

The Biomechanics of Arterial Aneurysms

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Annu. Rev. Fluid Mech. 2007. 39:293–319

The *Annual Review of Fluid Mechanics* is online at fluid.annualreviews.org

This article's doi:
10.1146/annurev.fluid.39.050905.110128

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0066-4189/07/0115-0293\$20.00

Key Words

abdominal aortic aneurysms, cerebral aneurysms, flow-structure interaction, enlargement, rupture

Abstract

The formation of an arterial aneurysm is believed to be a multifactorial and predominantly degenerative process, resulting from a complex interplay between biological processes in the arterial wall and the hemodynamic stimuli on the vessel's wall. Once an aneurysm forms, the repetitive pressure and shear stresses exerted by the blood flow on the weakened arterial wall generally, but not always, cause a gradual expansion. As the wall geometry, composition, and strength progressively degrade through the enlargement process, the aneurysm ruptures when the wall of the distended artery fails to support the stresses resulting from the internal blood flow. This review surveys recent progress in this area and provides a critical assessment of the contribution made by hemodynamics studies to the current understanding of the pathogenesis of the disease and to its clinical management.

Circle of Willis: a roughly circular connection of arteries located at the base of the brain and formed by the anterior communicating artery, the two anterior cerebral arteries, the two internal carotid arteries, the two posterior communicating arteries, and the two posterior cerebral arteries

1. INTRODUCTION

Blood is periodically pumped by the heart into a complex branching network of muscular elastic arteries that carry nutrients and oxygen to the tissues and organs in the body. During each cardiac cycle, the heart ejects 70 ml of blood at a pressure of 120 mm Hg into the aorta where the mean pressure is approximately 80 mm Hg. The pressure pulse generated by the heart travels along the network of arteries, partially reflects at each branching point, and is damped by the time it reaches the capillaries that irrigate the tissues. The blood then returns to the heart through a network of veins that are equipped with a complex system of valves whose function is regulated by secondary muscular activity and the action of the heart itself (Nichols & O'Rourke 1990). In a normal, healthy individual, the pumping process is repeated approximately 70 times per minute, 100,000 times per day, or almost 3 billion times throughout the expected lifetime (McDonald 1974). With each periodic ejection of blood across the aortic valve into the ascending aorta, a pressure pulse is generated that propagates throughout the elastic network of arteries inducing a pulsatile flow with a mean forward motion. Depending on its proximity to the heart and on the function of the organ that it supplies, each artery has a different degree of elasticity. The elasticity is determined by the structure and composition of the arterial wall. The stiffness is partially controlled by the regulatory activity of the endothelial cells that separate the wall from the blood stream. This feedback control system whereby the elasticity of the arterial wall is constantly adjusted by the regulatory function of the endothelial cells is remarkably stable, and allows the circulatory system to accommodate in a short time the large changes in the cardiac output dictated by the increasing demand of nutrients and oxygen to the tissue and organs during exercise and other extraneous activities. Arteries can also adapt to long-term physiological conditions by thinning or thickening the muscular layer, and altering the relative composition and organization of the various assemblies of structural proteins in a process generally known as "remodeling."

Throughout the entire lifetime of a healthy individual, the living components of the arterial wall must regenerate and remodel continuously to maintain the integrity and function of the system and to withstand the repetitive wall stresses. Unfortunately, in some cases, this otherwise remarkably stable system destabilizes, whether due to disease or other complex processes, and a portion of the arterial wall weakens and distends permanently, forming an aneurysm (from the Greek word "*aneurysma*," "*ana*" throughout and "*eurus*" wide). Although these pathological, blood-filled permanent dilatations form in many blood vessels, and even in the heart, they mainly appear in arteries, primarily in the abdominal and thoracic portions of the aorta and in the intracranial arteries surrounding the Circle of Willis.

Although the precise cause of this disease is still unknown, it is believed to be multifactorial and predominantly degenerative, arising through a complex interaction among several biological factors as well as from some specific changes in the hemodynamic stimuli on the vessel's wall that might destabilize the above-mentioned regulatory system. Once the aneurysm forms, the hemodynamic forces exerted by the pulsatile blood flow on the weakened arterial wall generally, but not always,

cause a gradual expansion. As the wall geometry, composition, and strength progressively degrade through the enlargement process, the aneurysm ruptures when the wall of the distended artery fails to support the stresses resulting from the internal blood flow. The rupture of an aneurysm often leads to sudden death or severe disability.

One of the most detrimental features of this disease is that aneurysms are seldom detected at early stages (Pokrovskii et al. 2003, Szilagyi 1982). In the vast majority of cases, they remain latent until symptoms occur as their size greatly increases, or they are found in an incidental exam. Once detected, due to the lack of knowledge of the role that the various factors play in the expansion process, there is currently no accurate technique to predict the aneurysm's expansion rate, nor to determine its critical size (or shape) at the point of rupture. Owing to a lack of any other reliable method, aneurysm diameter and its observed expansion rate are the current standard parameters by which physicians estimate the risk of rupture (Nader-Sepahi et al. 2004, Ujiie et al. 1999). Population-based statistics show that increasing size leads to a higher risk of rupture (Englund et al. 1998, Law et al. 1994). However, small-sized aneurysms have been found to rupture, whereas others have been observed to grow to very large sizes without rupturing. Depending on their location, treatment is currently recommended for aneurysms exceeding a maximal diameter, and/or a certain expansion rate, leaving physicians to face the therapeutic dilemma of either subjecting patients with small aneurysms to a complex surgery with high morbidity and complications or to an unknown, increased risk of rupture (Stringfellow et al. 1987, Taylor & Porter 1987).

Over the past 30 years, the study of the pathogenesis and progression of aneurysms has become a multidisciplinary effort involving a wide range of areas spanning from molecular cell biology to solid and fluid mechanics. These studies have been generally motivated by the need to provide answers to the critical questions that are essential to clinically managing the disease:

1. What is the exact pathogenesis of the arterial aneurysms? Why do some people develop aneurysms whereas others do not? Why are aneurysms more commonly seen forming at specific sites in certain arteries?
2. Once an aneurysm forms, what are the factors that determine the rate at which it enlarges? More importantly, can its enlargement rate be predicted?
3. In each specific case, can the risk of rupture be precisely quantified?
4. Finally, what is the patient-specific optimal treatment technique to prevent its rupture?

During the past three decades, a widely proposed hypothesis has been that specific changes in the hemodynamic forces acting on the vessel wall could be a key contributing factor to the origin and progression of the disease (Fox & Hugh 1996, Glagov et al. 1988, Hademenos 1995, Ku et al. 1985, Lei et al. 1995, Malek et al. 1999, Pedersen et al. 1993, Soliman 2001). Thus, much attention has been devoted to analyzing the characteristics of the blood flow inside aneurysms as well as to classifying the specific features of the flow in the arterial segments where aneurysms are predominantly known to form. This review surveys recent progress in this area and

Pathogenesis: the mechanism by which certain factors cause a disease

provides a critical assessment of the contribution that these studies have made to the current understanding of the pathogenesis of the disease and to its current clinical management.

