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Approaches to understanding vascular blood flow

Review Article

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Abstract: While Cardiovascular diseases (CVDs) indubitably remain among the leading cause of death, quality understanding of atherosclerosis remains an enigma. The ensuing work analyses a broad pertinent area to identify a variety of means to understand vascular blood flow. An in-depth study and analysis of quality literature available are performed and a portrayal of varied aspects of vascular blood flow attempted. The complete matter is then structured based on the criticality of topics, identified opportunities to make an impact, and an understanding of current and upcoming trends. We commence with an attention to commonly occurring locations of Atherosclerosis, moving next to discuss the importance of Wall Shear Stress (WSS). From there on further, we discuss the impact of plaque localization and approaches to plaque detection. Alternatives like an in-vitro assessment of blood flow and its potential are analyzed. Studies in dimensional modeling including zero-D, 1D, and higher dimension, coupled with multi-scale modeling discuss other key works. We then extend this discussion to, modeling interactions, and modeling of dynamic growth. In the final section, the focus shifts to an alternative systems biology view to study blood vessel growth and remodeling. A comprehensive and lateral slice of various topics of vascular blood flow leads to the development of a contemporary understanding of the subject. This article could serve as a baseline for researchers of vascular blood flow.

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Keywords: Atherosclerosis • Hemodynamics • Wall shear stress (WSS) • Oscillatory index (OSI) • Intimal plaque • Non-invasive • Zero-D model • 1D, 2D, 3D-Model • Multiscale modeling • Vascular blood flow • Dynamic growth • Systems biology • Vessel growth and remodeling

1. Introduction

Cardiovascular diseases (CVDs) are the number one cause of death globally. On the subject of CVDs, disorders of the heart and blood vessels, World Health Organization (WHO) has stated that four out of five CVD deaths are due to heart attacks and strokes. Identifying the risks of CVD and ensuring they receive appropriate treatment can preempt premature deaths. Acute events like CVDs mainly cause a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of plaque deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes can also cause bleeding from a blood vessel in the brain or from blood clots.

A quality and comprehensive understanding of atherosclerosis can go a long way in better managing the dread of CVDs. The intent of the paper is to provide a contemporary outlook to some of the aspects involved in developing such an understanding. Starting with the review of locations where atherosclerosis commonly develops, we move focus onto some of the key characteristics of the vessels like Wall Shear Stress (WSS) and its relation to plaque locations. We

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then proceed to look at one of the main triggers i.e. intimal plaque and its main cause-consequence, followed by a study of vascular blood flow characteristics. The subsequent section, details into the cardinal aspect of non-invasive mechanics Next we branch on to review the methodologies related to dimensional and multi-scale modeling and later branching to discussions of modeling of interactions. The penultimate section focuses on the interesting aspect of modeling growth and shrinkage. We finally conclude with a look into a potential alternate - Systems Biology view and the possibilities that it might offer.

2. Commonly occurring locations of Atherosclerosis

Atherosclerosis is among the most common disease where an artery starts thickening until it eventually occludes causing a cessation of blood. This often severely affects the organs perfused by the arteries, leading to severe illness to the patient. Atherosclerosis affects large, medium, and even small muscular arteries, a process that gradually develops in an individual over a period of about four to five decades.

In an effort to understand vascular blood flow, one approach would be to focus on the areas where atherosclerosis develops more frequently i.e. the larger arteries. An initial survey confirms that Atherosclerosis in the large arteries is often located in the branch ostia, bifurcations, or bends. The observation though, needs and would benefit from, confirmatory numerical and statistical evidence.

The carotid bifurcation remains a prominent area for investigation and the results by Ku et al. [1], Zarins et al. [2] not only reaffirm the locations' importance, but also that low shear stress presage plaque formation. Further, they also highlighted how oscillations in the direction of wall shear augment atherogenesis. While it is widely accepted that a correlation exists between the measures of carotid intimal-medial thickness (CIMT) and location of cardiovascular events, Finn et al. [3] have highlighted the need to deal with the confounding issues of CIMT measures at the proximal carotid location and the distal carotid location. It is better to focus attention specifically towards 'vulnerable' plaques, as noted by [4]. That the subsequent risk of thrombosis is enhanced at this vulnerable plaque location was emphasized by Fukumoto et al. [5]. The importance of the common carotid intima location receives further acclaim in Bots et al. [6], who also note the strong co-relation between the intima-media thickness and the ankle-arm index.

Missouris et al. [7] analyze and present a strong positive co-relation between renal artery stenosis and peripheral artery disease. Likewise Wilson et al. [8] draw a parallel between presence of abdominal arterial calcific (AAC) deposits, cardiovascular disease (CVD) and mortality.

The locations of occurrence of early-onset of Peripheral Arterial disease (PAD) varied with age, shared Barretto et al. [9], pointing to aortoiliac location and the superficial femoral artery as the commonest location of atherosclerotic plaque for older patients

Next, in this paper, we endeavor to understand the hemodynamic at these locations. While arteries adapt to and modify hemodynamic [10], unusual conditions could lead to an abnormal biological response. There are interesting factors differentiating the ecosystem at these branches and bends, especially in comparing a healthy individual and ones who have developed significant atherosclerosis at these locations, as presented by Glagov et al. [11]

3. Wall Shear Stress (WSS) and its relation to plaque localization

Consider fluid flow through a tube with a certain mean flow velocity and guided by a pressure difference, at a specified level of peripheral resistance. The main determinant of the flow is the cross-section area. If the volume flow is more or less constant from point to point, then velocity of the fluid is greatest where the diameter is the least and velocity is least where diameter is greatest.

In the case of blood flow through arteries, because of the frictional resistance at the blood endothelial layer, flow velocity is greater at the midstream than at the lumen surface and the gradient of the velocity from the center to the wall is symmetrical [12]. Where the lumen narrows eccentrically or vessel curves or bifurcates, the distribution of the velocities across the lumen is displaced. The vessel straightens or unbranches at a later point and the parabolic symmetry is restored.

Laminar flow is one in which the fluid travels smoothly or in regular paths, in contrast to turbulent flow, in which the fluid undergoes irregular fluctuations and mixing.

