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Flow Interactions with Cells and Tissues: Cardiovascular Flows and Fluid–Structure Interactions

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Abstract

Interactions between flow and biological cells and tissues are intrinsic to the circulatory, respiratory, digestive and genitourinary systems. In the circulatory system, an understanding of the complex interaction between the arterial wall (a living multi-component organ with anisotropic, nonlinear material properties) and blood (a shear-thinning fluid with 45% by volume consisting of red blood cells, platelets, and white blood cells) is vital to our understanding of the physiology of the human circulation and the etiology and development of arterial diseases, and to the design and development of prosthetic implants and tissue-engineered substitutes. Similarly, an understanding of the complex dynamics of flow past native human heart valves and the effect of that flow on the valvular tissue is necessary to elucidate the etiology of valvular diseases and in the design and development of valve replacements. In this paper we address the influence of biomechanical factors on the arterial circulation. The first part presents our current understanding of the impact of blood flow on the arterial wall at the cellular level and the relationship between flow-induced stresses and the etiology of atherosclerosis. The second part describes recent advances in the application of fluid–structure interaction analysis to arterial flows and the dynamics of heart valves.

Keywords

Arterial endothelium; Atherosclerosis; Heart valve dynamics

Introduction

Interactions between flow and biological cells and tissues are seen throughout the body. Such interactions are intrinsic to the circulatory, respiratory, digestive and genitourinary systems, and are critical to kidney function, the stress response of bone, the provision of neuroendocrine factors to and mechanical protection of the brain, organ development, and many other processes in living systems. Notwithstanding its ubiquitous importance, studies of these interactions from a fluid mechanics point of view are much more narrowly focused, with the principal system of study being the circulatory system.

In the circulatory system, an understanding of the complex interaction between the arterial wall (a living multi-component organ with anisotropic, non-linear material properties) and blood (a

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shear-thinning fluid with 45% by volume consisting of red blood cells, platelets, and white blood cells) is vital to our understanding of the physiology of the human circulation and the etiology and development of arterial diseases, and to the design and development of prosthetic implants and tissue-engineered substitutes. Similarly, an understanding of the complex dynamics of flow past native human heart valves and the effect of that flow on the valvular tissue is necessary to elucidate the etiology of valvular diseases and in the design and development of valve replacements.

In this paper we address the influence of biomechanical factors on the arterial circulation. The paper is divided into a section devoted to the impact of blood flow on the vessel wall and a section devoted to fluid–structure interaction. The first section contains insights regarding early and advanced atherosclerosis, while the second focuses on flows through both arteries and heart valves.

Blood Flow and the Vessel Wall

It is now accepted that atherosclerosis originates from dysfunction of arterial endothelium. Dysfunctional endothelium exhibits a syndrome of atherogenic characteristics, including elevated turnover and macromolecular permeability, expression of inflammatory molecules and production of reactive oxygen species, decreased production of anti-inflammatory and anti-thrombotic compounds, and leukocyte and immune cell recruitment.

It has been shown in controlled *in vitro* experiments and deduced from *in vivo* observations that hemodynamic forces are among the key factors that can cause arterial endothelial function to dysregulate. A particularly strong argument in favor of hemodynamic stress as a determining atherogenic factor derives from the fact that, in contrast to the systemic risk factors for disease that have been identified through epidemiological study, both the predisposition to atherosclerosis and measures of the hemodynamic environment vary spatially within the vasculature. Accordingly, a principal objective of research on the interaction of flow with vascular cells and tissue is the identification of the hemodynamic variables that promote atherosclerosis, and the elucidation of the mechanisms by which hemodynamic factors act on the vessel wall. It has also been noted that, once the atherogenic fluid dynamic factors have been identified, the likelihood that they are present at a given susceptible site in a given individual could be assessed through computational fluid dynamic simulations of the flow field in that individual using conduit geometries obtained from clinical imaging.³⁶ Geometric features shown to be associated with, or to exacerbate, adverse hemodynamic stresses have been called “geometric risk factors”.¹⁵

In principle, there are two ways in which the fluid mechanical environment can affect the arterial wall:

Directly, wherein the relevant hemodynamic variable is detected by a cellular mechanosensor or other molecule whose response is directly or indirectly atherogenic. An example would be the opening response of a mechanically gated ion channel or the biochemical response of a stressed adhesion molecule.