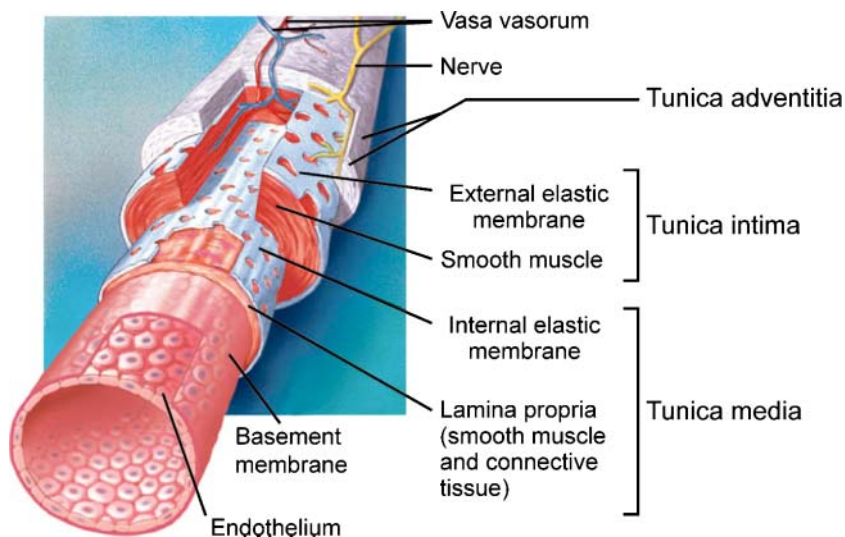
2. PATHOGENESIS OF ARTERIAL ANEURYSMS

Mechanically, the formation of an arterial aneurysm resembles the familiar problem found in structural engineering of the plastic deformation, permanent bulging, and subsequent rupture of a pipe under the effect of an oscillatory internal pressure, a process that often involves failure due to fatigue. However, in the case of arteries, the problem is dramatically more involved and difficult to analyze due to the fact that their walls are composed of a complex structure of living cells and a structural network of sheets and fibers of polymerized proteins capable of not only actively modifying their mechanical properties in response to changes in the mechanical stimuli from the internal blood flow, but more importantly, of undergoing permanent transformations (remodeling) as a result of inflammatory processes, infection, degenerative processes, and even aging.

The walls of all the large vessels in the human body are composed of three layers (or tunics): the tunica intima, the tunica media (or muscular), and the tunica external (or adventitia) (Fung 1993) (see **Figure 1**). The thickness and structural composition of each layer vary depending on the proximity to the heart and on the specific function of the organ or tissue supplied by the vessel. Arteries are generally thicker, more muscular, and more elastic than veins. The intima layer is made up of a single layer of vascular endothelial cells (VECs) that adhere to a basal lamina (80 nm thick) covering a subendothelial layer composed of connective tissue, elastic fibrils, and collagenous bundles.

Figure 1

Structure of a medium-size muscular artery. Used with permission of The McGraw-Hill Companies, Inc.



The median layer consists primarily of layers of smooth muscle cells (SMCs), a varied number of elastic sheets, a complex network of elastic fibrils, and bundles of collagenous fibers embedded in an extracellular matrix (ECM). The SMCs synthesize the protein and proenzymes of the ECM, which in turn influence the proliferation, differentiation, and migration of the cells. The median layer accounts for most of the mechanical properties of the wall and through its active (SMC) and passive (structural proteins) components determines the elasticity of the wall. Elastin fibers have a modulus of elasticity of 0.6 MegaPascals (MPa) (6×10^6 dynes/cm²) and can stretch in excess of 250% of its original length. Collagen fibers are much stiffer with a modulus of elasticity of 500 MPa (5×10^9 dynes/cm²), which is almost 1000 times larger than elastin (Dobrin 1978). The outermost layer is the adventitia consisting mainly of ground substances, collagen fibers, blood vessels (vasa vasorum, the vessels that supply the vessel), and nerves that extend into the median layer.

The VECs form a permeable barrier that prevents some substances from entering the arterial wall. VECs as well as blood cells (platelets and erythrocytes) are shear-sensitive. In particular, fluid shear forces imparted by the blood flow have long been known to regulate many of the VEC functions and activity through a process generically referred to as “mechanotransduction” (Blackman et al. 2002, Davies et al. 1984, Traub & Berk 1998). The generalized hypothesis is that an unidentified “mechanosensor” surface receptor (perhaps an ion channel) integrates the external flow forces and translates them into appropriate biochemical responses. Flow shear affects endothelial secretion of prostacyclin, a vasodilator and a potent inhibitor of platelet aggregation, and nitric oxide, which is thought to reduce leukocyte adhesion, and more importantly, to cause changes in the “contractile tone” of the SMCs in the medial layer (Ben Driss et al. 1997; Chiu et al. 2003, 2004).

There have been many clinical and laboratory studies aimed at characterizing the constitutive equation quantifying the nonlinear relationship between the wall stresses and the strain response of blood vessels (for reviews see Cameron 1999, Dobrin 1978, Greenwald & Berry 2000, Levy 1999, McVeigh et al. 2002, Vito & Dixon 2003). Although some of the models that have been proposed have been extremely valuable in analyzing certain aspects of the mechanics of the vascular system, the need still remains to obtain models capable of predicting the changes in the mechanical properties of the wall as it remodels under the poorly understood coupling between mechanical stimuli and the biological processes taking place at the wall. As will become apparent in the following sections, the current inability to precisely characterize the mechanical properties of the vessel as it undergoes long-term remodeling represents a key stumbling block precluding the prediction of both the expansion rate and the risk of rupture of aneurysms.

Thus, the perennial question being debated is: Does an aneurysm form as a result of a degradation process in the wall, or by anomalous changes in the hemodynamic stimuli that could result in an unstable degenerative response on the vessel wall, or by a combination of both? The current consensus is that the cause is more likely the result of a complex interplay between degenerative biological processes triggered by inherited biochemical or structural defects, aging, infection or disease, and specific hemodynamic factors (see **Figure 2**).

Elastin: also called elasticin, a protein often present in the form of sheets and fibers in connective tissue

Collagen: the main protein of connective tissue and the most abundant protein in mammals

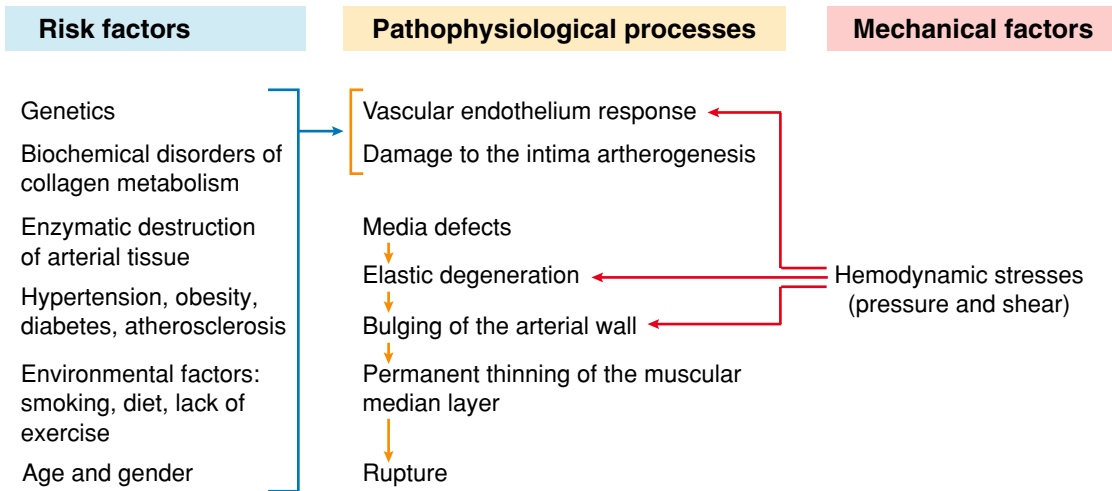


Figure 2

Pathogenesis of arterial aneurysms. Interplay between mechanical stimuli and physiological processes.