Reynolds' number provides a measure that signifies the relation of inertial forces to viscous forces in a liquid. Value $R_e < 2300$ means the liquid flow is laminar; $2300 \leq R_e \leq 4000$ means the flow is transitional; $R_e > 4000$ means the flow is turbulent

Departures from unidirectional laminar flow occur about branch points and at locations distal to a stenosis. In these locations, secondary flow patterns such as vortices and recirculation tend to form.

The gradient of the velocities near the artery wall determines the wall shear stress.

$$\text{Wall Shear Stress } \tau_w = \frac{4\mu Q}{\pi r^3} \tag{1}$$

where τ_w is the wall shear stress, μ viscosity, Q volume flow, and r is the radius of the conduit.

Small changes in radius can have marked changes in wall shear stress, given that the radius appears in the third power in the denominator.

The relation of any biological variable Y to body mass M is often characterized by the allometric scaling law $Y = Y_0 M^b$ where b is the scaling exponent and Y_0 characteristic of the organism. Interestingly, most biological phenomenas have been observed to scale as a quarter or its multiple. For instance , metabolic rates of entire organism scale as $M^{3/4}$; rates of maximal population growth scale as $M^{-1/4}$; also sizes of biological structures scale similarly with cross sectional area of aortas as $M^{3/4}$ [13].The shear stress-rate relationship is provided by $\tau = K.\gamma^n$ where n=1 for Newtonian Fluid and n < 1or n>1 for non-Newtonian Fluid. The non-newtonian equations are supplemented with boundary layer continuity and momentum equations to compute the shear stress. This important parameter γ can be numerically estimated as presented by Al-Ashhab [14], and improved accuracy obtained for larger values of n.

Plaque formation has been repeatedly pointed and correlated with low mean stress and oscillation in shear stress direction. Moore et al. [15] have experimented and analyzed the WSS of post-mortem of aortas. In comparing the values of intimal thickness of the artery and the WSS, they have found a strong correlation between these two attributes in distal region. Mean WSS and oscillatory shear index (OSI) had a high correlation to intimal thickness in these regions. One still needs to analyze the above results to verify any possible relationship and correlation to the subsequent immediate bifurcation of the aorta to the left and right iliacs. It is important to expressly connect WSS, OSI to plaque but also be able to discount any connections or correlations to the bifurcations.

Another study, by Gnasso et al. [16] analyzed the same aspects, but the study was performed in-vivo on healthy male subjects. An expanded experiment demonstrated an inverse relation between both peak and mean shear stress as compared to the intima-media thickness (IMT). They also recorded that the vessel organs could detect hemodynamic stimuli that cause release of vasoactive substances. These substances are among the key causes of the remodeling of the vessels, which happens over an extended period.

Pritchard et al. [17] performed a study to understand the relation between cell velocity and monocyte adhesion. They observed a linear correlation between wall shear stress and cell velocity. In addition, the spatial variation in WSS and the inertial difference between the cells and the fluid increased U937 cell and monocyte adhesion. Further, the same efforts also observed the decrease in cell adhesion with an increase in WSS.

The WSS around a stenosis is another topic often studied and analyzed. Deplano and Siouffi [18] performed numerical simulations and Doppler experiments to understand WSS evolution past a stenosis and observed that artery works in the opposite direction in the presence of stenosis. The resulting low values of WSS distal to the stenosis and the oscillating shear index (OSI), permits intimal thickening and subsequently leads to the progression of atherosclerosis.

In individuals traditionally classified as low risk for coronary heart disease, Irace et al. [19] observed a correlation between carotid atherosclerosis and low WSS. Further, supporting and confirming the impact of low WSS and OSI, Taylor et al. [20] in their study also observed that lower limb exercises increased pumping of blood flow. This lead to increased WSS and disappearance of flow oscillations observed earlier at rest.

In their extensive review, Shaaban and Duerinckx [21] discussed the relation of WSS and early onset atherosclerosis. Besides reaffirming the correlation between low, oscillating WSS and imminent atherosclerosis, they progressed further and related WSS to age, blood pressure and body mass index (BMI), although it was challenging for them to measure the WSS in-vivo, using non-invasive methods.

Ojha [22] note how WSS have a profound effect on smooth muscle cell proliferation and neointimal thickening. This point was also corroborated by observations in grafts. The graft results demonstrated low WSS promoting intimal thickening and high WSS inhibiting the thickening. OSI patterns also consistently correlate with intimal thickening, although they could not see regularity in the pattern across different positions in the vessel. Later Ojha [23], performed in-vitro studies to understand the relation of WSS to intimal hyperplasia - a precursor to arterial bypass graft failure. The study looked at the sharp temporal changes in the WSS from positive to negative values. Further, how this may lead to endothelial deformation or injury, and eventual intimal thickening.

Cecchi et al. [24] individually analyzed the hemodynamics of WSS in different scenarios. First, in the case of coronary atherosclerosis, the diagonal branch, and marginal branch were identified as locations with frequent occurrence of atherosclerosis. Second, in the case of cerebrovascular atherosclerosis, the outer wall of the internal carotid artery is observed as a location where atherosclerosis preferentially occurs. An interesting twist was raised as a result of the naturally occurring differences in the diameter ratios of the internal carotid arteries to common carotid arteries in females as compared to males. This ratio is larger in females who have a lower incidence of internal carotid atherosclerosis and see more in the external carotid artery. On the other hand, the male species have relatively more incidents of internal carotid affliction. Thirdly, intracranial aneurysm, making up 90% of the cases of cerebral aneurysm is located at the arterial bifurcation in the circle of Willis. It is understood that high WSS leads to the formation of the aneurysm. All the same, the subsequent growth of an aneurysm and possible rupture has been plausibly connected to low WSS. Lastly, the case of atherosclerosis in the abdominal aorta identifies the posterior wall of the intrarenal abdominal aorta as the preferred location. The position is also linked to the existence of the normal bifurcation that connects on the anterior side. All the above cases continue to confirm that bifurcation locations, associated with the incidence of low WSS and combined with oscillating shear have a preferential disposition to atherosclerosis.

4. Approach to detect location of intimal plaque

Experiments recorded have been more often conducted using glass and plastic tubes. In addition, flows observed are primarily steady rather than pulsatile. The situation demands models and data, collected with observations and simulations, based on realistic clinical experiments.

