# REVIEWS

# Macromolecular Transport Through Porous Arterial Walls

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Arteries are heterogeneous, composite structures that undergo large cyclic deformations during blood transport. Presence, build-up and consequent rupture of blockages in blood vessels, called atherosclerotic plaques, lead to disruption in the blood flow that can eventually be fatal. Abnormal lipid profile and hypertension are the main risk factors for plaque progression. Treatments span from pharmacological methods, to minimally invasive balloon angioplasty and stent procedures, and finally to surgical alternatives. There is a need to understand arterial disease progression and devise methods to detect, control, treat and manage arterial disease through early intervention. Local delivery through drug eluting stents also provide an attractive option for maintaining vessel integrity and restoring blood flow while releasing controlled amount of drug to reduce and alleviate symptoms. Development of drug eluting stents is hence interesting albeit challenging because it requires an integration of knowledge of mechanical properties with material transport of drug through the arterial wall to produce a desired biochemical effect. Although experimental models are useful in studying such complex multivariate phenomena, numerical models of mass transport in the vessel have proved immensely useful to understand and delineate complex interactions between chemical species, physical parameters and biological variables. The goals of this review are to summarize literature based on studies of mass transport involving low density lipoproteins in the arterial wall. We also discuss numerical models of drug elution from stents in layered and porous arterial walls that provide a unique platform that can be exploited for the design of novel drug eluting stents.

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## 1. Introduction

Mammalian circulatory systems have evolved through millions of years of evolution and are well adapted to handle extreme variations in blood pressure. The circulatory system itself consists of a heart powered by contracting cardiac muscle. A network of arteries distributes blood to various organs of the body whereas veins carry deoxygenated blood back to the heart. Cyclic contractions of the heart push blood into the arterial tree, causing pulsatile blood flow. In humans, the mean pressure varies from a relatively high value of 120 mm Hg in the largest arteries to about 20 mm Hg in capillaries and even lower in the veins.[4] In a day-to-day period, changes in blood pressure can often be sudden. In the absence of a robust cardiovascular architecture to handle these changes, rapid variations could be fatal because efficient transport of oxygenated blood *via* arteries is crucial for the normal functioning of an

Abbreviations and Acronyms

BMS     bare metal stent
DES     drug eluting stent
EC      endothelial cell
ECM     extracellular matrix
LDL     low density lipoprotein cholesterol
SMC     smooth muscle cell
IEL     inner elastic lamina
EEL     external elastic lamina
PTCA    percutaneous transluminal coronary angioplasty
CABG    coronary arterial bypass graft

**Atherosclerotic plaque:**
Accumulation of material that may be comprised of cells, lipids, fibrous proteins and calcium in the normally smooth arterial wall that leads to disruption in blood flow.

**Atherosclerosis:** A progressive and chronic disease of arteries that is caused by thickening of the wall due to accumulation of various materials, collectively called plaque.

**Low density lipoproteins:** Commonly known as "bad cholesterol", these lipoproteins primarily transport lipids in the body for use by cells.

**Drug eluting stents:** These are stents placed in blocked arteries that release drugs to prevent cell proliferation that could, in time, lead to re-narrowing of the arterial lumen.

organism. Frequently, transport of blood may also be disrupted due to the presence and build-up of atherosclerotic plaques in arterial vessels, leading to coronary arterial disease—a leading cause of mortality worldwide.[1,2] According to the World Health Organization, coronary heart disease will be the number one killer in 2030, and cause 14.2% of all deaths worldwide. India will account for 60% of these cases.[5] The past five decades has seen an increase in the rate of coronary disease among urban Indian populations from 4 per cent to 11 per cent. There is hence a clear need to understand the progression of arterial disease and to devise methods to detect, treat and manage the disease through early intervention.

Coronary arterial disease is usually associated with the onset and progression of atherosclerosis in the vessel supplying blood to the heart muscle; which may lead to partial or total occlusion of the lumen due to the deposition of a heterogeneous material, collectively called *plaque*. At times, the plaque may rupture, causing leakage of its lipid contents with subsequent clotting and deprivation of blood to the organs downstream of the blockage. When the vessel is located in the heart, this may lead to a heart attack or a stroke when present in the carotid vessels that supply blood to the brain. Various invasive or minimally invasive surgical treatments, in combination with pharmacological alternatives, are used to treat the disease and alleviate symptoms due to atherosclerosis. Placement of a stent, or a slotted metal tube, in the occluded artery following a balloon angioplasty procedure can restore blood perfusion to the tissues downstream of the blockage. However, damage to the arterial wall, stiffness mismatch between the stent and wall, delayed wall healing and possible hypersensitivity can, in time, lead to re-narrowing (or restenosis) of the vessel lumen. Mechanical methods seem to provide a feasible alternative to treat atherosclerotic plaques, but are again plagued by restenosis problems in the long term. It is hence essential to integrate mechanical methods with an understanding of biological phenomena leading to vessel stenosis.

Recent efforts are aimed at coating the metallic stent with therapeutic drugs to reduce biological phenomena that contribute to the problems of restenosis. Other methods, such as use of biodegradable and coated stents that mechanically degrade and allow the vessel to bear the loads and locally deliver known amounts of drug over a desired time provide exciting options to potentially alleviate problems associated with bare metal stents (BMS). Because animal studies are expensive and time consuming, computational models are an attractive option that may be used to understand the progression of atherosclerotic plaques in the vessel wall, design desired degradation rate of stent material and also locally deliver known concentration of drug to the vessel wall over the required time duration. A discussion of computational methods to study mass transport in arterial walls is a main goal of this review.

We treat the arterial wall as a porous medium and combine the physics of fluid dynamics associated with blood flow in the arterial lumen with mass transport phenomena in the arterial wall. The theoretical description of mass transport in heterogeneous composite arterial walls, undergoing large nonlinear deformations under pulsatile flows, is a complex phenomenon and presents several challenges to researchers aiming to model the physical, chemical and biological processes. Hence, it becomes necessary to simplify and make assumptions to make the problem tractable and get meaningful results. We specifically focus on two parts for the scope of this review. First, we discuss models of transport of low density lipoproteins (LDL), a precursor to atherosclerotic disease, in the arterial walls using porous media formulations. Second, we summarize literature that models mass transport in arterial walls to study the transport of drugs from drug eluting stents (DES). Finally, we discuss current challenges in the newly evolving designs for biodegradable stents that combine decreasing mechanical strength of the stent with a corresponding increase in that of the arterial wall with controlled mass transport to facilitate biological phenomena associated with wound healing and increasing the strength of the arterial wall.

## 2. Structure of the Arterial Wall

Arteries are complex, heterogeneous, and composite structures that are well adapted to withstand the propagation of pressure waves; while minimizing pulsatility of blood flow and curtailing loads on the heart. Much of this versatile adaptation

**Elastin:** Insoluble components of the extracellular matrix of vertebrates that allow for the long range extensibility of the tissue.

**Collagen:** A main component of connective tissues of mammals, collagen complements the role of elastin in the wall and serves to contain the vessel from ballooning at higher stretches.

has evolved as a result of a judicious exploitation of material architecture in combination with use of a vast repertoire of material properties. The arterial wall itself consists of mechanically passive extra-cellular matrix (ECM) proteins, elastin and collagen, that allow the vessel to undergo cyclic and large nonlinear deformations while also actively serving as signaling molecules involved in the attachment of cells to the ECM through integrin proteins.[6] Smooth muscle cells (SMC) present in the wall provide for active contraction of its luminal diameter, secrete ECM components and enzyme inhibitors. Together, the active and passive components of arterial walls are arranged in a definite lamellar architecture comprising of a *tunica intima*, *tunica media* and *tunica adventitia* (Figure 1). The layout and material constituents of the wall ultimately determine its nonlinear and anisotropic mechanical properties while also controlling mass flux into the wall.