Until the past few decades, the most common cause of aneurysms was infection on the arterial wall due to syphilis, the lodging of bacteria (most commonly *Clemencia Pneumonia*) from an infected heart valve, or from bloodletting. Today, these primary causes of wall degradation have been greatly diminished and other factors such as genetic disorders, mycotic infection, high blood pressure, effects of cigarette smoking, atherosclerosis, and simply aging have become dominant.

Two hereditary collagen vascular disorders are known to cause aneurysms: the Marfan's and the Ehlers-Danlos's Syndromes (Wilmink et al. 2000). Both contribute to abnormalities in the synthesis and organization of the structural proteins (elastin and collagen), and thus to a pathological weakening of the wall. These two conditions are very rare and although a familiar aggregation of some types of aneurysms (mainly intracranial) has been extensively reported, other specific possible genetic factors have not yet been discovered. Candidate genes for aneurysm's predisposition are expected to be involved in cross-linking for collagen and elastin or other structural components.

Several predisposing risk factors have been statistically shown to play an important role in the formation of aneurysms: cigarette smoking, alcohol consumption, hypertension, and atherosclerosis (Juvela et al. 2001, Krex et al. 2001, Singh et al. 2001, Wanhainen et al. 2005). Smoking has long been known to be a factor, although the precise mechanism of action is still being debated (Auerbach & Garfinkel 1980, MacSweeney et al. 1994, Reilly & Tilson 1989). Hypertension is one of the most frequently studied risk factors because it is found twice as often in patients with aneurysms than in patients without. Hypertension gradually distends the vessel and causes a gradual thickening of the wall. Atherosclerosis has historically been attributed as the most common cause of wall degradation in some aneurysms such as abdominal aortic aneurysms (AAAs). However, this theory has been continuously

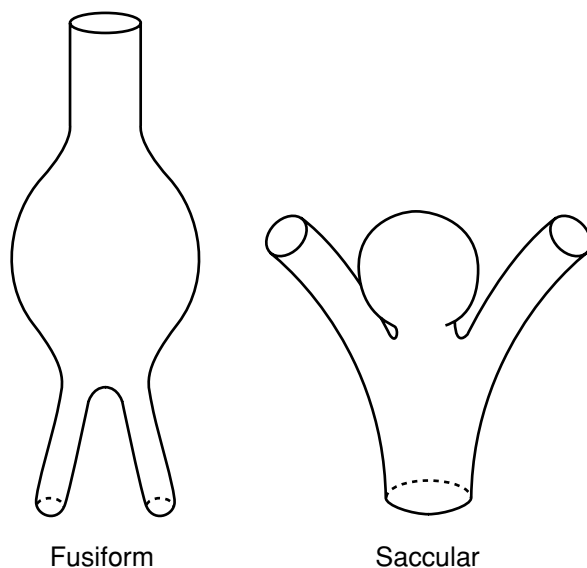


Figure 3

Aneurysm classification based on the shapes of the aneurysms.

challenged over the past two decades as aneurysms are often observed in patients with no atherosclerosis disease, and arterial sites with the most concentrated plaque deposits are very rarely the sites where aneurysms form (Lee et al. 1997). The current thought is that atherosclerosis may aid the progression of the disease in some cases, but it alone is not the primary cause of the weakening of the wall.

Aneurysms are often classified according to their shape and location in the human body into two main groups: fusiform and saccular aneurysms (see **Figure 3**). Fusiform (spindle-shaped) aneurysms are most commonly found in the abdominal aorta or in the popliteal artery behind the knee, whereas saccular (berry-like) are predominantly found in the main arteries of the cerebral circulation, especially along the Circle of Willis.

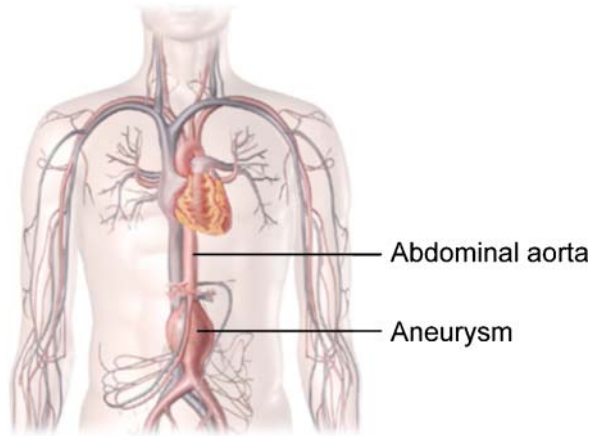
The marked differences in their shape as well as the distinct structural composition of the arteries where they form (muscular elastic aorta vs cerebral arteries) suggest that the pathogenesis of these processes is most likely somewhat different. This hypothesis has been further strengthened by the fact that the incidence of AAAs (the most common fusiform aneurysm) increases dramatically with age (Singh et al. 2001, Wanhainen et al. 2005), whereas intracranial aneurysms do not exhibit such a strong dependency on aging (Fox 1983, Gibbons & Dzau 1994). Owing to the above-mentioned differences in their shape as well as their wall structure, we analyze the possible mechanical and hemodynamic factors responsible for the formation of each type of aneurysm separately in the following sections.

2.1. Pathogenesis of Fusiform Aneurysms

Most fusiform aneurysms are found in portions of elastic muscular arteries in locations upstream of major bifurcations or branch points. The most commonly found fusiform

Figure 4

Abdominal aortic aneurysm (AAA)



aneurysm in the human body forms in the abdominal portion of the aorta, below the renal arteries and upstream of its bifurcation into the iliac arteries. Below, we analyze this AAA as a representative case of the fusiform type. Like the one shown in **Figure 4**, AAAs very rarely appear in individuals under 50 years of age, but their incidence increases drastically at age 55 and peaks in the early 80s. A large screening study conducted in Norway in 1994–1995 showed that AAAs are present in 8.9% of men and in 2.2% of women over 60 years of age (Singh et al. 2001). It has also been found that with the gradual increase in life expectancy, the incidence of AAAs has increased steadily over the past decades, although this may simply be a result of a larger awareness of the disease in the medical community and improved screening methods (Best et al. 2003, Collin 1988).