Indirectly, in which the hemodynamic variable promotes an environment that aggravates a potentially atherogenic situation, which might be systemic or local in origin. Examples include the influence of reduced shear stress on endothelial permeability in the presence of hypercholesterolemia,³⁵ or an increase in the residence time of leukocytes over an inflamed endothelium.

In attempting to identify the hemodynamic characteristics that predispose to local atherosclerosis, primary emphasis has been placed on the laminar shear stress at the vessel wall. This seems reasonable, since, except possibly in the aortic arch, the flow field is laminar

under normal conditions, and blood pressure seems to act systemically and not as a localizing variable. Numerous *in vitro* experiments have shown that vascular endothelial biology is influenced by shear stress, though the shear environment used in these experiments has been, with few exceptions, qualitatively different from that seen in computational simulations of real vascular flows. Most *in vitro* experiments expose cultured cells to uniform shear, commonly steady as well, while real vessel walls are exposed to shears that are spatially non-uniform and periodically vary in magnitude and direction.

There are other differences between the *in vitro* and *in vivo* situations that extend beyond the flow field. The media on the luminal side, as well as the abluminal substrates, are different. But perhaps most important, cells *in vivo* have had the time to truly adapt to their natural environment, while the achievement of a steady state replicating that *in vivo* cannot be ensured in an *in vitro* setting. Interestingly, the least adapted cell culture experiment, the response to flow onset, has been regarded as representative of the response of cells chronically exposed *in vivo* to “disturbed” shear.⁵⁹

In vivo, many more metrics are needed to characterize the varying shear vector acting at a vascular site. These include the time-average shear magnitude, the near-wall residence time²³ (which is related to the time-average magnitude through the oscillatory shear index²¹), shear gradients in space and time, and metrics based on the variation of the direction of the shear vector.¹⁹ We have some idea of the change in atherosusceptibility that accompanies changes in individual shear-related variables from the nominal atheroprotective range, but no overall concept of the interaction of the various parameters. Put another way, we have only isolated projections of the surface in multi-parameter space that separates the environment with which cells can cope from that in which they cannot. Thus it is not surprising that when correlations are sought between a single hemodynamic variable and atherosclerotic disease, exceptions that violate the hypothesis often arise.^{18,20} Such observations do not reflect a failure of the model, but rather provide an opportunity to make it more complete and improve its predictive capability.

Nor is it surprising that *in vivo* experiments, in which the vessel is exposed to a complex mix of fluid and solid mechanical stresses, do not always agree with generalizations derived from the simpler flow chamber experiments that are more commonly used to dissect the vascular response to the flow environment. There are many instances in which the conclusions from *in vitro* experiments are mirrored *in vivo*, and it is tempting to discount deviations between the two as anomalous. Yet these “anomalies” may in fact carry important information that cannot be obtained from conventional *in vitro* experiments.

The most common description of atherogenic flow is that such flow is “disturbed”, involving low and directionally varying shear. This may be a convenient term, but it is misleading. Of course, atherogenic vascular flows are in general not disturbed according to the rigorous requirements of fluid mechanics. We have begun to use the term “complex” to describe the fluid dynamic environment that seems to be present where lesions form. The limitation to low and directionally varying shear as the criteria for atherogenicity is also misleading because, as noted above, there are many other fluid dynamic metrics that might also differentiate between lesion-prone and lesion-resistant areas.

The search for the *sine qua non* of atherogenic flow is inseparable from that for the mechanisms by which fluid mechanical stresses affect vascular biology and effect biological response. Most studies of mechanism have used laminar flow chambers, and in almost all of these, the spatial gradients and temporal changes in direction that exist *in vivo* are absent. Nonetheless, these experiments have provided important insights into the mechanisms by which the endothelial phenotype is modified by exogenous forces. These putative mechanisms have been reviewed

elsewhere (e.g., Hahn and Schwartz¹⁹) and will not be discussed here. Even so, it is still not clear whether the response *in vivo* is determined primarily by the shear magnitude, which has been the lone variable in almost all flow chamber experiments, or some other flow metric for which magnitude may be a surrogate *in vitro*. There is also evidence, at the gene expression level, that different genes are promoted by different aspects of the shear field,³⁴ suggesting that atherogenesis may be served by multiple pathways stimulated by different aspects of the shear environment.