*Tunica intima* is the innermost layer of the arterial wall and mainly consists of endothelial cells (EC) aligned axially with the blood flow. The EC layer (Figure 2) converts mechanical stimuli, for example shear stress, into biochemical responses that are crucial determinants for mammalian vessel development, regulation of arterial tone and adaptive mechanisms that may ultimately lead to vessel morbidity.[7] Due to its location, EC are constantly subjected to shear stresses due to blood flows and circumferential, axial and radial stretching due to wall deformations. In addition to detecting mechanical signals, EC mediate vessel pathology, respond to wound healing and are involved in atherogenesis and angiogenesis or formation of new blood vessels, using cues from the blood flow. They also possess anticoagulant properties to prevent blood clots from forming at the blood-wall interface that can prevent blood from traveling downstream. EC also controls wall vasodilation to allow expansion and contraction through release of chemical factors to control lumen diameter changes. Finally, the EC layer also modulates vessel permeability that allows transport of various materials into and out of the arterial wall. The mechanotransduction processes of

Figure 1: Schematic showing the intima, media and adventitial layers forming the arterial wall.
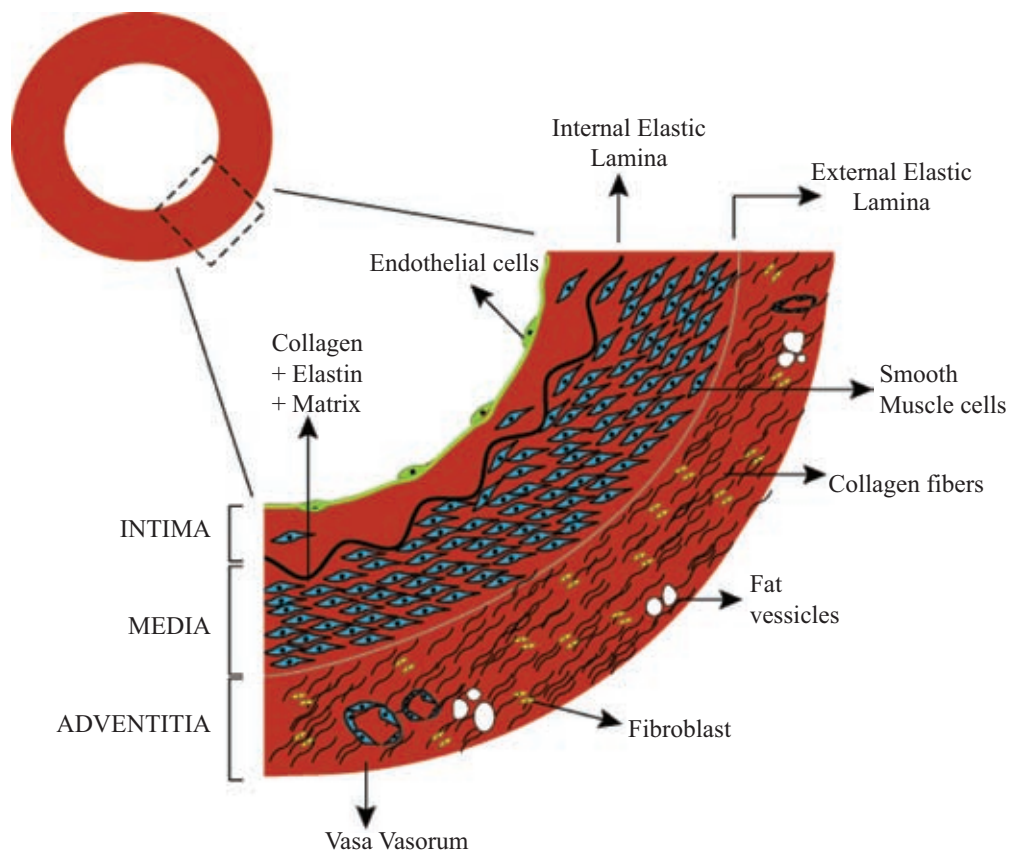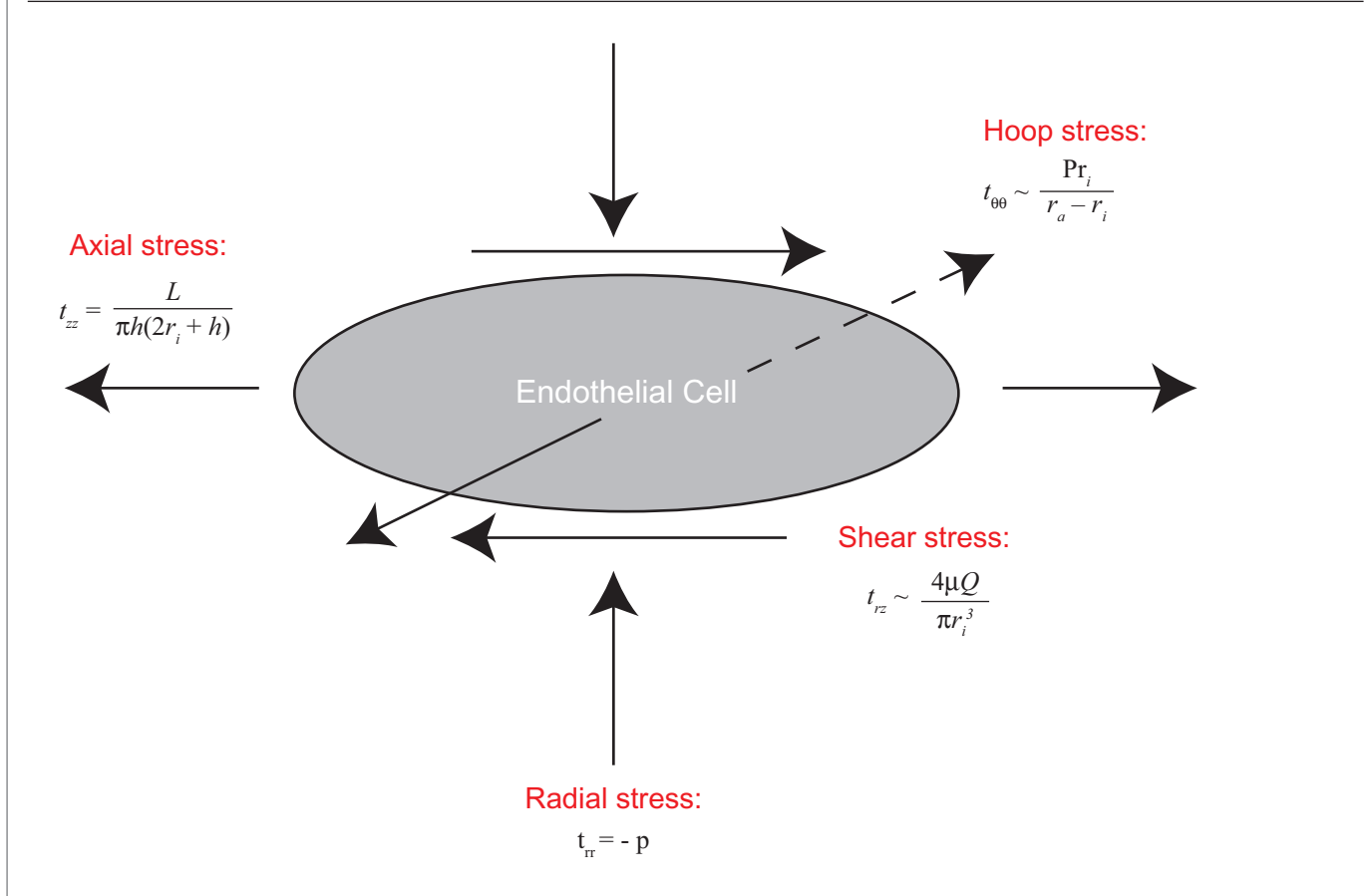
Figure 2: Cauchy stresses ($t_{ij}$; i,j = r,θ,z in cylindrical polar coordinates) seen by an endothelial cell in the arterial wall.

**Hoop stress:**

$$t_{\theta\theta} \sim \frac{Pr_i}{r_a - r_i}$$

**Axial stress:**

$$t_{zz} = \frac{L}{\pi h(2r_i + h)}$$

Endothelial Cell

**Shear stress:**

$$t_{rz} \sim \frac{4\mu Q}{\pi r_i^3}$$

**Radial stress:**

$$t_{rr} = -p$$

endothelial cells and its role in disease is hence the focus of research in many leading laboratories.