2.1.1. The aging hypothesis. Because age is the most dominant factor in AAAs, it seems reasonable to assume that the primary cause of their formation should lie on the coupling between the specific changes in the architecture of the vessel (length, diameter, and wall structure) resulting from the normal aging process and the changes they induce in the hemodynamics. The postulate is that under specific conditions this coupling may lead to an unstable response whereby a portion of the wall of the abdominal aorta degrades, and its diameter gradually increases.

There has been a large body of work devoted to the underlying mechanisms of aging in the arteries of humans (for a very detailed description of the effect of aging on the vascular system, see Braunwald 1988, Kissane 1985, Nichols & O'Rourke 1990). When elastic systemic arteries age over the years, their diameters increase and become stiffer, and their walls thicken. However, the major structural changes caused by aging occur in the median layer, which thins out and loses its orderly arrangement of elastin lamins and fibers, which become fragmented and unorganized (Lakatta et al. 1987). The degeneration of elastic fibers is accompanied by an increase in the collagenous substance (the stiffer structural component). As the ratio of elastin to collagen decreases, the vessel progressively loses its elasticity. The stiffening of the wall causes an increase in the speed of the pulse wave. For example, in the aorta, the

wave speed increases from 6.5 m/s in a 10-year-old child to upwards of 11 m/s in a 60-year-old adult (Nichols & O'Rourke 1990).

A prevailing hypothesis for the mechanism of arterial degeneration with age is based on the fatigue failure of the wall components. Nichols & O'Rourke (1990) suggest that the fatigue of the cycle stresses causes the fracture of the load-bearing elastic sheets. Elastin sheets are very inert and stable with an estimated lifetime of over 40 years (Rucker & Tinker 1977). Under the cyclic fatigue stresses, the polymerized structure of the elastin sheet and fibers reorganizes, causing them to fail at levels of tensional stresses below those they were previously able to withstand. The tearing of the elastin sheets and fibers, and the associated loss of some of the elastic recoil, cause a progressive permanent dilatation of the vessel. The permanent stretching of the smooth muscle is then accompanied by a remodeling process whereby the collagenous content in the muscular layer increases. The end result of the above-mentioned, irreversible process is the creation of an aneurysm. This process can be compounded and amplified by other architectural changes that occur in these elastic arteries with age.

In the portion of large elastic arteries located upstream of a bifurcation, such as the abdominal aorta, and the iliac, femoral, and popliteal arteries, the amplitude of the pressure wave (pulse) is considerably modified as a result of the reflexion of the wave in the bifurcation (Fung 1993, 1997). An increase in this amplitude amplification effect may also initiate and accelerate the formation of the aneurysms in the elder population. The amplitude of the reflected wave in the abdominal aorta increases as the ratio between the cross-sectional area of the bifurcated arteries (iliacs) and the parent vessel decreases. With aging, these arteries also elongate slightly and gradually change their shape. Over time, the iliac arteries become more tortuous and the cross section of their lumen may decrease considerably (Greenwald & Berry 2000). Atherosclerotic deposits of plaque in this portion of the iliacs could further decrease the cross-sectional area of their lumen. The progressive changes in the wave speed of the transmitted wave caused by aging, together with the increase in the ratio of cross-sectional areas, may then result in an increase in peak systolic pressure in the abdominal aorta, causing an increase in the wall stresses. Over time, the increased wall tension compounds and accelerates the initiation and propagation of cracks in the elastic sheets in the median layer described in the preceding paragraph, and results in an irreversible increase in the artery's diameter. The permanent increase in the arterial diameter leads to a further decrease in the area ratio and thus to the unstable progression of the disease.

The described pathological changes that occur with aging can be compounded or accelerated by hypertension, excessive alcohol consumption, cigarette smoking, lack of exercise, and other dietetic or environmental factors. Hypertension can be viewed as an accelerated form of aging, causing similar degenerative arterial dilatation, stiffening and increased wave speed, but at an earlier age (Carlson et al. 1970, Merillon et al. 1982, Nichols & O'Rourke 1990, Ting et al. 1986). The observed increase in the peak systolic pressure in the abdominal aorta in older patients with hypertension results from the above-described process of a faster wave traveling down the artery and merging with a stronger, reflected wave (O'Rourke 1982). Cigarette

Smooth muscle: a type of nonstriated muscle, found within the walls of hollow organs, such as blood vessels, the bladder, the uterus, and the gastrointestinal tract

smoking is believed to produce similar effects to hypertension (Bonita 1986, Juvela 2000).

The above hypothesis based on the interplay between the mechanical stimuli and the pathological changes in the arterial wall caused by aging and other known risk factors has not been fully tested, and certainly represents an area in need of research. Studies involving the analysis of the flow-structure interaction in realistic arterial geometries using specific constitutive material properties of the arterial walls could help shed valuable light in determining the various scenarios of geometrical changes and degradation of the material properties of the wall that could lead to fusiform aneurysms upstream of bifurcations.

2.1.2. The vascular endothelium: flow shear-mediated initiation hypothesis.

Cultured VEC studies show that “disturbed flow conditions” and unsteady turbulent stresses damage the endothelium, and the loss or malfunctioning of their regulatory processes may provide a first step to the degradation of the wall (Davies et al. 1984, 1986, 1995). Several studies have shown that there is a correlation between very low shear stresses and the loss of permeability of the endothelial cell membrane (Chappell et al. 1998, Chiu et al. 2003, Davies et al. 1986, Helmlinger et al. 1991). Furthermore, it has also been found that high temporal and spatial gradients of wall shear stresses can modify the endothelial cell expression and affect their proliferation and migration (Bao et al. 1999, Blackman et al. 2000, Davies et al. 1995, Lei et al. 1995, Nagel et al. 1999, Zhao et al. 2002).

These VEC studies have been the basis of an alternative, or even complementary, mechanism responsible for the origin of these aneurysms. As mentioned above, during the normal course of aging, the abdominal aortic artery gradually undergoes conformal changes in its geometry (increasing its length and diameter, thickening its wall, etc.). Over time, the relative unstricted nature of this artery inside the abdominal cavity may lead to the formation of bends, kinks, and other morphological changes that, in turn, create “disturbed flow” conditions inside the vessel (i.e., unsteady flow separation and weak turbulence). It is then argued that the anomalous response of the VEC to the high shear stresses, very low shear stresses, low, but oscillating shear stresses, and the anomalous temporal and spatial gradients of wall shear stress associated with these disturbed flow conditions could contribute to an unstable progressive degradation of the arterial wall and to the formation of the aneurysm.

This VEC-shear activation hypothesis has triggered numerous computational and experimental flow studies aimed at characterizing the spatial and temporal variation of the wall shear stresses characteristic of various arterial configurations (Egelhoff et al. 1999; Finol & Amon 2001; Finol et al. 2003; Fukushima et al. 1989; Morris et al. 2004; Peattie et al. 2004; Perktold 1986; Salsac 2005; Salsac et al. 2004, 2006; Scherer 1973; Viswanath et al. 1997; Yip & Yu 2003; Yu et al. 1999, and many others). Unfortunately, due to the lack of specific models quantifying the response of the endothelial cells to each of the above-described anomalies in the flow shear stresses, these studies have been inconclusive and unable to fully prove this hypothesis.