The geometry of the area of the frequently located atherosclerotic aortic bifurcation is of special interest. Proximal areas of such branches are a typical region of flow separation and low wall shear stress. Further, wall shear stress is high in the region of the flow divider. For instance, review of abdominal aortic bifurcations shows that the lateral walls, opposite the central flow divider, are preferred sites for plaque formation and low wall shear stress.

The term *increased residence time* refers to the delay in particle clearing. The increase typically results in an increase in the duration of exposure of the lumen surface to conditions favoring intimal entrapment or transendothelial diffusion. This duration of exposure is increased in low shear regions.

Arteries normally undergo enlargement as plaques deposit, tending to conserve lumen diameter and the behavior continues up until a point of threshold is reached by the lesion. It is only subsequent to this threshold that the lumen narrowing takes place.

Turbulent flow continues to draw attention as a possible determinant of plaque localization. In general, in the absence of abnormal configurations such as stenoses or shunts, one is less likely to encounter turbulence or other random flow patterns.

Platelet-derived growth factor (PDGF), is a molecule composed of two identical simpler molecules, two homologous polypeptide chains A and B. Wilcox et al. [25] have demonstrated that PDGF mRNA is expressed in atherosclerotic plaque. Importantly the distribution of PDGF receptor mRNA was predominantly localized to the plaque intima.

On the topic of atherosclerotic plaque, of more interest are plaques that fissure. Additionally, we are interested in knowing where the fissure occurs. Richardson et al. [26] undertook a study and observed that in the cases, where the patients had died due to coronary thrombosis; the plaques contained an eccentric pool of extracellular lipid in the intima. Moreover, in a majority of these cases the plaque had ruptured at the junction of plaque cap with adjacent normal intima. Understandably, these regions of tears were ones with high circumferential stress. The prognosis of these cases, being that once the tear occurs, blood penetrates into the arterial wall. This may later lead to the formation of thrombus in the lumen.

In another such study, Ebrahim et al. [27] looked at intimal-media thickness (IMT) at common carotid artery, bifurcation, internal carotid artery, and plaques. Their study also noted plaque rather than IMT as a key criterion for identifying the prevalence of CVD.

Another interesting factor observed is thermal heterogeneity in human carotid atherosclerotic plaques. Stefanadis et al. [28] captured the heat released by activated inflammatory cells of atherosclerotic plaque and observed a consistent and progressive difference in temperatures with individuals having stable angina, unstable angina, and acute myocardial infarction. Individuals in the control group did not show any temperature heterogeneity. Much along the lines of this approach Brown [29] patented a device where an infrared carrier mounted on a catheter passed through arteries measures the infrared radiation with elevated temperatures indicating inflamed plaque.

Low-density Lipoprotein (LDL) closely resembles lipoprotein(a) [LP(a)], with similar lipid composition and both containing apoprotein(B) [apoB]. Apoprotein B is the primary apolipoprotein of VLDL, IDL, and LDL. It is responsible for carrying fat molecules (lipids), including cholesterol, around the body to all cells within all tissues. Further, LP(a) contains apoprotein(a)[apo(a)] that is attached to apoB by sulfide bonds and binds to LDL receptors with lower affinity than LDL. Niendorf et al. [30] observed a staining pattern for apo(a) and apoB in the intima of arterial walls with a preference for the lesion, supporting the epidemiological observation that Lp(a) is associated with atherosclerosis. They conclude that LP(a) as an atherogenic particle can be detected immunologically by the demonstration of apo(a) with a preferential deposition to atheromatous lesions.

It is well known that human atherosclerotic plaque contains a significant amount of T lymphocytes. Notwithstanding Hansson et al. [31] found the large amounts of T lymphocytes, surprising. On analysis, they found that smooth muscle cells in the plaque express class II MHC (Ia) antigens, which are not seen in normal smooth muscle cells. The class II MHC (Ia) antigens are induced by interferon–γ, a secretory product of *activated* T cells. The authors found that a high frequency of the T cells expressed HLA-DR (Human Leukocyte Antigen - antigen D Related) and the very late activation antigen-1 (VLA-1), which are markers of activation in these cells. They also found expression of interleukin-2 receptors (IL2R), an early marker of T cell activation.

Atherosclerosis is accelerated in patients undergoing hemodialysis (HD). Hojs [32] found advanced atherosclerosis in the carotid artery in these patients undergoing HD, as compared to the normal control group. In the continued quest looking for early signs or markers for atherosclerosis, London et al. [33] studied the impact on cardiovascular prognosis based on the type of calcification viz. intimal or medial, in patients undergoing HD. They found that while arterial intima calcification (AIC) was more prevalent in older patients with a clinical history of atherosclerosis, Arterial media calcification (AMC) was seen among young and middle-aged patients without any risk of atherosclerosis. They concluded that AMC was a strong prognostic marker for CV mortality in HD patients, with the principal effect of AMC on an arterial function being increased arterial stiffness.

Celermajer et al. [34] studied endothelial dysfunction as an early harbinger of atherogenesis preceding plaque formation. In measuring the superficial femoral and brachial arteries when they experimentally caused dilatation, they found endothelial dysfunction in children and adults with atherosclerosis risk, and this was prior to any evidence of plaque formation.

5. In-vitro, non-invasive methods for assessment of blood flow

In general, the promise of MRI as a non-invasive simple way to measure blood flow has achieved limited success. The principal reason for that being that the blood flow affects the intensity of MRI images in myriad ways [35]. In Phase-contrast MRI (PC MRI), the object is to visualize fluid in motion. Flowing nuclei moving in the direction as that of the applied magnetic field develop phase shift. This phase shift is proportional to the velocity of the motion. In a simpler of the methods, bipolar gradients (two gradients with equal magnitude but opposite direction) are used to capture the velocity of spins. The result is that the net phase of the magnetization from the stationary spins is zero. And the net phase of magnetization from moving spins in non-zero. When the two data sets are subtracted, the signal contribution from stationary nuclei is eliminated and only flowing nuclei are seen. Before PC MRI data are acquired, the anticipated maximum flow velocity must be entered into the pulse sequence protocol (velocity encoding (VENC)). VENC value is the maximum velocity value that can be encoded. Models of the carotid artery are reconstructed from high-resolution material-enhanced MR angiographic images i.e. gated PC MRI. Based on the Navier-Stokes equation and further developed using numerical techniques, the blood flow is modeled [36]. The results of the modeled equation provide parameters for the visualization of several hemodynamic quantities.