Some vessels like the aorta (the large artery that comes out of the heart) may, in addition, contain a subendothelial layer comprised of a thin layer of axially arranged smooth muscle cells and connective tissue. An internal elastic lamina (IEL), comprising a fenestrated network of elastic fibers, separates the intimal layer from the *tunica media*. In the medial layer, SMC, elastin and collagen protein networks are embedded in a ground matrix substance. Elastic fibers form concentric fenestrated lamellae around the wall and alternate with SMC layers whereas collagen fibers are oriented helically in the arterial wall.[6] Together, these constituents form the most important structural layer of the arterial wall. An external elastic lamina (EEL) forms the border between the *tunica media* and *tunica adventitia*. The latter, constituting about 10% of the aortic wall, is the outermost covering of the artery and mainly consists of randomly oriented collagen fibers, some elastin, nerves, fibroblast cells and vasa vasorum. Although the orientation and distribution of individual constituents depends

on location along the arterial tree and may change between species, the arterial structure is found to be generally conserved in all species; from mouse to man.[6] In general, the ratio of elastin to collagen in tissues decreases distally from the heart whereas the amounts of SMC increase and contributes to the muscular nature of the vessel wall that eventually determines wall mechanical properties. These changes in structure also correlate with changes in the Reynolds number in the arterial lumen that varies from about 2000 in the aorta, located just downstream to the heart and characterized by turbulent flows, to about 40 in coronary vessels and even lower (~ ≤ 1) in the smaller arterioles and capillaries where exchange of nutrients and oxygen takes place between the cells and the blood vessel.[4]

## 3. Athereosclerosis and Coronary Arterial Disease

Atherosclerosis is an arterial disease that occurs due to build-up of lipids, cholesterol and other substances in the arterial wall, collectively called *plaque*, leading to narrowing or stenosis of the vessel lumen and, in time, disruption to the blood

**Smooth muscle cells (SMC):** In the arterial walls are specialized contractile cells that can actively allow expansion and contraction of the arterial lumen to maintain the tone of the vessel.

**Vasa vasorum:** Small blood vessels to nourish cells in the thick arterial wall.

supply (Figure 3). Although a number of risk factors contribute to the process of atherosclerosis, it is currently well accepted that atherosclerosis is an inflammatory disease.[8] A principal risk factor for atherosclerosis is high plasma concentration of low density lipoprotein cholesterol (LDL) that penetrates into the intimal layer and undergoes oxidation. The presence of oxidized-LDL starts a cascade response of the immune system through the release of chemo-attractants that mediate the adhesion of monocytes in flowing blood to the EC surface in the arterial wall. Once adhered, monocytes penetrate the intimal layer and are converted into macrophages that phagocytose oxidized-LDL into foam-like cells that cluster and accumulate into fatty streak in the arterial wall. In this process, the macrophages also produce numerous pro-inflammatory chemical markers, such as cytokines (TNF-α, IL1), that increase and lead to auto-amplification of the inflammatory processes in the injured area. This in turn leads to migration and proliferation of SMC that lead to the formation of fibrous connective tissue over the lipid core. In due time, the vasculature geometry changes with accompanied by microstructural alterations, including formation of calcification, that will further alter the blood flows at the injured site. Calcified plaques also express molecules such as osteopontin and bone morphogenetic protein 2a (BMP-2a) that suggest that the mechanisms of bone mineralization may also play an important

**Cytokines:** A small and diverse group of protein molecules secreted in the body that are primarily involved in communication between cells.

Figure 3: Image of a severely stenotic ruptured plaque taken from a surgical procedure to remove the atherosclerotic plaque, a large dark mass on the left, from the carotid artery that supplies blood to the brain and neck.[57] The plaque is at the forked region in the bifurcation of the common carotid into the internal and external carotid arteries.



role in vessel calcification.[9] Plaque rupture, when present in coronary vessels supplying blood to the heart, may lead to myocardial infarction or to a stroke when the carotid blood flow to the brain gets disrupted. Coronary arterial disease is the leading cause of mortality worldwide[1,2] with an estimated 1.2 million myocardial infarctions occurring each year occurring in the United States alone.[10] Coronary disease is projected to be a leading cause of mortality and morbidity in the developing world by the year 2020 that necessitate urgent prevention, control measures and seek treatments to the disease.[11] Abnormal lipid profiles, associated with diet and sedentary lifestyles, diabetes mellitus, smoking and a history of hypertension are major risk factors for coronary arterial disease.[2]
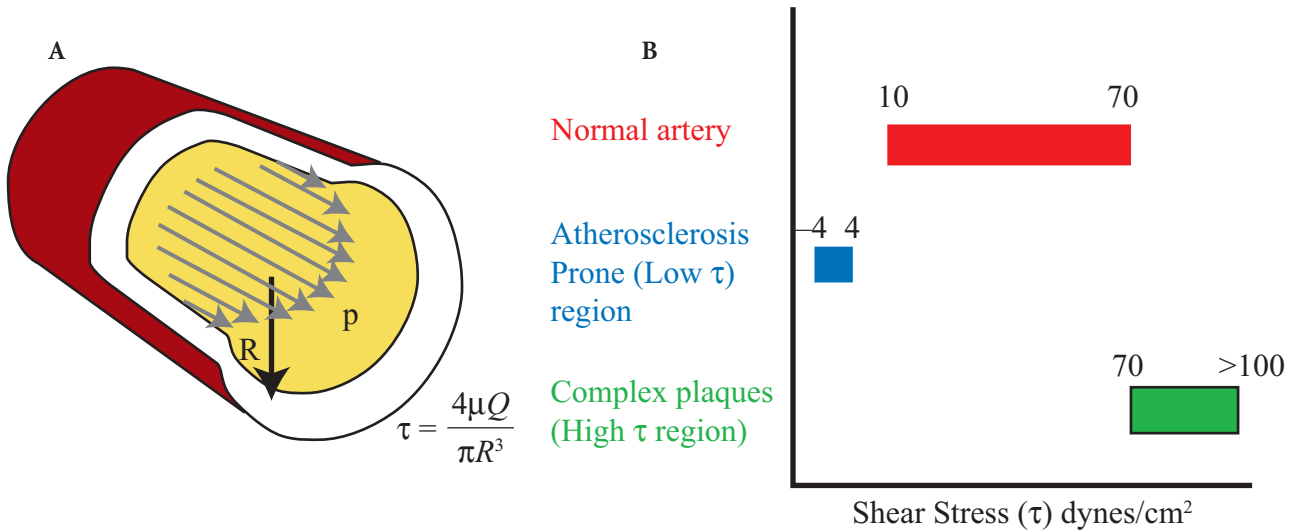
## 4. Flows in the Vicinity of Plaques

Blood flow, due to shear stress, plays a critical role in the developmental, homeostatic and adaptive mechanisms that occur in arterial vessels.[12] Shear stress is also a key factor that ultimately determines the location of atherosclerotic plaques and its rupture from the arterial wall. There were two main hypotheses proposed in 1970's[13] to link local non-uniform hemodynamics to biological factors contributing to occurrence of atherosclerotic plaques in arterial walls. Low average shear stress, constantly changing shear stress gradients, flow reversals and secondary flow regions are generally associated with the presence of atherosclerotic plaques (Figure 4). The low shear stress hypothesis argues that this a main reason for the early occurrence of atheroma in arterial vessels. In contrast, high shear stress regions are atheroprotective,[14] provided the shear stresses are not large enough to detach the endothelial cells from its matrix (>400 dynes/cm²). Progress in the past three decades now verify the low shear stress hypothesis that serves as a basis for the causal linkage between association of low shear stress regions with inflammatory mechanisms and the proliferative mechanisms involved in atherogenesis. Studies also show that regions of high wall permeabilities correlate with regions of elevated wall shear stress gradients in a bifurcating arterial wall.[15] Flow separations and disturbances occurring in the vicinity of branched vessels are also known to contribute to the pathogenesis (Figure 5). From a mechanical perspective, shear stresses mainly determine the propensity of atherosclerotic plaque fracture in the vessel wall. Using a computational fluid dynamics scheme, Stroud and coworkers showed that the degree of stenosis, or luminal blockage,