2.2. Intracranial Aneurysms

Intracranial aneurysms arise in the main arteries of the cerebral circulation, primarily at specific fixed locations along the Circle of Willis. More than 90% of them are of the saccular type, having berry-like, spherical, sharply circumscribed sacs connected to the vessel by a neck. As opposed to the fusiform aneurysms, which form upstream of bifurcations, saccular aneurysms are found exclusively at the apex of bifurcations, at the origin of small arteries branching from large ones, and on the sidewall of arteries with sharp curvatures (Foutrakis et al. 1999). The Circle of Willis is supplied by the two internal carotid arteries, each carrying about 40% of the blood flow to the brain, and the basilar artery, which supplies about 20% or less of the flow. The Circle of Willis often exhibits many anatomic differences; in fact, approximately 60% of the population does not have a completely closed circle. This despaired anatomy has led some to speculate that each specific vessel anatomy should exhibit a different propensity for aneurysm formation, since each will result in a distinct distribution of hemodynamic stresses (Kayembe et al. 1984). Over 85% of the brain aneurysms form in the anterior part of the circle, which is supplied by the two carotid arteries. Furthermore, in contrast to AAAs, the incidence of intracranial aneurysm rupture is higher among women than men (56% vs 44%) (Lee 1995).

2.2.1. The fatigue/remodeling initiation hypothesis. The walls of intracranial arteries exhibit the same general organization and composition of all arteries. However, their structure and elasticity are different from that of the large muscular elastic arteries described in the previous section. Intracranial arteries have a thin, and in some cases absent, elastica lamina, and at the apex of their bifurcations, the median muscular layer is usually absent (Lee 1995).

The same hypothesis formulated above for fusiform aneurysms can also be extended to intracranial arteries. The increase in the cyclic stresses on the arterial wall resulting from the various known risk factors, i.e., hypertension, cigarette smoking, heavy alcohol drinking, etc., can lead to a fatigue-like remodeling process in the elastin sheets and fibers. This failure of the structural protein assembly manifests itself predominantly at the apex of the bifurcation where the absence of the muscular layer makes this location the most vulnerable to undergoing a permanent dilatation. Any congenital defect or genetic factor associated with the elastin/collagen metabolism would obviously compound and aggravate the initiation process.

2.2.2. The vascular endothelium flow shear-mediated hypothesis. The fact that intracranial aneurysms arise at bifurcation, origins of branching, and regions of sharp curvatures has also been the basis for the often-proposed hypothesis that some of the specific flow characteristics of these geometries, through the regulatory effect on the VEC function, should play a key role in the initiation of the disease. This hypothesis has been the motivation for many computational and experimental flow studies aimed at characterizing the spatial and temporal variation of the wall shear stresses associated with pulsatile flows in bifurcations and sharply bended arteries (Friedman & Ehrlich 1984, Kawaguti & Hamano 1980, Liesch & Moravec 1984, Perktold & Rappitesch

CT scan: an X-ray procedure that combines many X-ray images with the aid of a computer to generate cross-sectional views

1995, Shipkowitz et al. 2000, and many others). Most of these studies were also motivated by the fact that bifurcations and sharp bends are not only the preferred sites for the formation of these aneurysms, but also the primary location for lipid deposition and atherosclerotic plaque formation (Buchanan et al. 1999, Malinauskas et al. 1998). These numerical and experimental studies of flows in bifurcations have shown that the flow impinges on the apex, and unstable, helical flow patterns form in the proximal portion of the branches. The transition to turbulence is accelerated by the pulsatility of the flows, which is a function of the Reynolds, Strouhal, and Womersley numbers (Ferguson & Roach 1972). Pulsatile flows in sharply curved vessels also exhibit similar, unsteady, secondary helical flows that may lead to a weak turbulence state during diastole (Chang & Tarbell 1988, Ling & Atabek 1988, Oshima et al. 2001, Perktold et al. 1987).

Unfortunately, although these flow studies have greatly improved the current understanding of the specific features that these pulsatile flows exhibit in the complex and tortuous geometry in and around the Circle of Willis, all of them have been inconclusive and unable to prove the hypothesis that the secondary, unstable flows forming in these bifurcations and sharp bends are responsible for the initiation of the intracranial aneurysms. This is, once again, the consequence of a lack of reliable models to quantify not only the response of the endothelial cells to the specific anomalies in the flow shear stresses resulting from the unstable secondary flows, but, more importantly, of the absence of models capable of quantifying the response of the wall structure to the endothelial-mediated processes.

3. PROGRESSION AND ENLARGEMENT RATE

After the aneurysm forms and the wall undergoes a small permanent dilatation, one would expect that the natural progression would be that of gradual expansion. However, this is not always observed clinically. Some aneurysms grow steadily at an undetermined rate, whereas others seem to grow rapidly, reach a certain size, and then suddenly slow down their expansion. The realization that knowing the rate at which an aneurysm enlarges is one of the most valuable pieces of information required by physicians for the optimal clinical management of the disease has motivated a great deal of multidisciplinary research in this area, including a large number of flow dynamic studies.

3.0.1. Fusiform aneurysms. It appears reasonable to expect that the very same factors that lead to the formation of the aneurysm should determine the enlargement process. Thus, the flow shear–endothelium-mediated initiation hypothesis has motivated many numerical and experimental fluid mechanics studies aimed at determining the characteristic of the flow shear stresses on the walls of AAAs at different stages of their development. These studies have consisted mainly of experiments and numerical simulations in ideal symmetric and nonsymmetric shapes of fusiform aneurysms and in realistic geometries reconstructed from three-dimensional volume rendering of high-resolution CT scans and angiographies (Asbury et al. 1995; Budwig et al. 1993; Egelhoff et al. 1999; Finol & Amon 2001, 2002, 2003; Fukushima et al. 1989;