An important observation in the presence of flow separation was that flow was either stagnant or reversed. A method developed for non-invasive assessment of blood flow was tested on rigid flow through the carotid artery with 65% stenosis in the ICA. The geometry was reconstructed from 3D fast spin echo contrast enhanced MR angiographic images. A finite element mesh (max element size 0.2mm) generated from the reconstructed surface, contained approx. 400,000 elements and 79,000 points [37].

Artoli et al. [38] have identified Lattice Boltzmann method as an effective mesoscopic solver to time dependent blood flow in the arterial system although investigations have not been completed on complex aorta model.

Micro-electromechanical systems (MEMS) provide an interesting avenue to understand and characterize the spatial and temporal variations of the WSS. Ai et al. [39] developed a polymer-based sensor - flexible, biocompatible, and deployable into the arteries to assess shear stress in complicated arterial geometries.

Significant advances have been seen in the areas of cardiovascular imaging like angiography, ultrasound, computerized tomography, and magnetic resonance. Lieber et al. [40] observed that while understanding vasculature structure had improved, the progress in understanding related flow was restrained. Stressing on the need for overall progress in this area, they have highlighted some of the shortcomings and open opportunities as under.

1. Despite all the progress in the past decades, angiography still maintains its lead as the preferred imaging modality for vascular intentions. All the same, the invasive procedure is still unable to provide a view of vascular wall or structure.

2. Likewise, while significant improvements have been made in the ability to visualize vascular lumen and quantify the amount of atherosclerosis, not much improvement has occurred with regards to connecting anatomical information and functional consequences of coronary disease.

3. Finally, there is a need to combine patient specific anatomic information gained from imaging with hemodynamic measurements and modeling, to assist in diagnosis and therapy development properly supported with reasonable risk estimation.

Yagi et al. [41] successfully developed a 3D laser flow diagnostic technique, fluorescent scanning stereoscopic particle image velocimetry (FS-SPIV) and studied the WSS dynamics of aneurysmal jets and their impact. Their study demonstrated the transition from a laminar regime in patient specific aneurysmal haemodynamics, in addition to the temporal and spatial dynamics of the WSS, all effected by the flow impingement. A departure from the viscous laminar flow assumptions made in CFD analysis, it highlighted the value of modern and novel experimental studies.

Patel et al. [42] provide an extensive review of the issues related to atherosclerosis from a hemodynamics perspective. For one they elaborate on the localization of atherosclerosis in regions of orifices, bends and vessel entrances as a fundamental arterial response to hemodynamic stress. Next, they analyze the blood flow field from both finite element approach and new experimental techniques. Finally, the work reviews the rheology of the vascular tissue, understanding the mechanical properties of the vascular tissue, given the impact of the blood flow characteristics on the vascular bed.

Velocity contours obtained from the PC MR angiographic measurements were compared with those from the CFD simulation. Although a good agreement in the profile is noted, there is difference in the maximum velocities closest to the stenosis. Importantly, a large recirculation region distal from the stenosis is observed; also, an increase in wall shear stress at the stenosis is noted.

An aspect that needs to be incorporated is robustness and quantitative rigor as one arrives at conclusive statements. For instance, when we say that the profiles agreed, what is the degree of agreement and more importantly its statistical significance? It is insufficient to claim that the degree of variance is 10% and hence acceptable. One must detail and establish that 10% variance in the context is statistically insignificant.

5.1. Curved Tubes

The aortic arch, the main systemic artery from the heart, is a 3D-bend twisting through more than 180 degrees

The main systemic artery from the heart is the aortic arch, which is a 3D bend, twisting through more than 180 degrees. Dean(1928) analyzed flow in a curved tube and developed a parameter relating the centrifugal forces to viscous forces.

$$\text{Dean Number} = (2\delta)^{\frac{1}{2}} 4Re \tag{2}$$

where $\delta = \dfrac{\text{radius of tube cross section}}{\text{radius of curvature of the centreline}}$ and Re is the Reynolds number.

Dean number helps us gauge the property of flow in the aortic arch. A higher Dean Number indicates the presence of a flow that is not developed. The core of such a flow may act like a vortex, skewing inwards and one that may lead to a subsequent flow separation.

5.2. Few flows for special consideration

Oxygenated blood is transmitted from abdominal aorta to the different organs in the abdomen and lower limbs. In the normal resting condition, the leg requires little blood flow and also the resistance to flow is high in that state. As a result, only about a third of the thoracic aorta blood flow passes into the legs via the abdominal aorta. Notwithstanding and surprisingly, in many individuals atherosclerotic disease extends along the posterior wall of the abdominal aorta below the renal arteries. Also in stark contrast, little disease has been observed in the upstream thoracic aorta. This calls for a special detailed review of the flow in the abdominal and thoracic aorta to understand the peculiarities of both flow and vessel properties [43].

The carotid artery bifurcates along the sides of the neck and in the process supplies blood to the brain and the face. It is atherosclerosis that develops at this bifurcation that causes the majority of strokes. An interesting aspect of human anatomy is the carotid bulb that develops at the base of the internal carotid artery just above the bifurcation.

Often factors like elasticity of vessels and non-Newtonian viscosity of blood are termed as secondary factors in the context of atherosclerosis, and conveniently neglected [44]. However, variations in structure of the branch and in pulsatile flow waveform and distribution could have significant effects. Arteries, as we recognize, are not fixed tubes; they are biological organs that remodel themselves over time in response to their surrounding conditions. Among others, they also seem to adapt to long-term increase or decrease in wall shear stress.

5.3. Modeling the cardiovascular system

Recent years' advances in CFD coupled with the dramatic improvement in performance of computing power hold the promise of revolutionizing vascular research. Properties like shear stress, that are normally difficult to measure in-vivo, can be computed for real geometries with the support of non-invasive technologies like nuclear magnetic resonance, digital subtraction angiography, spiral computerized tomography.