Figure 4: **A.** Cross-section of the arterial wall showing velocity vectors in the direction of the flowing blood. **B.** Shear stresses, calculated using Poiseuille's equation, shown for various cases in normal and diseased arteries.



$$\tau = \frac{4\mu Q}{\pi R^3}$$

alone is not sufficient to assess the risk of rupture of plaque in the vessel wall.[16] These studies were however performed in ideal vessels consisting of smooth, axisymmetric straight walls with regular and normal pulsatile waveforms for ease of computation. Other important characteristics that are yet to be considered include the stenosis curvature and surface irregularity and the shape of the pulsatile waveform in modeling the presence of realistic plaques in the vessel lumen. The reason for the fracture of a vulnerable plaque is hence not linked to the degree of stenosis alone but is crucially determined by the plaque constituents and microstructure. There are two kinds of plaque: the vulnerable plaque which has a lipid rich core with a thin fibrous cap and a stable plaque which has a less dense lipid core with a thick fibrous cap. Fracture of the plaque, with infiltration of the vessel lumen with foam cells, followed by clot formation over the lipid spillage lead to myocardial infarction or stroke.[17]

## 5. Treatments for Cardiovascular Arterial Disease

Treatments span from pharmacological palliative approaches, generally using statins, to minimally invasive treatments such as percutaneous transluminal coronary angioplasty (PTCA), to a surgical approach of coronary arterial bypass graft (CABG) through a closed heart procedure. CABG surgery reroutes blood via autografts, taken from mammary arteries or saphenous veins

of the patient, attached from the aorta directly to the affected coronary artery distal to the obstruction to improve blood flow and oxygen. Acute thrombogenicity of the graft, intimal hyperplasia, associated with proliferation and migration of vascular SMC from the media to the site of injury, and a corresponding remodeling of the arterial wall lead to formation of aneurysms which are localized enlargements of the vessel, and ultimately cause failure of small caliber grafts in the long term.[18] Besides, the atherosclerotic process can also involve the graft vessels thereby causing their failure. Although bypass surgery was a gold standard for the treatment of coronary arterial disease, minimally invasive treatment is the preferred method for most patients when pharmacological methods to control the coronary heart disease fail.

Minimally invasive methods to treat atherosclerosis involve use of PTCA, a method introduced in the 1970's, in which the blocked arteries are dilated using a catheter fitted with a balloon at its tip. PTCA has however been plagued with a high occurrence of restenosis caused by the process of scarring initiated by damage to vascular cells (EC) lining the blood vessel wall. There is a consequent need for redoing the procedure in about 30% of the patients, especially those with other co-morbidities such as diabetes mellitus, small coronary vessels and long lesions.[19] To avoid these problems, a slotted expanded mesh, called stent, is commonly inserted into the artery during

Figure 5: **A.** Instantaneous streamlines and velocity vectors for axisymmetric radial reduction. **B.** Vessel with asymmetric cratered plaque affecting one side only. Adapted from.[44]
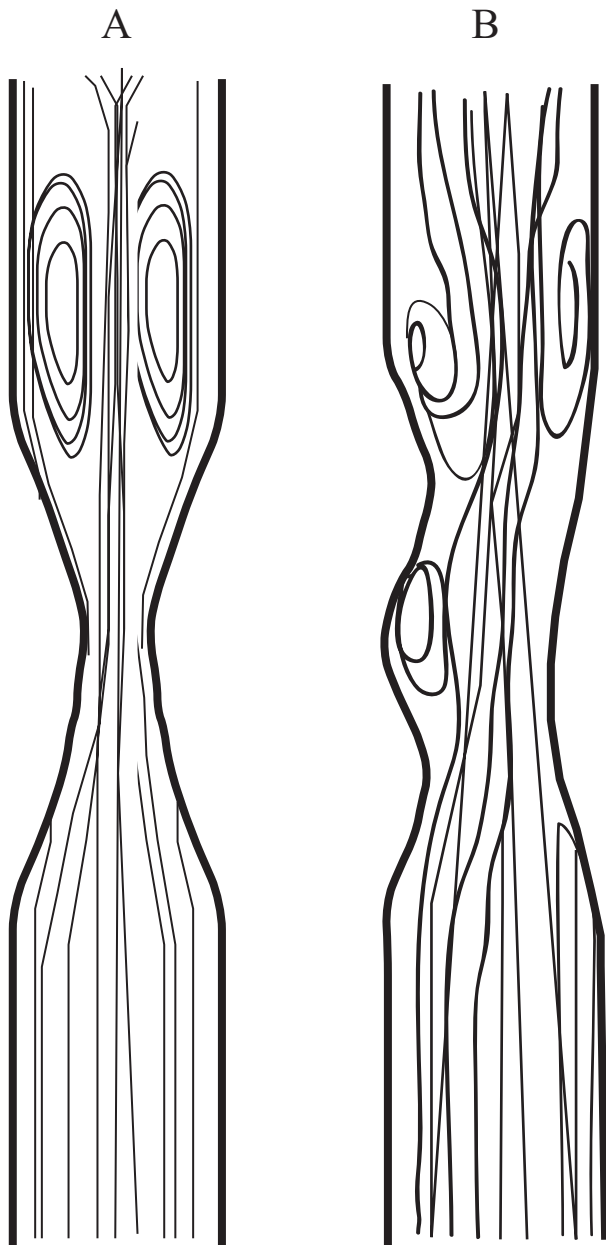
coronary angioplasty to help keep the lumen open (Figure 6). Stenting is now widely seen as a measure to reduce the incidence of restenosis and eliminate antiplatelet therapy after angioplasty. Bare metal stents (BMS), first introduced in 1977 and seen as a major breakthrough in clinical practice for treating blocked arterial vessels, had by 1986 become a standard procedure that followed angioplasty. The stenting method showed a marked improvement in arterial diameters by about 41% and routinely decreased clinical features of angina associated with stenosed vessels.[20,21] Stent placement is however associated with stretching of the artery, de-endothelialization and compression of the arterial plaque that induce substantial local inflammatory response in the arterial wall. This is next followed by proliferation of the vascular constituents such as SMC and extracellular matrix that lead to the formation of a neo-intima and restenosis of the vessel.[3] During the early stages after device deployment, inflammatory cells (neutrophils, monocytes, activated leucocytes and platelets) play an important role in the wound healing process. A layer of fibrin is laid out at the injury site that is soon populated by other inflammatory cells. Quiescent SMC in arterial walls have remarkable ability for change in their phenotype from one of contractility to that of accelerated proliferation under specific stimuli.[22] Further, they migrate from the media to the region of the injury across the IEL to form another intima, or the *neo-intima*. Several molecules are now known to contribute to SMC migration, including growth factors such as transforming growth factor, TGF-β, and platelet derived growth factors. Several questions still have incomplete answers that are necessary to understand the process of vessel remodeling in response to injury like in balloon angioplasty and stents. First, what are the molecular mechanisms underlying proliferation and migration of cells in forming the neointima? Second, do the intimal SMC belong to different lineages? This question is important from the context of migration potential of specific cells to the diseased area. Investigations along these directions are necessary in the design of drugs that may be used to prevent the phenomenon of restenosis. The risk of restenosis is currently 15–20% in all stented vessels following balloon angioplasty. Attempts to reduce the risk of restenosis through use of systemic drugs were met with frustration until the introduction of local delivery of drugs at the site of injury, hence serving a dual purpose of maintaining vessel integrity while delivering drugs to the wall injury site to prevent migration of SMC that is hoped to bring down the risk of restenosis below 10% after implantation.