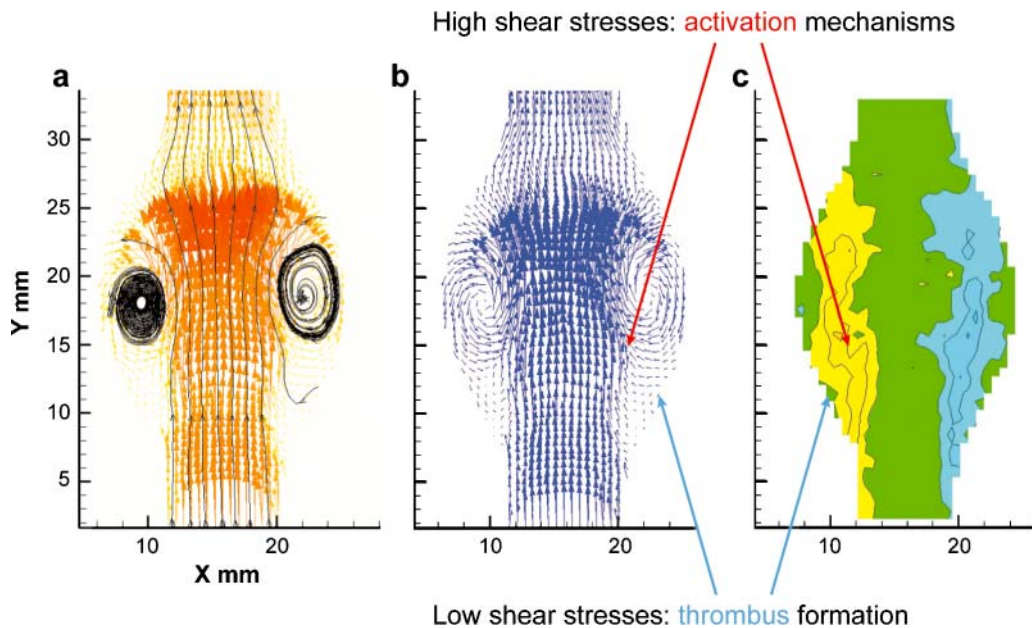


Figure 5

Digital particle image velocimetry (DPIV) measurements of the (a) instantaneous velocity field, (b) instantaneous streamlines, and (c) shear stress field in a symmetric model of a abdominal aortic aneurysm (AAA) fusiform aneurysm. The measurements correspond to the beginning of the deceleration after peak systole.

Peattie et al. 1994; Salsac 2005; Salsac et al. 2006; Schrader et al. 1992; Taylor & Yamaguchi 1994; Viswanath et al. 1997; Yip & Yu 2001; Yu 2000; Yu & Zhao 1999, 2000, among many others).

Although all of these numerical and experimental studies have inherent uncertainties that result from the difficulties of setting up the appropriate initial and boundary conditions, as well as account for the precise elastic properties of the wall, they clearly show that once a fusiform aneurysm forms, the flow is dominated by the onset of an unsteady, massive separation from the walls that occurs immediately after the peak systole. When the flow separates from the walls during the deceleration portion of the cardiac cycle, a relatively coherent array of large vortices forms and the blood flow slowly recirculates (Figure 5). Salsac (2005), Finol et al. (2003), and others have also shown that as the aneurysm grows mostly nonsymmetrically, the location and magnitude of the regions of high gradients of temporal and spatial shear stresses, as well as the extent of the regions of low but oscillatory shear stresses along the wall, vary significantly.

The obvious shortcomings of all these studies is that although they provide a possible cause for the continual expansion of the aneurysm through the response of the endothelial-regulated processes to the “anomalous flow” conditions outlined above, they cannot be used as the basis for a predictive model for the aneurysm’s expansion.

Endoluminal thrombus: a blood clot that stays attached to an artery wall partially occluding its lumen, the cross-sectional area through which blood flows

Hypoxia: a pathological condition in which the body as a whole (generalized hypoxia) or region of the body (tissue hypoxia) is deprived of adequate oxygen supply

Necrosis: unprogrammed death of cells/living tissues

Once again, the reason they are of very limited value is the lack of knowledge of the precise mechanism whereby the flow shear regulates the endothelial function and its action on the SMC activity. More importantly, the hypothesis that the effect of the large gradients of fluid shear and other anomalous conditions resulting from the separated flow on the endothelial activity determines the expansion process is further brought into question by the fact that in more than 90% of all AAAs, an endoluminal thrombus forms early in the expansion process. This thrombus covers the aneurysm's wall and causes the destruction of the endothelial layer by hypoxia. After the endoluminal thrombus forms, the blood is no longer in contact with the vessel walls and flows through an internal lumen with an approximate cross-sectional area equal to the original abdominal aortic artery. During the subsequent expansion, new layers of thrombus form, and the internal lumen remains with an approximately constant cross-sectional area. Thus, once a thrombus forms, the flow shear–endothelium-mediated processes do not play any role in the further expansion of the aneurysms.

Nonetheless, the above-mentioned flow studies have been valuable in providing a qualitative explanation for the formation of the endoluminal thrombus, and the observed rechanneling of the blood flow through an internal lumen (Salsac 2005). The hypothesis is that platelets may become activated in the regions of high shear in the internal shear layers (shown in **Figure 5**), and then be transported to the slowly recirculating regions where they will accumulate on the wall of the aneurysm, initiating the formation of the endoluminal thrombus due to the anomalous response of the endothelium to the low and oscillating shear stresses (Salsac 2005, Wurzinger et al. 1985).

It has also been argued that the formation of the thrombus could play an important role in the further degradation of the wall structure in AAAs by causing the hypoxia of the inner part of the median layer, the necrosis of the vascular SMCs, the previously mentioned destruction of the endothelial cells, and the associated absence of endothelium-derived vasodilators and vasoconstrictors. Furthermore, leukocytes accumulated in the thrombus generate inflammatory enzymes that may further degrade the muscular layer (Wang et al. 2001).

Owing to the above discussion, it appears that the flow shear stresses may not be the determinant factor controlling the expansion of this type of aneurysm. Thus, it is reasonable to argue that the remodeling of the arterial wall caused by the increase in tensional stresses should be the main controlling factor. Once the aneurysm is initiated, the permanent stretching of the median layer is then accompanied by a remodeling process whereby the collagenous content in the muscular layer increases and the wall becomes stiffer (MacSweeney et al. 1992, O'Rourke 1990, Thubrikar et al. 2001). As the arterial wall distends and stiffens, the permanently stretched SMCs are progressively deprived of the cyclic stimulation needed for the synthesis of connective tissue and their healthy proliferation. This leads to a progressive loss of connectivity and the apoptosis of the SMCs, resulting in the gradual thinning and ultimate destruction of the muscular layer (Lopez-Candales et al. 1997, Thompson et al. 1997). To predict the enlargement rate of AAAs, one requires not only information on the magnitude of the progressive changes in the systolic pressure inside the bulge (resulting from the possible presence of the endoluminal thrombus and the changes in

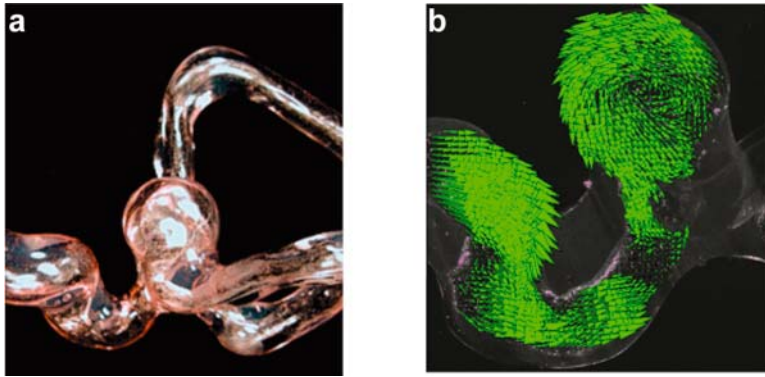


Figure 6

(a) Silicone flexible model of an intracranial aneurysm cast from a cadaver. (b) Instantaneous velocity field in a longitudinal plane. The measurements were obtained by digital particle image velocimetry (DPIV) and correspond to peak systole (Cantón 2004).

the geometry and stiffness of the wall), but more importantly, on the dynamics of the above-described arterial remodeling process, which could also be compounded and accelerated by inflammation, infection, and other causes (Ghorpade & Baxter 1996). Although much progress has been made recently in improving the understanding of the various biochemical processes involved in the degradation of the wall, no precise quantitative models describing this dynamic remodeling have been developed.