Altered flow conditions like separation, flow reversal, and low or oscillatory shear stress area are important factors in the development of arterial disease [45]. While in the past, analyses were possible in only limited morphological regions and under mathematical assumptions bordering towards being unrealistic, today the road towards realistic simulation has become a lot more encouraging.

5.4. Role of hydrodynamics

Hydrodynamics is recognized as a factor, among the leading causes, during the initial stage of development of arterial lesions, like atherosclerosis [46]. Other factors being, resistance or impedance of the constriction as characterized by pressure drop and flow; distribution of pressure and shearing stress; nature and extent of separated regions of flow and additionally presence of turbulence.

Experiments conducted to analyze the above role - although only conducted in-vitro, throw light and draw some interesting insights. At low Reynolds numbers, the pressure drop is due to viscous effects. Laminar separation occurs at low Reynolds number. Pressure drop decreases with increasing values of Reynolds number. With an increase in Reynolds number, the flow becomes unstable, turbulence develops, and at high Reynolds number, the pressure loss is due primarily to turbulence [47].

Yoganathan et al. [48] in their influential work on hydrodynamics guide how the quantitative studies of laminar to turbulent transition in pulsatile flow express the Reynolds number as a function of frequency leading to the Womersley Number a.k.a unsteady Reynolds number.

5.5. Womersley Number

Womersley Number is a dimensionless parameter, much like the Reynolds number. It represents the ratio of transient forces, originating from pulse waves to the viscous force, or shear force[43].

$$\begin{aligned} \text{Reynolds Number} &= \frac{\text{Inertial Force}}{\text{Viscous Force}} \\ \text{Womersley Number} &= \frac{\text{Unsteady or Transient Force}}{\text{Viscous Force}} \\ \alpha &= R\sqrt{\frac{\omega}{\nu}} \end{aligned} \tag{3}$$

R is the tube radius; ω the angular frequency and ν kinematic viscosity

When the Womersley parameter is low, viscous force dominates, velocity profiles are parabolic, and the centerline velocity oscillates in phase with the driving pressure gradient. For Womersley number above 10, the unsteady inertial force dominates and the flow has a flat velocity profile.

The general interest in understanding aneurysms and atherosclerosis have continued for many decades and attempts to correlate hemodynamic factors to the pathology of these disease has also captured interest. Understanding the geometric factors, if any, those that have a higher influence on formation of aneurysm, or correlation of pressure effects on bifurcations as a cause for aneurysm, aspects like these cast an interesting perspective to interests in understanding vascular flow.

Hemodynamic plays an important role in the initiation of aneurysms Mechanical forces such as pressure and shear force acting on the apex region of the bifurcation could trigger the onset of the aneurysm formation[49]. The local pressure is mildly elevated at the region of bifurcation due to the momentum transfer. The wall shear stress found near the apex region varies along the neck of the bifurcation and is elevated near the apex. The local forces found at the apex could damage the wall near the bifurcation and thereby lead to the development of aneurysm.

6. Zero-D, 1D, 2D and higher dimensional modeling

Occam's razor is a widely accepted and revered principle devised by William of Ockham. The principle is applied in problem-solving and focuses on parsimony, economy, and succinctness. The selection of an appropriate dimension for a model being developed, from zero-D to 1-D and possibly even a higher dimension depends on the aims, the required accuracy and the problem on hand.

Zero-dimensional or lumped parameter models assume a uniform distribution of the variable attribute e.g. pressure or volume within a particular compartment vessel of the model, at any instant of time. [50, 51]. Zero-dimensional models bring about a set of simultaneous differential equations (ODE's). Zero-D is often used to model blood flow in arterioles, capillaries, and venules.

One, two, and the higher dimensional models bring about a series of PDE describing conservation of mass and momentum, supported by equilibrium equations [52]. Studying how pressure and flow waves propagate in the blood vessel remains one of the challenging problems. Important properties like the function of the heart, the elastic properties of the vessels are believed to be encoded in the two wave form relationships. 2D and 3D models could possibly reveal pressure and velocity distribution in a vessel.

Morris et al. [53] expound on the benefits of cardiovascular CFD modeling highlighting how they enable investigation of both pressure and flow fields at a temporal and spatial resolution not available by clinical methods. CFD benefits afforded are greater when CFD models are used and fluid mechanics with cellular response together analyzed. Given the benefits, both short term and much better in the longer term, they also restate the need to demonstrate and establish the equivalence of in-silica results to invasive measurements. This affirms the trust that CFD could become a standard method in the clinical practice proceedings.

There has been a spurt of interest to coupling models that are heterogeneous with regards to some of their model properties. The efforts of Malossi et al. [54] have been to devise strategies for coupling dimensionally homogeneous flow models through averaged/integrated coupling quantities. These quantities are defined according to lower dimensional fluid models. A 3D computational domain is partitioned into complementary, non-overlapping sub domains, imposing at the interface conservation of flow rate and continuity of the coupling stress. The efforts saw success in the use of the traditional Newton Iterative Fixed Point method in solving the reduced problem of interface variables; emphasizing the need and value of modeling at different dimensions.

Kalita and Schaefer [49] in their comprehensive review of models of artery walls observe that model that are constructed are 'specific purpose' driven and in their view, it is unlikely that a universal model would be developed. Both 0D and 1D model have the strength of flexibility. Despite the simplifying assumptions, they note, both 0D and 1D models are popularly used to model arterial bifurcations and networks. Under some specific conditions, an exact representation of vessel geometry attracts special significance for instance, on blood flow or wall movement simulations. Consideration of factors such as heterogeneity, anisotropy, incompressibility, viscoelasticity, pulse, load, and non-linear displacement; a combination of factors like these, call for 2D, 3D, and higher dimensional modeling.

Typical efforts to develop 1D to 3D model and predict blood flow, pressure, vessel area assume that walls are elastic. In a departure from this approach, Steele et al. [55] couple a 1D fluid dynamics model with a generalized viscoelastic constitutive model relating the blood pressure and vessel area. The results showed that introduction of viscoelastic dampening of the arterial walls provided more realistic predictions of blood flow and vessel area.