## 6. Coated and Drug Eluting Stents
Coatings used over BMS are one of many variants used to decrease thrombogenicity of the stent and accelerate healing while reducing SMC migrations. In one case, a coating of phosphorylcholine

Figure 6: PTCA procedure showing stent mounted on catheter deployed in stenosed arterial vessel.
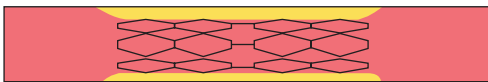
A: PTCA procedure in stenosed artery
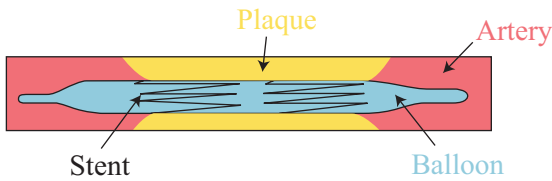
B: Expanded stent during balloon inflation
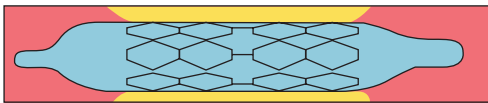
C: Expanded stent in stenosed artery

(Biodiv Ysio™ AS, Abbott Labs, CA) or amorphous silicon carbide (Rithron-XR®, Biotronik GmbH, Germany) is deposited on the BMS such as a standard 316 L stainless stent.[2] In a second variant, drug eluting stents (DES) are used to limit in-stent stenosis by coating the BMS with a polymer loaded with a drug. DES combine the advantages offered by mechanical support of the arterial wall with localized delivery of drug to the tissue to essentially minimize the healing mechanisms that cause restenosis of the wall. The main idea is to load a polymeric scaffold with a drug that elutes from the substrate at a designated rate. Several factors need to be considered in the effective design of DES. These include time of contact of the drug in the wall lumen and its transport in the arterial wall, complex interactions between the stent material with the blood and finally the healing process of the vessel wall that together influence rates of neo-intimal formation. Local drug delivery via the stent shows immense potential in decreasing the restenosis rates and reducing the revascularization of the vessel but has some several concerns regarding the late stent restenosis, hypersensitivity responses and endothelial dysfunction.[23,24] However, there is much we do not currently know about effectively designing DES. First, how do these devices function in acute thrombosis? Second, are there any advantages to using these devices in patients with diabetes mellitus? Third, how can we control the rates of drug delivery

with the vessel healing for effective treatment and long term patency of the device? The process of developing DES is hence an interesting problem that allows integration of mechanical properties of the stent, with interactions of the drug with locally interrupted fluid properties, to transport of drug in the arterial wall to produce the biochemical effect. The desired effect involves balance of injury related mechanisms with fine control of cell migration pathways that ultimately change the cellular composition, the ECM and ultimately the stress state of the vessel.

## 7. Drugs used in DES

DES technology enables anti-inflammatory, immunomodulatory, and/or antiproliferative agents to be released in appropriate amounts and distributed at the site of arterial injury during the initial 30-day healing period.[25] Drugs released from the stent are designed to exert distinct biological effects such as activation of signal transduction pathways and inhibition of cell proliferation. Although DES are mainly aimed at reducing the proliferation and migration of vascular SMC after stent placement, they also impair reendothelialization and induce tissue factor expression.[26] Thrombosis is an important phenomenon and requires further investigation because this is a main cause for failure and mortality associated with DES implants (Figure 7). Although use of DES in minimally invasive procedures has revolutionized the treatment of coronary arterial disease, the ranges of drugs that can be delivered to the injury site remain relatively small in number. Because restoring blood flow to the diseased region is a prime requirement of the stenting procedure, a downside is that a portion of the drug will be washed off downstream. Heparin coating of stents increases compatibility of the stent with blood and was hypothesized to reduce the occurrence of in stent stenosis. Other researchers have used immuno-suppressive agents (such as sirolimus, tacrolimus, and everolimus) anti inflammatory (e.g. dexamethasone), anti-migratory and anti-proliferative drugs (such as paclitaxel, actinomyconD) loaded in a polymer coating deposited on the BMS surface[27]; Table 1). Drugs like paclitaxel inhibit arterial smooth muscle cell proliferation and migration but also seem to impair the re endothelialization of the arterial lumen.[28] The drug placed in the stent is generally a potent anti-mitotic agent that prevents SMC proliferation and matrix growth by stabilizing the activity of microtubules in the cell cytoskeleton; thus preventing the formation of a neointimal thickening and restenosis. Several DES

Figure 7: Image of neo-intimal hyperplasia in a non-coated (a) and drug (cerivastatin) eluting stent (b) shown at a magnification of 50 x. The tissue strut coverage is similar in both cases as shown in (c) and (d) respectively. Representative immunohistochemically stained sections for von Willebrand factor (dark colour), a marker of endothelial cells, are also depicted in (e) within a non-coated stent and (f) within the drug eluting stent (magnification 200 x).With permission from the journal.[60]



control    cerivastatin
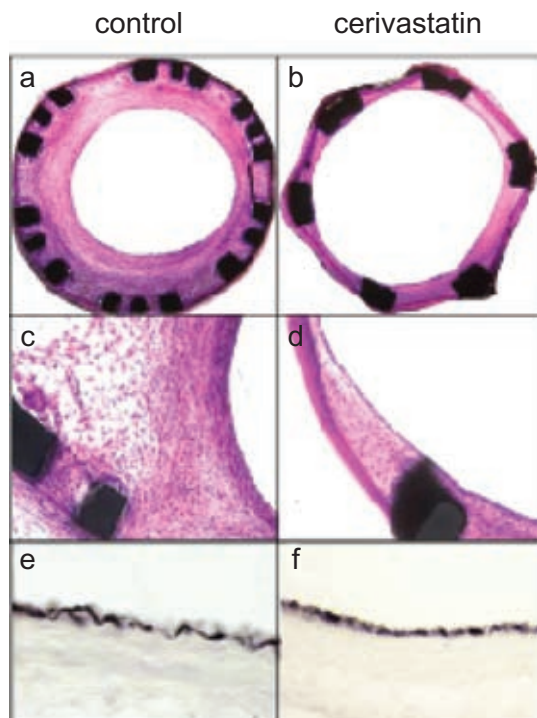
have been tested for their clinical efficacy but most are ineffective in preventing restenosis in the long term. DES may also prevent endothelial function in the segment downstream of the stent placement that may in part contribute to the device.[29,30] This may lead to the idea that DES will not contribute to an overall improvement in the long term prognosis of the device. In addition, although the use of DES has greatly increased over the last several years, the long term risk assessments of these stents need to be evaluated. Large scale studies, such as the SCAAR study, showed that DES were associated with an 18% increase in the relative long-term risk of death, as compared to BMS, about 6 months post implant in Swedish patients.[31] Recent studies evaluating databases of published results comparing DES with BMS and show that rates of mortality, myocardial infarction and stent thrombosis showed similar results at 6–12 months for DES and BMS except for a higher rate of stent thrombosis with BMS in small diameter vessels and with DES in bifurcation legions.[32] Other publications of patients receiving DES have suggested that sites for thrombosis, which continue to be a major cause of death and morbidity after PTCA, extend far beyond those for BMS.[23] Multi-center and multi trial studies are now set to look into the statistics of the patency and risk factors of these devices.

The primary goal however remains: to design stents that offer the advantage of the DES to prevent initial biological phenomena that

Table 1: Manufacturers of drug eluting stents, drugs, and the coatings used.[27,61]

| Manufacturer | Stent Type | Drug type & Description | Stent material/Polymer Scaffold | Drug Duration |
|---|---|---|---|---|
| Cordis Corp., Johnson & Johnson (Miami, FL) | Cypher™ | Sirolimus | 316 L Stainless steel/Poly (ethylene-co-vinyl acetate) (PEVA) and poly (n-butyl methacrylate) (PBMA) | 80% in first 30 days; rest by 90 days |
| Boston Scientific (Natick, MA) | Taxus™ | Paclitaxel | 316 L Stainless steel/ Translute ™ Poly (styrene-b-isobutylene-b-styrene) triblock copolymer) | Burst pressure first 48 hours, slow release next 10 days and rest by 30 days |
| Conor Medsystems Inc. | Conor Medstent™ | Paclitaxel | Cobalt chrome alloy/Poly (lactide-co-glycolide) (PLGA) | Layering to aid drug release |
| Guidant Corp. | XienceV | Everolimus | Cobalt chrome alloy, PBMA and PVDF-HFP with fluoropolymer coating | Low doses of drug remained undetected after 4 months |
| Sorin Biomedica Cadio SpA | Janus Carbostent | Tacrolimus | Carbofilm coating on barestainless steel with no polymer coating | Peak drug within few days after implant; steady concentration following month |
| Endeavor RESOLUTE™ | Medtronic | Zotarolimus | Cobalt alloy, Biolinx™ coating with phosphoryl-choline | 85% in first 60 days |
| Infinimum matrix™ | Sahajan and Medical Technologies Pvt Ltd, Surat, India) | Paclitaxel | 316 L Stainless Steel/PGLA copolymer with polyvinyl pyrrolidole coating | Each layer has different elution rate |