3.0.2. Saccular aneurysm. Owing to their preferred location either at the apex of bifurcations or on the side walls of sharply bent arteries, the blood flow inside saccular aneurysms is drastically different from those in the above-described AAAs. The flow entering the sharply circumscribed sac forms a three-dimensional pattern composed of either one or two three-dimensional vortices (Figure 6). This rotational pattern persists even during the diastolic portion of the cardiac cycle (Cantón 2004). As opposed to AAAs, the constant flushing off of the blood inside the sac together with the persistent nonvanishing circulation preclude the formation of a thrombus inside the sac.

The hypothesis that the specific spatial and temporal changes in the flow shear stresses acting on the endothelial cells on the walls of the sac could be the key factor controlling the rate at which the aneurysm enlarges has motivated many numerical and experimental flow studies (Burluson et al. 1995; Cantón 2004; Foutrakis et al. 1997; Perktold et al. 1988, 1989; Steiger et al. 1987a,b, 1988a,b; Steinman et al. 2003, and many others). Unfortunately, as with other types of aneurysms, all these flow studies have been inconclusive and unable to make an impact in the clinical management of these aneurysms due to the lack of specific models quantifying the response of the endothelial cells to each of the specific anomalies in the flow shear stresses. Furthermore, the fact that the median muscular layer is absent in the late stages of development of saccular aneurysms casts more doubt on the hypothesis that an endothelium-mediated mechanism controls the expansion rate.

What appears to be more reasonable is that the prediction of the rate of enlargement of saccular aneurysms should be based on the knowledge of the dynamics of the progressive remodeling of the structure of the wall under the effect of the internal

blood pressure. In other words, the effect of the flow shear stresses does not seem to be the determinant factor controlling the expansion of the aneurysm, but rather the tensional stresses on the wall resulting from the internal pressure.

Incidentally, the peak systolic pressure inside the sac of the aneurysm changes very little throughout its expansion. Additional effects such as the sometime-observed high-frequency vibration of the wall could also play an important role in wall remodeling. Unfortunately, due to the lack of information on the thickness and composition of the wall and the specific changes they undergo during expansion, we are currently far from reaching this goal.

4. PREDICTION OF THE RISK OF RUPTURE

For lack of any other reliable method, aneurysm diameter is the current standard by which vascular surgeons estimate the risk of rupture. For example, surgical treatment is currently recommended for AAAs exceeding 5 cm in maximal diameter and those with expansion rates >0.5 cm/year (Brown et al. 2003). Although size is also the current criteria for treatment, no general consensus appears to exist on the critical size or shape beyond which surgical repair is recommended for intracranial aneurysms. In each case, the risk of rupture must be weighed against operation morbidity. Therefore, a patient-specific assessment of the risk of rupture is the most important information that clinicians need to better manage any aneurysm and to improve guidelines for intervention.

Regardless of what the process (or complex combination of physiological and mechanical processes) may be whereby the arterial wall's composition and strength change, it is clear that the onset of aneurysmal rupture is due to the failure of the wall's structure to support the wall's stresses resulting from the pulsatile internal blood flow. Calculating the risk of rupture simply requires the calculation of the tensile stresses on the aneurysm's wall and knowledge of the corresponding stress failures. This is an area where solid and fluid mechanics could truly contribute to the better management of this disease.

Over the past 10 years there have been numerous studies aimed at modeling the flow-structure interaction in idealized geometries of aneurysms as well as in three-dimensional reconstructions of aneurysms obtained from CT scans or other medical imaging techniques (Di Martino & Vorp 2003; Di Martino et al. 1998, 2001; Fillinger et al. 2003; Li & Kleinstreuer 2005, Raghavan & Vorp 2000, Raghavan et al. 2000, 2005; Vorp & Vande Geest 2005; Wolters et al. 2005). The outcome of these studies represents a great improvement over the population-based statistical criteria currently used in the clinical setting. For example, some computational studies have shown that the wall tension depends on the specific curvatures and asymmetries of the aneurysm's wall. In AAAs, the wall tension is larger on the flatter surface (which would typically correspond to the posterior surface of an AAA due to the presence of the spinal column) and at the inflection points of the bulge (where the surface curvature changes from concave to convex). These results are consistent with the fact that many AAAs rupture in the posterior part of the side wall. However, these