Quarteroni [56] besides detailing the techniques of modeling local phenomenon, espouse on the mechanics of modeling the whole circulatory system. The approach involves an integration of multiple scales in space and time and integration of actions and reactions in the different cardiovascular compartments.

The understanding of flow in collapsible tubes has drawn special interest as a problem that involves the interaction between vessel walls and flowing fluid. While more often studied after introducing simplifying assumptions and spatial dimensions of the problem, Makinde [57], Ismail et al. [58] investigate flow of viscous incompressible fluid in a collapsible tube using a special approximation technique. The Hermite-Pad*é* approximants technique is used to analyze flow structure. A development from the Maclauri Series which is typically a good polynomial approximation of a function evaluated at 0 (zero). Pad*é* approximants estimates that function as a quotient of two polynomials P(x) of order m and Q(x) of order n, such that $\frac{P(x)}{Q(x)}$, called the Pad*é* approximant of order [m/n]. They observed that the fluid axial velocity profile was parabolic with maximum value at centerline and minimum at the plates. Further, fluid axial velocity generally decreases with an increase in tube contraction due to the strong influence of the negative transmural pressure caused by the significant reduction of rigidity.

The benefits of structured analysis using mathematical models were noted by Kokalari et al. [59]. In particular, organizing both the knowledge and observations from experiments, in the time and space dimensions, has important significance. With simplified assumptions, the 0D model considers a uniform distribution of variables like pressure, volume, and flow rate in every single compartments i.e. organ, blood vessel, etc. of the model, in every moment of time. On the other hand, the models of higher dimensions account for the spatial variation of these parameters. The authors highlight the success of 0D models with two differential equations and one algebraic equation to model cardiovascular vessel dynamics.

In an uncommon, yet interesting study, Bessonov et al. [60] review and analyze the blood rheology using a 1D model. In studying the properties of blood as a fluid containing a suspension of particles, many studies view the situation as a study of non-Newtonian behavior of fluid flow in blood vessel. The authors have adopted an alternate approach that views blood as complex fluid containing plasma and cells. They present analysis of flow employing Dissipative Particle Dynamics (DPD) a mesoscale method where each particle describes a small volume. Additionally, they also look at 1D-flow models given its reduced computational load and simplicity. Unfortunately, the work comes short of presenting a conclusive recommendation.

7. Multi-scale Modeling

Recent periods have seen rapid development in the application of multi-scale modeling in which Zero-D, 1D, 2D and/or higher dimension models are coupled with each other, to form a complete representation of the cardiovascular system. Typically, local hemodynamics is computed in a detailed 3D model of the organ while the lower dimensional models provide boundary conditions for this domain.

In a discussion highlighting the computational demands of 3D CFD models, Lee and Smith [61] compare them to the performance of 1D model. A specific 3D simulation activity reported 24 hrs' running on 256 core, per cardiac cycle while 1D counterpart required only 20 min per eight cardiac cycles on a single-core. The authors presented the above as one important justification for use of heterogeneous 3D-1D-0D coupled models. The well-recognized challenge of coupling in this multi-dimensional model remains a knotty issue. The authors further present, as benefits of the multi-scale modeling, clinical indexing techniques developed following the application of modeling in a real-time clinical analysis. Fractional flow reserve (FFR) is a pressure-derived index that estimates the functional severity of a coronary stenosis. The instantaneous wave-free ratio (iFR) is an alternative stenosis severity index that requires pharmacological administration. iFR is defined as the instantaneous ratio of translesional pressures.

Based on an assumption that one spatial dimension prevails over others Di Carlo et al. [62], Pontrelli [63] present 1D models constituted to understand the wave propagation phenomenon in the vessels. They develop a comprehensive model of global circulation by coupling a lumped model describing the boundary conditions and the distributed model describing the wall-fluid interaction.

With a desire to provide utmost clarity Formaggia and Veneziani [64] use for this purpose the term "geometric multi-scale modeling", to distinguish from other forms of multi-scale modeling. The authors present the typical nu-

merical issues in multi-scale modeling, key being the one related to managing interfaces in the different models having different levels of details. Inevitable is the use of mean averaged or such similar less accurate data being provided, at the boundary of a higher dimension model being integrated with a model of lower dimension. The authors recommend approaches to contain the perturbation like for example use of Lagrange multiplier approach for flow rate boundary. They also recommend obtaining (mean) Dirichlet data by using the recent technique of *Dirichlet-Neumann substructuring iterative method* a method then widely adopted for solving complex real problems by means of *domain decomposition method (DDM)*

Xiao et al. [65] present an analysis of age-related stiffening hypertension and pressure pulse propagation. The simulation confirmed their expectations that increase stiffness would correspondingly increase pulse pressure and separately observed decrease in pressure amplification with age. In a first of the efforts, the work combined four different methodologies to produce a physiologically realistic solution: a coupled-momentum method for fluid-structure interaction, a multi-domain method for outflow boundary condition specification and two other components combined together. The account observed that clinical haemodynamics metrics like pulse wave velocity, pulse pressure, augmentation index, arterial distensibility, and so forth have found positive acceptance as indicators of cardiovascular function and predictors of cardiovascular risk. Among them, carotid-to-femoral pulse wave velocity (CF-PWV) is regarded as the "gold standard" of measurement of arterial stiffness. The computing requirement trade-off between 3D and 0D models understood, the authors recommend a balanced use and build of multi-scale models. An efficient modeling strategy is recommended, one that uses 1-D models to quickly estimate inflow and outflow boundary conditions for the 3-D model

Formaggia et al. [66] present and discuss the concept of *multiscale nature* in the context of blood flow. In referring to time and space variables, an atherosclerotic plaque formation, according to them, is for one a response of the vascular tissue to specific stresses induced by the blood. On the other, it is a macroscopic development of a plaque over a temporal scale of months or even years. Authors note that in comparison to one-dimensional (hyperbolic) models, simple systemic models are unable to detect downstream and upstream traveling waves unless many compartments are connected in complex topologies. To address the challenge and complexity of coupling a lumped model with a 1D model, care at the interface matching was employed by the use of an algorithm based on characteristics analysis

In distinction to the focus on the multi-scale modeling of blood flow rate, Stylianopoulos and Barocas [67] focus on the 3D network structure of the collagen in the artery. Recognizing the strengths of structural modeling over phenomenological modeling, the authors progress from modeling multi-layers of the artery to modeling fiber-fiber interaction. The application of volume-averaging theory to the collagen network gives it a multi-scale framework. The models results were in line with expectations and showed increased circumferential compliance for increased axial stretch and limited sensitivity to open angle. The authors observed the importance of collagen even at small strain and noncollagenous material supporting the network.