contribute to tissue remodeling but later revert to those offered by the BMS in terms of providing mechanical support alone. Many questions remain unanswered as regards why DES seems to work in the few months after implantation or could generate potentially increased risk, due to restenosis, of morbidity and mortality for the patient in the long term. Restenosis involves a healing reaction of the vessel wall in response to the wound caused by the balloon and stent deployment procedures and is characterized by the inflammation, granulation, migration and proliferation of smooth muscle cells in the vessel wall and the associated extracellular matrix remodeling.[3] There is much we still do not understand about the mechanisms of local drug delivery and restenosis that are required before we can answer why these devices function or potentially generate an increased morbidity risk in the short, medium or long term for patients. A key goal is to also optimize drug characteristics with several factors including the polymer type used in fabricating the stents, material properties of the complex and heterogeneous plaque and finally the hemodynamic conditions in the stented blood vessel that may increase the effectiveness of the drug-stent system. It is intuitively known that complexity of the plaque legions determine transport and distribution of drugs in the arterial wall; but there is also a current dearth of literature in the understanding of how DES stents function in acute thrombosis, chronic metabolic derangements and in vessels other than the coronaries.[33] There is also a dearth of information on incorporating the transport through the multilayered and porous arterial substructures. Although experimental models are key in quantifying some of the many variables that contribute to these complex phenomena, mathematical and numerical models of mass transport in the vessel wall have proved useful to delineate the effects of various parameters on the transport of species in the arterial wall. Computational tools are thus a powerful means to that may be used to assess the impact of the stent on the fluid transport, mass transport into the diseased arterial wall and the compressive effects of the stent struts on the arterial wall. Such methods also provide a manufacturer a handle on various factors that may be important in the design of DES. The models including these terms will be covered in the remaining sections of the article.

## 8. Numerical Models of Mass Transport in Arterial Walls

Biological tissues are generally porous structures and consist of solid material with interconnected voids that allow the flow of fluids in the material. A representative volume, consisting of nonuniform voids, is considered and all parameters are averaged over this volume element (Figure 8). The fraction of void space to total volume is called the porosity ($\varepsilon$). Unlike engineered materials, most biological materials have porosities (Table 2) that are less than 0.6.[34] Tortuosity is the path taken by a species through a porous medium relative to a direct route ($T = \frac{L_e}{L}$). The macromolecular flux into the wall is driven by both hydraulic pressure and osmotic pressures respectively. Analogous to the Navier Stokes equations in fluid dynamics, we write the governing equations for the fluid transport into the porous arterial walls, called the Darcy-Brinkman-Forchheimer equation, and the continuity equations as

$$\rho\left[\frac{1}{\phi}\frac{\partial \mathbf{v}}{\partial t} + \frac{1}{\phi^2}(\mathbf{v}\cdot\nabla\mathbf{v})\right]$$
$$= \nabla p + \mu_e \nabla^2 \mathbf{v} - \frac{\mu}{K}\mathbf{v} - \frac{c_F \rho}{K^{1/2}}v\mathbf{v}$$
$$\nabla \cdot \mathbf{v} = 0 \qquad (1)$$

In these equations, $\mathbf{v}$ is the Darcy velocity that is obtained by averaging over the medium and is related to the intrinsic velocity V (velocity averaged over the pore space) by $\mathbf{v} = \varepsilon V$, where $\varepsilon$ is the porosity. The Darcy equation neglects boundary conditions and convective terms and is hence a simplistic model that has been used in studies related to flows in soft connective tissues and tumors.[35] Terms on the left are inertial terms that are obtained based on the assumption that the spatial averaging commutes with the derivative with respect to time. The advective inertial term involving $(\mathbf{v} \cdot \nabla)\mathbf{v}$ is of a small value in most practical situations because its value is of a small magnitude in comparison with the quadratic drag term. Terms on the right represent the Darcy terms, a Laplacian viscous term introduced by Brinkman and the last is a form drag term called the Forchheimer term.

In equation 1a, the pressure gradient term is balanced by the Darcy viscous linear drag that is generally valid only for laminar or low velocity flows for each layer in the wall with $\mu$ being the fluid viscosity. The Brinkman viscous shear stress term is analogous to the momentum diffusion term in the Navier-Stokes equation and has a significant effect only in thin layers which are within a dimensional distance of the order of $K^{1/2}$ from the solid wall. $\mu_e$ is the effective dynamic viscosity of the medium. The Brinkman model considers the Darcy resistance and accounts for the boundary conditions but fails to consider the convective

**Darcy-Brinkman-Forchheimer:** A generalized model, used to describe the flow transport in porous media, and analogous to the Navier-Stokes equation in fluid dynamics.

**Darcy equation:** The Darcy model, showing a linear proportionality between the flow velocity and the pressure gradient vector, is a simple model that ignores the boundary effects on the flow.

**Brinkmann:** The Brinkmann model, accounting for boundaries of the porous medium that are not considered in the Darcy model, has been employed in several biomedical works.

**Forchheimer term:** In addition to the Darcy resistance, an additional term for the form drag and convection needs to be included to account for the large flow velocity through porous media.

**Navier Stokes equations:** These are nonlinear partial differential equations that describe the spatio-temporal relationship between the velocity, pressure, density and viscosity of a moving fluid. The Navier-Stokes formulation combines the laws of conservation of mass, momentum and energy to explain how fluid motion and internal forces within the fluid are influenced by the inherent inertia and viscosity of the moving fluid.

Figure 8: Flow of solute in porous medium formed by solid matrix with interconnected void space that may be filled with fluid shown in a small averaging volume. The porosity ($\varepsilon$) and tortuosity ($\tau$) are also defined.
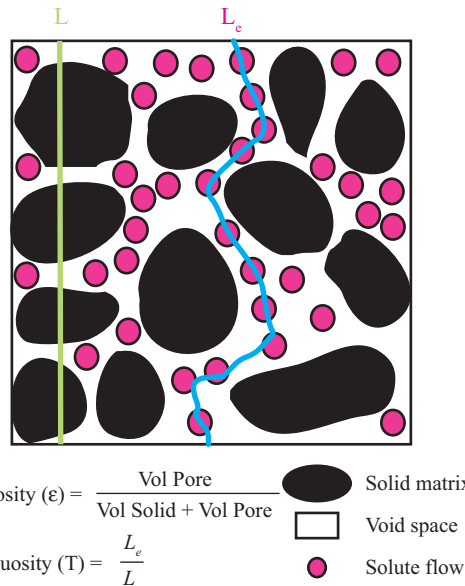


$$\text{Porosity } (\varepsilon) = \frac{\text{Vol Pore}}{\text{Vol Solid} + \text{Vol Pore}}$$

$$\text{Tortuosity } (T) = \frac{L_e}{L}$$

Solid matrix

Void space

Solute flow

**Advection:** Refers to the transport of material within porous media due to fluid motion from one region to another in a specific direction that is not due to simple diffusion.

Table 2: Porosity for various materials.[37,59]

| Material | Porosity |
| --- | --- |
| Soil | 0.43–0.54 |
| Sand | 0.37–0.5 |
| Brick | 0.12–0.34 |
| Limestone | 0.04–0.10 |
| Biological Tissues | 0.0005–0.15 |

terms. This has however been used in modeling biological processes such as vessels blocked by cholesterol and blood clots. The last term is the Forchheimer nonlinear form drag that arises in porous layers with increasing Reynolds numbers. This accounts for the boundary conditions, form drag and the convective terms and must be used for applications encountering large inertial effects where the form drag exerted by the fluid on the solid becomes significant. $K$ is the Darcy permeability that depends on the pore size, the porosity, $\phi$, and also on the detailed geometry, and $p$ is the pressure.