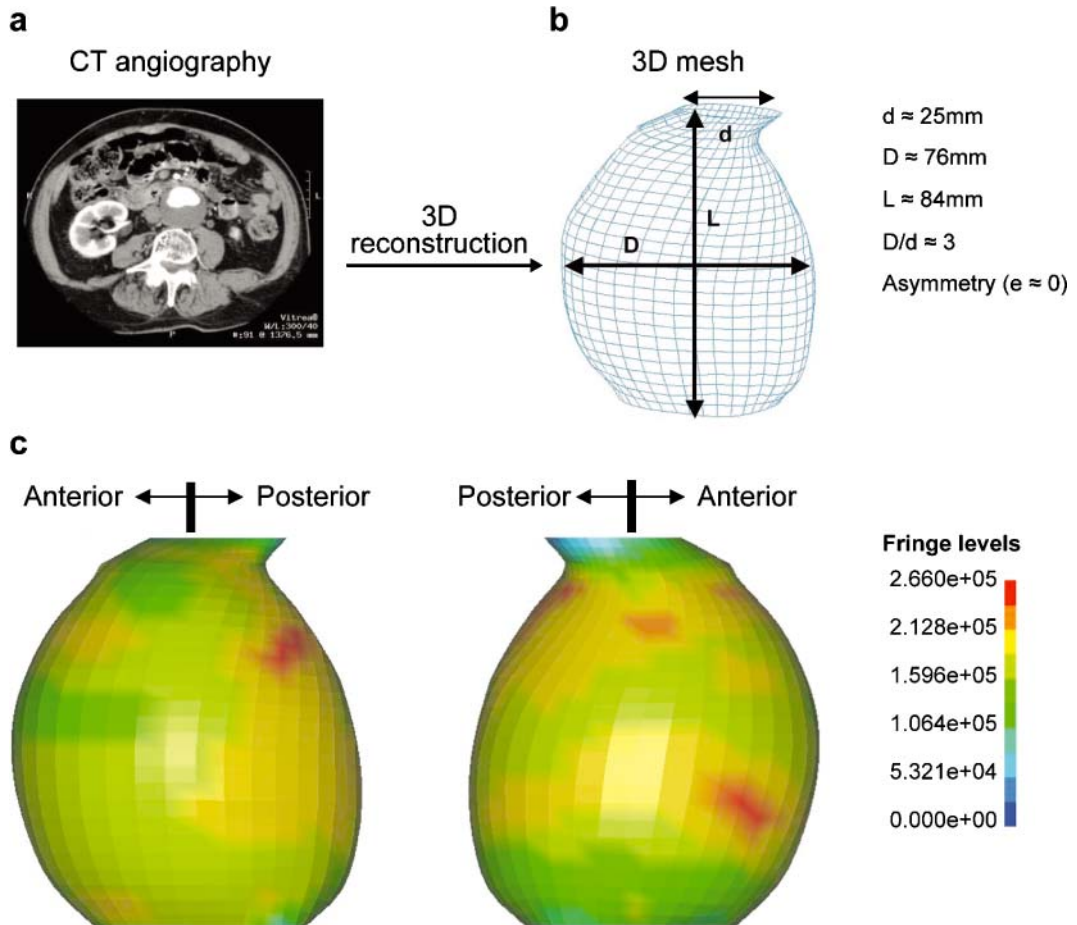


Figure 7

von Mises stresses calculated along the wall of a reconstructed model of an abdominal aortic aneurysm (AAA) of a 75-year-old male patient. (a) Slice of a CT scan showing the cross section of an AAA 6 cm in diameter. (b) Three-dimensional reconstruction of the AAA from the CT scan frames. The distance between CT sections was 0.75 mm. (c) Left and right view of the aneurysm showing that the maximum value of the von Mises stresses on the wall are along the side and in the posterior region of the aneurysm.

flow-structure models are far from being capable of being used as a reliable tool to guide the clinical management of the disease (see **Figure 7**).

To compute the wall tension throughout the entire aneurysm, one requires (a) a precise description of the three-dimensional geometry of the aneurysm's wall, (b) the three-dimensional geometry of the endoluminal thrombus (if present), and, more importantly, (c) the values of the wall thickness throughout the entire aneurysm, (d) the mathematical models that characterize the nonlinear anisotropic biomechanical properties of the tissue at each location along the wall, and (e) the precise description of

Magnetic resonance imaging (MRI): an imaging technique based on the principles of NMR

Nuclear magnetic resonance (NMR): a spectroscopic technique used by scientists to obtain microscopic chemical and physical information about molecules

the external constrain from surrounding tissue and organs in contact with the arterial wall.

The accuracy of the computed wall tension distribution depends on how rigorously these five components are defined in the analysis. Although the setting of the proper initial and boundary conditions, and the relatively complex shape of the elastic walls present some difficulties, the real deficiencies arise from the current inability of the various medical imaging techniques to provide precise information on not only the thickness of the wall, but, more importantly, on the precise composition and structure of the wall at each location, and therefore of its mechanical properties.

Owing to its large size and relatively simple geometry, the three-dimensional shape of AAAs and other fusiform large aneurysms can be reconstructed with relatively good accuracy. However, current medical imaging techniques and image processing tools are unable to provide a precise three-dimensional reconstruction of intracranial aneurysm, accounting for the exact curvature and connectivity to parent and daughter arteries. Current imaging techniques are also unable to resolve the distribution of nonuniform wall thickness throughout the entire aneurysm and this is by far the most important contributing factor to the wall tension. Furthermore, as the wall distends, and the various remodeling processes discussed in the preceding sections take place, its nonlinear anisotropic mechanical properties (stress-strain relationship) gradually change. These biomechanical properties of the wall are not available in a patient-specific form, rendering the calculation even more inaccurate. New advances in magnetic resonance imaging (MRI) techniques appear promising and perhaps in the near future will provide some much needed information.

The current inability to compute the precise distribution of the tensional stresses in the aneurysm's wall has motivated many researchers to look into surrogate methods to determine the risk of rupture (Cebal et al. 2005). The aim of all these studies is to find robust correlations linking either specific features of its geometry or particular features of the flow and rupture that could represent an improved criterion, which is currently based solely on the maximum diameter of the artery.

5. TREATMENT TECHNIQUES

It is telling that even though there is no apparent general consensus regarding the causes of aneurysm formation and the specific factors determining its enlargement, all current treatment techniques are solely designed to simply address the mechanical factors. Currently, fusiform aneurysms are treated by excluding the distended wall from the circulation by surgically placing a graft along the affected area either through open surgery or through endovascular techniques. Intracranial aneurysms are treated by placing a metallic clip across its neck via open surgery (craniotomy), or by packing the aneurismal sac with either platinum coils [Guglielmi Detachable Coils (GDCs)], hydrocoils, onyx, hardening polymers, or even glue, using minimally invasive endovascular techniques. These packing techniques are either designed to fully occlude the sac and to exclude it from the circulation, or to cause a large reduction in the flow velocity inside the sac to promote the formation of a stable thrombus (Cantón et al. 2005a–c).

Fluid mechanics studies have greatly contributed to the development of many of these devices, and are expected to continue guiding the search for new devices. For example, Cantón et al. (2005b,c) recently showed that the sequential placement of certain type of stents across the neck of saccular aneurysms cannot only greatly modify the circulation inside the sac at peak systole, but also drastically reduce it during diastole.

6. CONCLUDING REMARKS AND FUTURE DIRECTIONS

Over the past few years, impressive advancements have been made in the understanding of the relevant biomechanical processes that take place in the vascular system. These studies have contributed to an improved qualitative understanding of the role that many of the known risk factors play in the initiation and progression of this disease. Unfortunately, however, conclusive answers to the key questions (What causes an aneurysm? How fast do they expand? When do they rupture?) have remained elusive.

To date, real progress that could directly impact the way in which this disease is treated clinically has been impeded by three main factors: (*a*) the lack of specific models to quantify the response of the endothelial cells to anomalies in the flow shear stresses; (*b*) the lack of patient-specific models capable of determining the composition and mechanical properties of the arterial wall as it distends and remodels under increasing values of the tensional stresses; and (*c*) the inability of current medical imaging techniques to provide accurate information on the geometry, thickness, and composition of the aneurysm's walls and its parent vessel at each stage during the expansion process.

Numerical and experimental flow studies still need to improve their inherent uncertainties resulting from the difficulties in setting up the appropriate initial and boundary conditions, as well as in accounting for the precise elastic properties of the wall. However, even if these issues are fully resolved, these flow studies will remain of very limited value in answering the above key questions until substantial progress is made in improving the resolution of the medical imaging techniques, and until the "mechanotransduction" mechanism of the endothelial cells is well understood and quantified.

ACKNOWLEDGMENTS

I wish to gratefully acknowledge the contributions of my former and current doctoral students: Dr. Anne-Virginie Salsac, Dr. Gador Canton, Rubing Tang, and Pierre Badel. Many of the ideas expressed in this review resulted from extensive discussions of their research. I am also indebted to Drs. Steve Sparks, Erik Owens, and Niren Angle for many conversations in the area of abdominal aortic aneurysms, and to Dr. David Levy for conversations on clinical aspects of intracranial aneurysms, including endovascular treatment techniques. Dr. Christian Geindreau performed the simulations shown in **Figure 7**, which correspond to one of Dr. Sparks's patients. Drs. Javier Rodriguez-Rodriguez and Tony Maxworthy provided insightful editorial comments.

Stent: either an expandable wire mesh or hollow perforated tube inserted into a hollow structure of the body to keep it open. The main purpose of a stent is to overcome important decreases in vessel or duct diameter.

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