification of the state (in vivo or unloaded/fixed), a situation that must be corrected.

Table 3

Twelve representative nonlinear finite element analysis (FEA) and fluid-solid interaction (FSI) studies and the assumptions upon which they are based. G&R simulations should recover appropriate FEA and FSI results as special cases (i.e., at particular times during G&R), which can thereby provide guidance for future model development. G&R models naturally account for potential regional variations in material symmetry, thickness, and homogeneity, however

Paper	Material Symmetry	Thickness	Homo-geneous	Stress Metric	ILT	Comments
Raghavan et al. (2000)	Isotropic R&V	Uniform 1.9 mm	Yes	Von Mises	--	Nonlinear, Patient Specific
Wang et al. (2002)	Isotropic R&V	Patient-Specific	Yes	Von Mises	Nonlinear, Isotropic	ILT thickness 1.75–1.95 mm
Fillinger et al. (2002)	Isotropic R&V	Uniform 1.9 mm	Yes	Maximum Principal	--	Stress Better than Diameter
Wolters et al., (2005)	Isotropic neo-Hookean	Uniform 2.0 mm	Yes	Maximum Principal	--	Early FSI
Lu et al. (2007)	Isotropic R&V	Uniform 1.9 mm	Yes	Von Mises	--	Inverse method (reference state)
Speelman et al. (2007)	Isotropic R&V	Uniform 1.5 mm	Yes	Maximum Principal	Nonlinear, Isotropic	Calcification Included
Scotti et al. (2008)	Isotropic R&V	Variable 0.5–1.5 mm	Yes	Von Mises	--	FSI, idealized geometry
Rodriguez et al. (2008)	Anisotropic Holzapfel	Uniform 1.5 mm	Yes	Maximum Principal	--	Idealized geometry
Rissland et al. (2009)	Anisotropic Holzapfel	Uniform 2.0 mm	Yes	Von Mises	Linear, Isotropic	FSI
Dorfmann et al. (2010)	Isotropic Demiray	Uniform 2.0 mm	Yes	Maximum Principal	--	Blood pressure gradients
Maier et al. (2010)	Isotropic R&V	Uniform 1.0 mm	Yes	Von Mises	Nonlinear, Isotropic	Vorp's Rupture Potential Index
Gasser et al. (2010)	Isotropic R&V	Variable 1.1–1.5 mm	Yes	--	Variable Stiffness	Modified Rupture Index

Note: R&V denotes the invariant-based, two-parameter model proposed by Raghavan and Vorp (2000) whereas "Holzapfel" denotes one of multiple variations of the two-fiber family model proposed by Holzapfel et al. (2000). The nonlinear models for the intraluminal thrombus (ILT) range from the two-parameter invariant-based model proposed by Wang et al. (2001) to a neo-Hookean type model.