In addition to the conservation equation and momentum balance equations (1), we write mass transport equations in arterial lumen as

$$\frac{\partial c}{\partial t} + v\nabla c - D\nabla^2 c = 0 \qquad (2)$$

**Darcy permeability:** The permeability, K, of the medium in the Darcy equation is generally a second order tensor quantity, with units of (length)$^2$, that depends on the geometry of the medium.

where $c$ is the average species concentration in the fluid, $D$ is the diffusion coefficient and all parameters are local volume- averaged quantities. Although this equation works for the lumen, we are required to modify these for transport into the porous medium. Here, we define a Staverman filtration ($\gamma$) coefficient to account for selective permeability of biological tissues to certain solutes. Equation (2) is hence modified in biological tissues to

$$\varepsilon\frac{\partial c}{\partial t} + \nabla\cdot(\gamma v c - \tau\varepsilon D\nabla c) = 0 \qquad (3)$$

The equations are written to account for the porosity of the medium ($\varepsilon$) and the tortuosity ($\tau$) as shown in Figure 8. Another important parameter for consideration in these models is the dimensionless Peclet number (Pe) that relates the rate of advection of flow to its rate of diffusion. Diffusion is caused by motion of one species into another, leading to complete mixing without the interaction of external forces. In a porous medium, diffusion takes place in a confined tortuous space and its progression is impeded with tortuosity increases and decrease in the porosity. Physiological Peclet numbers range from 0.1 to about 10.[36] A small Pe ($Pe \ll 1$) indicates that diffusion is the dominant species transport mode in the substrate. In contrast, a high Pe ($Pe \gg 1$) indicates convection dominated mass transport.

Mathematical models of macromolecule transport in arterial walls have been addressed by many researchers.[37–40] These models have incorporated varying levels of detail of the arterial wall starting with using a wall free model to add suitable boundary conditions to the fluid flow.[39] Although these yield details regarding the fluid flows in the lumen, they clearly cannot provide any details about mass concentrations in the arterial wall. The fluid-wall model, proposed by Ethier's group,[38] was an improvement to the wall free one by using a homogeneous wall to represent the arterial wall. While providing an important direction, this study however missed specific details of layered arterial walls with differing properties in each layer. We look at two problems in this review. First, to understand the transport of LDL in the arterial wall that is useful to study disease progression. Second, to study the process of mass transport in DES using computational models that can be used to design optimized criteria for localized drug delivery.

### 8.1. LDL Transport in Arterial Walls
The accumulation of LDL from blood plasma in the arterial wall intima is an important step in atherogenesis. High plasma levels of LDL is

known to be causally linked to the development of atherosclerosis.[41] Macro molecules present in the blood are transported through the arterial lumen as well as transmurally across the arterial wall. It is important, in the context of understanding diseases such as atherosclerosis, to study the transport and accumulation of key macro molecules, such as LDL, from the blood in arterial walls. Blood pressures inside the lumen are high as compared to pressures at the outer surface of wall. Further, the concentrations of macromolecules are correspondingly higher in the lumen as compared to the arterial walls. As a result, LDL molecules get transported and accumulate in the arterial wall due to pressure driven convection flows through the wall and diffusion phenomena due to the concentration gradient across the arterial wall. The IEL is a complex fenestrated lamina consisting primarily of elastic fibers that allows transport of macromolecules into the wall. Tada and Tarbell were the first to assess the importance of IEL fenestrations to the transport of small molecules.[40] They performed a two dimensional study of interstitial flow and mass transport model to show the complex entrance conditions in the media produced due to a fenestrated IEL layer. Cells are exquisitely sensitive to their mechanical environments and we are only now beginning to understand the complex methods of sensing used by cells to probe their physical environments that ultimately determines their biochemical responses.[42] This complex entrance conditions to the arterial media due to the presence of IEL can sometimes elevate the shear stress experienced by the SMC in the media by about ten-fold; which can have a significant effect on the downstream remodeling processes. These processes are a key in the migration of SMC from the media to the intimal layer which leads to the development of intimal hyperplasia.

Ai and Vafai extended these ideas and incorporated a multilayered description of the arterial wall that adapted an advection-diffusion porous media formulation to specify the properties of each layer.[37] Based on the layered arterial model, they asked questions related to the transport of LDL in the arterial wall by simulating conditions such as hypertension.[37] Their results showed that hypertension greatly increases the transport of LDL in the wall. Several factors were used to explain these results. First, the increased transmural LDL flux is mainly due to the increase in the pressure caused due to hypertension. The increased pressure may also change the concentration flux in the wall, assuming unchanged values for the permeability. This, however, is a very strict assumption given known remodeling effects of the wall under hypertension. A further criterion is that the permeability is not a constant factor but is dependent on the pressure. Although various criteria were laid out and discussed, these have unfortunately not been sufficiently addressed using computational models. Finally, all studies have assumed an intact endothelium with identical properties as control vessels. This clearly is a gross oversimplification to predict the progress and growth of atherosclerosis based on our current understanding of the biological events preceding the development of atherosclerosis. LDL filtration velocity and concentration profiles are highly dependent on different boundary conditions that may be used to make specific predictions.[43] For ease of computation, most simulations use smooth and straight walls with axisymmetric geometries. In contrast, atheroprone regions are characterized by sudden changes in geometry where wall shear stresses are low or may change in time.[44] Thus although such studies provided a computational framework that one could use to study the progression of atherosclerotic disease in the arterial wall, most published results are currently based on parameters for a healthy vessel with a smooth wall for computational ease which do not apply either to diseased vessel walls or in branched vessels that seem to have a predisposition for the deposition of plaque.

More recent studies from our laboratory used a 2D analytical solutions in combination with a computational CFD model, using a commercial solver FLUENT 6.2.16 simulating LDL transport into a four layered arterial wall (Figure 9), modeled using a porous medium formulation.[45] Blood was modeled as a Newtonian fluid because the transport through the arterial wall would primarily include protein and plasma (fluid component) constitutes in the blood. The layers start from a thin ($2\ \mu m$) endothelial cell, to the intima ($10\ \mu m$), the IEL ($2\ \mu m$) and end at the media ($200\ \mu m$). Boundary conditions for steady and pulsatile flows were imposed for fully developed (parabolic) flows at inlet of lumen and zero at the sections of the aortic wall. Further, constant pressure at lumen outlet and the media-adventitial surface were imposed with a zero cross-flow condition at the axis of symmetry. To account for reaction rates of the species to satisfy mass conservation, we add a term to the left hand side of equation (3) that is a product of porosity and the species concentration. Further, we assume the reactions occur only in the arterial media so the species diffuse through the wall and are consumed at the medial layer.

**Newtonian fluid:** The fluid viscosity for Newtonian fluids, given constant temperature and pressure, is a constant of proportionality that linearly relates the fluid shear stress to the strain rate. In contrast, non-Newtonian fluids, such as ketchup, yogurt and biological fluids, do not however obey this relationship; thus making the concept of viscosity inadequate to describing the fluid properties.

The model was validated based on previous results and used to study variations in LDL concentration in the arterial wall simulated under healthy and diseased conditions.[37] These results show that the LDL concentration decreases from the vessel lumen into the arterial wall and is very sensitive to the sieving coefficient $(\gamma = {}^{c_r}\!/_{c_d})$, defined as the ratio of the solute filtrate concentration $(c_r)$ to that in the incoming plasma $(c_d)$. A sieving coefficient of 1 indicates complete transfer of the species from the lumen to the wall whereas a value of 0 indicates that the solute is completely rejected and no mass transport has occurred. The EC layer, modeled with a low sieving coefficient, allows for the largest drop in the concentration of LDL. The media has a high value of k and the LDL concentration is fairly constant in this layer. Parametric studies, performed by varying the endothelial cell permeability from $10^{-19}$ m$^2$ to $10^{-21}$ m$^2$, to study the uptake and presence of LDL in the arterial walls, are hence relevant in this regard to study the effect of endothelial permeability as a barrier to the accumulation of LDL in the arterial wall. Because the non-Newtonian character of blood is mainly caused by presence of hematocrit, the model also used a non-Newtonian Carreau model for viscosity and showed no changes in the mass transport of species in the vessel wall. However, computations in the vessel lumen should assume a non-Newtonian model to more accurately represent the properties of the blood to yield realistic results with the simulations. Such models may hence be required to understand the complex interactions between the chemical, biological and physical phenomena occurring in the transport of LDL through arterial walls.