An interesting mathematical challenge that must be addressed is the development of multi-model simulations, in which models of different levels of complexity are coupled - in a mathematically sound way. Lumped parameter model and one-and-three dimension models can coexist even with microscopic-scale models. These potentially enticing hybrid multi-scale models must be set on a solid mathematical basis as noted by Quarteroni [68]. There must be a facility to reproduce essential physical behavior with dimensional downscaling, without losing relevant conservation properties at the interfaces.

8. Modeling Interactions

Mathematical and numerical models are seemingly becoming more important in many areas of applied science, including biology and medicine. Mathematical and numerical investigations of blood circulatory system, in particular, continue to elicit interest and potential [69].

Physical quantities like shear stress, which are difficult to measure, can today be possibly computed by non-invasive data acquisition technologies (e.g. nuclear magnetic resonance, digital angiography, spiral computerized tomography, and three-dimensional construction algorithms.)

Blood flowing in a blood vessel interacts both mechanically and chemically with the vessel walls, leading to a complex fluid-structure interaction problem. Rubenstein et al. [70]

Fluid Structure Interaction(FSI) has two definitions - at a broader level, it is the interaction of a flowing fluid and a deformable boundary; another being the interaction of components within the fluid and the surrounding containing medium an example being the platelets and white blood cells, that can interact and adhere to the endothelial cells.

An endeavor to understand the influence of Hemodynamic factors in blood vessels by developing a numerical fluid-structure analysis technique was performed by Torii et al. [71]. The focus was to comprehend the interaction between the blood flow and the arterial wall for a patient-specific cerebral aneurysm with hemodynamic conditions, like hypertension. They concluded that WSS and the mechanical stress in the aneurysmal wall are affected by hypertension, implying that hypertension affects the growth of an aneurysm and the damage in arterial tissues.

Non-uniform rational basis spline (NURBS) is a mathematical model commonly used in computer graphics for generating and representing curves and surfaces. It is recognized for the flexibility and precision for handling both

analytic and modeled shapes. Isogeometric fluids structure analysis, an emerging approach, offers simplified refinement process, improved accuracy at reduced computational costs. Bazilevs et al. [72] constructed vascular models for isogeometric analysis. They developed NURBS geometries directly from patient-specific imaging data. The models delivered successful and acceptable results on the tests conducted with benchmark data

Shell theory predicts, according to Ciarlet and Mardare [73], the stress and the displacement arising in an elastic shell in response to given forces. The prediction is made either by solving a system of partial differential equations or by minimizing a functional, which may be defined either over a 3D set or over a 2D set. Kalita and Schaefer [49] focus on presenting through models the biomechanical and physiological phenomena that take place in the artery walls. Besides other models, a model based on the physically non-linear shells is also presented. The authors observe that though the thinness assumption is required to use the shell as artery wall model, the advantage is the significant reduction of computational complexity of the numerical solution.

Takizawa et al. [74] present a special space-time and Arbitrary Lagrangian-Eulerian (ALE) technique developed for patient-specific cardiovascular fluid-structure interaction (FSI) modeling. They demonstrate how the special technique deals with the challenging computational issues in FSI problems

Hsu and Bazilevs [75] observed that the elastic motion of the arterial wall has a significant effect on the hemodynamic study and that the *rigid wall* assumption overestimates the WSS. The authors in earlier works introduced a correction based on the study of zero-stress geometry, which was an improvement but an approximation all the same. In the current work, the authors directly compute the state of prestress in the blood vessel using an iterative procedure. Later they incorporate the prestress using the additive decomposition of the second Piola-Kirchhoff stress tensor.

Sinha and Mondal [76] present a creative recommendation, flowing from the observation that erythrocytes, which have small negative charge, account for about to 93% of the total number of the elements in the blood and to about 45% of the blood volume. They study the unsteady hydro magnetic pulsatile blood flow in the artery and obtain numerically the velocity profile solution using the finite difference method. The results demonstrate that a vibration environment, one's that occur in the course of daily activities of life, affects velocity and temperature of the blood. These findings render an opportunity to control blood flow using magnetic field, especially during surgical events.

Vito and Dixon [77] present blood vessel constitutive models, providing a relationship between stress and strain fields' interactions. Among the different application benefits of these constitutive equations, they highlight the value in understanding atherosclerotic plaque stability, studying effects of angioplasty and stenting.

Tezduyar et al. [78] model the arterial fluid mechanics problems with the stabilized space-time fluid-structure interaction (SSTFSI) technique. The technique includes, among others, use of an estimated zero-pressure arterial geometry and pre-FSI computations that improve the convergence. The technique showed good performance when the authors tested computations for cerebral and abdominal aortic aneurysms.

Interested in understanding the hemodynamics, Bathe and Kamm [79] study and analyze an axisymmetric, fully coupled fluid-structure interaction (FSI) of pulsatile blood flow through a compliant stenotic artery using the finite element method. The study noted that large variation in fluid pressure caused by an acceleration of flow at the stenosis lead to the deformation of the arterial wall, possible damage, and even significant flow alteration because of this changed vessel dimension. Further, they noted that large pressure drops occurring in the models during peak flow significantly increased arterial hoop stretch amplitude both within, and just downstream of, the stenosis.

Torii et al. [80] give an alternative view to predicting forces on the aneurysmal wall and estimating the risk factors for an aneurysm. The effort was intended to investigate and understand the influence of the wall-structure model, assumed as either linearly elastic or hyper-elastic, on patient-specific FSI simulations. They observed that the maximum displacement for the hyper-elastic model is 36% smaller as compared to the linearly elastic material model. Also, the minimum WSS at the apex is equally smaller with the hyper-elastic model. Finally, they observe and agree that the constitutive model of the wall is better represented by using hyper-elastic model.

9. Modeling dynamic growth of Atherosclerosis

Whilst CVDs are known to be the primary cause of death globally, atherscleortic CVD is responsible for the majority of those and a 2012 estimate attributes 71% of all CVD to atherosclerotic CVD [81]. Co-morbidities that drive CVD were expected to grow with a global increase of 55% in cases projected up to 2050.

Despite the growing importance and its implication for health, the pathogenesis of atherosclerosis is not fully understood. Traditionally viewed as the build-up of lipids (including cholesterol) within the innermost layer of 'tunica intima', our understanding has since developed. Atherosclerotic CVD is now viewed as a chronic inflammatory condition, advanced by lipid build up and triggered by innate immune responses.

Atherosclerosis emergence is a result of multiple dynamic cell processes. Elaborating on the contemporary view presented above, damage to endothelial cells recruits monocyte to the site of inflammation via inter and intracellular signaling. As a result, monocytes migrate into the artery walls alongside lipoprotein, before differentiating into macrophages and phagocytosing oxidized LDL (oxLDL). The migration rate of these cells and particles is dependent on haemodynamics and vascular stress. The accumulation of cholesterol-laden macrophages within artery walls leads

to plaque formation.

Pasterkamp et al. [82] focus on arterial remodeling, both kinds, expansive e.g. enlargement and shrinkage e.g. constriction. The former prevents, while the latter accelerates lumen narrowing. They highlight that expansive remodeling is both a boon and a curse. While the remodeling can prevent the lumen from being occluded in some cases, in the others it constitutes a group of lesions that are vulnerable and prone to rupture. Further, to better understand the specific aspects that influence remodeling, detailed knowledge of mRNAs and proteins must be developed. Finally, the case of successful blocking of constrictive remodeling after balloon dilatation, although tested only in animals, is a good example of success and potential.

Geometric remodeling is defined as the structural change in arterial circumference because of atherosclerosis or angioplasty [83]. The outcome could be either enlargement or shrinkage. In that sense, it can either compensate for or worsen the effect of plaque or hyperplasia. No correlation was observed or recorded between the two factors i.e. intimal hyperplasia and geometric modeling that cause lumen narrowing.

Naturally, an important framework to consider such emergent behavior is mathematical and computational modeling coupled with simulation. The models can take a range of forms, including Ordinary differential equations (ODE), PDEs and stochastic ODEs. Further, Process Algebra such Pi and kappa calculus have been used in some cases to capture the structure of pathways.

10. Alternative - systems biology view of blood vessel growth and remodeling

Blood vessels serve as highways for blood traffic, including delivery of oxygen, inflammatory and progenitor cells and removal of waste [84]. An interesting aspect, as noted earlier, is that the seemingly rigid structure of the blood vessels is not completely static - as a matter of fact, it is a truly living, sensing dynamic organ. Indeed, it is the regulation of the growth, maintenance, and regression that enables the blood vessel to complete its physiological roles. The blood vessels surround all tissues and interact with numerous cells and myriad microenvironments. The multicellular, multidimensional, multi-environmental nature calls for an integrated comprehensive approach - called Systems Biology Approach.

We focus our attention on Angiogenesis, the growth of new blood vessels from pre-existing vessels. Normally angiogenesis in adults is understood to be initiated by conditions requiring an increase in blood and oxygen supply, including reproduction, repair, and exercise. Endothelial cells existing in the blood vessels are induced to sprout by growth factors and the resulting new vessel sprouts pathfind through the tissue, anastomoses with existing blood vessels [85], forming new channels.

Conway et al. [86] inform that while endothelial cells have garnered most attraction on the topic of vessel growth, they alone cannot complete the growth process. Pre-endothelial cells and matrix components also play a key role. In studying the subject of Angiogenesis, the objective is to be able to understand and control angiogenesis. Being able to combat angiogenesis in the event of inflammations and, enhance angiogenesis in the event of ischemic events or as a treatment for ischemic events, would serve well. The authors provide a detailed understanding of the processes of vasculogensis, angiogensis, and arteriogenesis along with their respective stimulators and inhibitors. An appropriate growth of new vessels or collaterals can be critical in situations of cardiovascular remodeling. Angiogenic approaches [87] to stimulate the growth of new vessels involve delivery of vascular endothelial growth factor (VEGF) or basic fibroblast growth factor (bFGF) to the tissue. Visconti et al. [88] extend this discussion of angiogenic factors and shed light on *collaboration* between two such classes of angiogenic factors. The observation was VEGF and angiopoietins collaborate to regulate angiogenesis. Ang2 collaborates with VEGF-A to induce capillary angiogenesis. Within the heart though Ang1 acts as a negative influence for VEGF-induced angiogenesis.

Angiogenesis is a factor involved in many diseases including cancers, vascular malformation, and pulmonary hypertension. Uncontrolled blood vessel invasion permits growth of tumor beyond oxygen diffusion limit and actually provides the tumors a potential metastasis route. On the other hand, some diseases may be ameliorated by angiogenesis and these diseases have a characteristic absence or regression of blood vessels. It includes crohns disease, atherosclerosis, and osteoporosis disease - among others.

Systems Biology takes an integrative and holistic approach to understanding the mechanism. Given the emergent nature of growth and the inherent complexity of interconnected gene, protein and cell pathways within tissues, the high-throughput experimental techniques that are pursued, can be combined with heuristic modeling approach guided by Swarm Intelligence. The multi-step process of angiogenesis as professed under Systems Biology includes trigger from angiogenic stimuli, leading to sprouting followed by elongation and branching later leading to tubulogenesis, lumen formation, and anastomosis, and finally to stabilization or regression. The above approach bears a potential similarity to Swarm intelligence (SI) which conceptually reflects the collective behavior of decentralized, self-organized systems, natural or artificial [89].

11. Summary

A detailed understanding of a problem area, being the development and morphology of atherosclerosis, must align to a typical problem-solving approach. One must focus attention on the commonly occurring areas of the problem, the larger arteries, and regions surrounding bifurcations. A complete study of the Hemodynamics in the identified region will both supplement and complement the problem resolution. This study in a Zero-0, 1D, or higher, incorporating factors that account for the dynamic growth of atherosclerosis, modeled and simulated mathematically, would lay emphasis on the importance of simplified mathematical models.

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