## 8.2. *Drug Release Kinetics*

The introduction of stents in stenosed vessels heralded a new era in the treatment and management of atherosclerotic vessels. Drug eluting stents (DES) combine mechanical advantages, offered by the presence of stents in vessel walls, with local drug delivery to the desired site that may aid in delaying and preventing device failure. DES stents are now preferred over their BMS counterparts with a progressive increase in the number of DES implants.[2] Biological restenosis is a main reason for the proliferation of SMC radially in the arterial wall that leads to obstruction of the lumen and necessitates re-intervention procedure. Anti-proliferative drugs when delivered locally may alleviate these events but tailoring of specific dosage and drug release rates need quantification for optimized drug uptake and retention in diseased arterial walls that may produce desired short and

long term effects. The importance of drug release rates is shown in clinical trials involving oral medication and those related to release from stents in a multitude of studies.[46–49] Drug elution generally occurs from short initial bursts to sustained release until complete depletion.

Mass transport due to DES in the vessel lumen is subjected to normal hemodynamic forces that place limits on the ability of the stent to deliver required therapeutic quantities; given that some drug washout would occur under hemodynamic flows. The highest drug concentration is clearly in the lumen-arterial wall interface.[50] Transport of the drug into arterial walls may be facilitated by carrier proteins, such as albumin, that increase transport rates as compared to that by free diffusion alone. The hydrophobicity of drugs is now known to play a central role in the transport and retention of local drug concentration in the arterial walls.[36] Hydrophilic drugs, such as heparin, tend to wash away from the stenosed region due to blood flow. In contrast, hydrophobic drugs, such as sirolimus and paclitaxel, in the vessel bind to specific arterial proteins in the wall and diffuse transmurally through the wall, albeit at a slower rate, as compared to that in the circumferential and axial directions.

Advances in drug delivery platforms allow us to critically design the release characteristics of the drug. A key step in this direction is to optimize parameters to ultimately deliver specific quantities of drug over a desired times to achieve the optimum biological benefits. Various parameters, for example choice of drug, polymer type and thickness, spacing between the individual struts of the stent, length of the stent, drug elution profile etc require to be quantified that will also depend on the material properties of the diseased vessel, geometrical factors and patient characteristics such as presence of diabetes that may complicate these effects. As compared to expensive animal and clinical trials, computational methods can be tuned to study variations in drug type, pressure fluctuations and the material properties of the diseased wall.

Simple Fickian diffusion rules have been applied to model the elution of drugs from polymeric coatings on stents that depends on drug diffusivities, porosity and tortuosity of the polymeric coatings. Pontrelli and Monte used a porous wall approach using a one-dimensional analytical approach to yield important physical insights to the mass transport of drug into a porous medium, akin to the conventional heat diffusion problem through a bi-layered structure.[51] Dynamics of drug elution from the stent was

Ficks diffusion laws: The diffusion of solute in the medium occurs in response to a concentration gradient. The first law linearly relates the solute flux from higher concentration to the lower one through a diffusion coefficient. The second law combines this with the continuity equation to yield a relation that links the concentration dependence over time as a function of the second derivative of the concentration gradient through the diffusion coefficient.

modeled as diffusion dominated process. Mass transport in the arterial wall is however governed not only by diffusion but also by convection and an advective transport term as highlighted in the section above. Other assumptions also required to describe the arterial wall include drug diffusion coefficient, wall porosity, plasma viscosity and the wall permeability. A key unknown variable is the volume averaged filtration velocity of the plasma carrying drug over a volume averaged region of the arterial wall that is generally assumed in most studies. Hwang and coworkers suggest that drug diffusion in the arterial wall is anisotropic and that transport in the circumferential direction is an order of magnitude higher than that in the transmural direction.[52]

Studies from the Edelman group have looked into several factors that are related to drug deposition from stents in the arterial walls.[46,50,53] Strut positioning, thickness and arrangement in the stent structure is key to determining local fluctuations in the arterial wall. Previous studies worked on a central hypothesis that thinner struts were better in ensuring enhanced drug delivery capabilities. Further, because of the biological role of albumin in the arterial wall, DES with albuminal coatings were used for optimized drug delivery in the wall due to minimized drug losses associated with hemodynamic flows. Computational studies have since shown that albuminal coatings are related to less than 50% of the drug present in the wall.[53]

However, regions of high circulation, for example immediately behind the stent strut, will be a likely place for mass transfer to occur in the wall. Although species transport in the wall depends on many features of the drug type, a main factor is the arterial wall properties starting at the intimal layer. Were the plaque to be very dense, for example in the case of a calcified and heavily blocked vessel, the transmural velocities would be very low. To simplify the problem, researchers have used many assumptions to make the problem tractable and yet yield important factors that determine the transport of drugs into the vessel wall. One such simplification is to neglect the properties of the diseased intimal layer that presents the first and main barrier to mass transport into the arterial wall. The assumption is justified by researchers on the grounds of denuding the endothelial layer caused due to the injury the wall during stent placement; clearly a simplistic assumption. Further, lesser drug concentration is delivered to the wall with thin struts that may instead cause more localized injury to the wall.[53] Unlike earlier generation of DES, current day stents now use a irregular cell designs that combine flexural rigidity

while allowing for retaining the drug in the arterial wall for effective mass transport in the wall.[36]

The polymer coating on the stent plays a vital role in regulating drug delivery in the lumen. In addition to the challenges of a complex fluid environment, the presence of the polymer must not cause an inflammatory response in the adjoining arterial tissue. Further, the entire stent-polymer-drug system must be sterilized prior to implantation without undergoing changes to either the mechanical properties of polymer characteristics to cause differential leaching of the drug when implanted in the patient. If the drug is released too rapidly, there is a likely possibility for this to exceed tissue absorption rates. In contrast, a very slow drug release rate will also not be useful from a biological perspective.[46,54] Studies from our lab model the drug elution from DES in a composite four walled arterial wall and show that regions distal to the stent strut have recirculation zones that may aid in the transport of drug to the wall.[45] Most models use a constant drug elution rate to study mass transport due to DES. Because the drug elution varies exponentially in the lumen, these studies would be greatly enhanced with including variable drug elution rates in composite layered arterial walls.

Other factors such as presence of thrombus, or blood clot, in the arterial wall will also affect mass transport of drug from the stent and its presence is hypothesized to be a key parameter responsible for experimentally determined poor drug diffusion in the arterial walls.[55] Delayed healing of the injured vessel, post stenting procedure, and the subsequent re-endothelialization of the wall also suggest a possible link between the injured sites with local thrombus development. A variety of reasons may contribute to the formation of thrombus; including fracture of the heterogeneous plaque during implantation, material properties of the metal or polymer coating of the stent causing an immunological reaction, local vascular biology of the wall and anti-platelet patient specific characteristics, among others. Clinical results show a six-fold increase in thrombosis when DES is placed in pre-existing thrombosis.[56] Thrombus induced fluctuations in drug release is hypothesized to increase the risk for local toxicity, given the narrow range of drugs that are approved for use in DES. Although some degree on thrombus presence may prove beneficial for retaining the drug in the arterial wall, a large and dense thrombus will increase the risk for myocardial infarction. Computational drug transport models show that an adherent focal and diffuse thrombus may be helpful in elevating drug deposition in the artery

**Thrombus:** A blood clot, formed mainly of blood cell aggregates bound by fibrous protein, fibrin, a thrombus usually forms in regions of disturbed blood flows and sites of rupture of an atherosclerotic plaque.

by eliminating part of drug washout associated due to normal blood flows and allowing for an increase in the drug available for transport in the arterial wall.[50]

Use of computational models is hence very important to provide insights into the process of mass transport in arterial walls or to design drug elution rates from stents. Future designs of DES will greatly benefit from numerical models that can tailor the stent material degradation along with controlled drug release for better efficacy of the device and for the desired biological effects.

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