Our search for the hemodynamic origins of atherosclerosis is further confounded by other factors that may explain in part the non-uniformity of the disease. The elastin-rich intimal substrate is non-uniform in arteries and has been shown³³ to be less continuous in areas known to be atherosusceptible. Indeed, we have found that the gene expression profiles in the coronary and iliac arteries are distinctly different, and that the differences are consistent with the greater atherosusceptibility of the former vessels.⁶⁶

In recent years, studies have indicated that deviations of the physiological shear pattern may predict plaque progression, even in advanced stages of (human) disease,^{5,29,48,61–63} showing an important role for rheological theories in advanced human disease. While in carotid arteries—a bifurcation—varying shear stress directions was a strong predictor of plaque progression, in the coronaries—a curved arterial segment—time-averaged shear stress is the strongest predictor of disease. These observations in humans have been supported by animal experiments, where low shear stress and complex flow dynamics were induced in mouse and rabbit carotid arteries, and where plaque size and morphology were associated with these complex flow patterns. It appeared that low, non-reversing shear stress and low, reversing shear stress were both pro-atherogenic, but each shear stress pattern induced a different morphology. These studies have been confirmed using pig coronary arteries, indicating that this observation was independent of species. This is rather surprising, as mice exhibit shear stress values 7–10 times those in pigs, and suggests that the *relative* low shear stress (with respect to a reference value) induces regions more sensitive to plaque development, rather than *absolute* shear stress.

Advanced atherosclerotic plaques are heterogeneous, both in the circumferential and longitudinal direction, with a higher incidence of rupture in the upstream shoulders of the plaque and a stable morphology downstream of the plaque. These observations have been made in different vascular beds, in humans and in experimental animals applying a variety of techniques and due to their local nature cannot be explained by systemic risk factors (e.g. high cholesterol) alone. The underlying mechanism is still unknown; a preliminary insight into the mechanism comes from animal studies, where it was shown that in the upstream region of the plaques, LDL is accumulating, leading to increased expression of adhesion factors, accumulation of macrophages and ox-LDL, and foam cell formation. Foam cells are associated with high MMP-2 and MMP-9 activities, leading to matrix breakdown and local weakening of the plaques. If these weak spots coincide with high solid stress gradients, plaque rupture may ensue.

We have made considerable progress in understanding the mechanics of arterial flows and that of the arterial wall. With continuing advances in computer power and simulation software, and with image-based techniques to provide vascular geometry, flow rates, and velocity profiles, computational fluid dynamics now provides us with a good understanding of the dynamic macroscopic flow field to which the arterial wall is exposed *in vivo*. By combining this with models of fluid-structure interactions (discussed elsewhere in this paper), we can make reasonable estimates of wall mechanics as well. The mechanics of the interaction of the flow field with the wall at the cellular scale is much less well understood.

Future Directions

To understand the role of hemodynamics in the localization of vascular disease, we must unravel the mechanical and biological mechanisms by which a hemodynamic stress causes endothelial dysfunction using computational fluid mechanics, we can describe the fluid dynamic environment in sufficient detail; after all, in laminar flow, shear is merely a vector whose magnitude and direction change with time. The inclusion of near-wall transport processes adds complications, but the governing equations are known and only computer power limits the detail of the simulation. Wall motion can also be included, as discussed elsewhere in this review, though there is uncertainty regarding the spatial variation of wall mechanical properties, but it may be that the simulations that are now being performed capture the most important fluid-solid interactions, and their mediation of near-wall flow and transport.

As was pointed out earlier, we have not yet identified the *specific* feature or features of the flow that drive the atherogenic vascular response, but their list is manageably small and they can all be derived from the computations. Some new ones have lately been proposed—an objective measure of residence time,²³ and measures of the harmonic content of the shear history at a site²²—but they too can be quantified computationally. Hypothesis testing in animal models, particularly atherosclerosis-susceptible models with rapid progression like apoE^{-/-} mice, would seem a particularly promising application for flow simulation, and research along these lines has already begun.^{12,51,68} *In vivo* investigations should be complemented by cell culture experiments in which more realistic flow environments are used, to tease out the hemodynamic metrics that are responsible for endothelial dysfunction.

In trying to identify the important hemodynamic variables in this regard, we note that they are not all strongly correlated with one another, and that uncorrelated variables which can each affect endothelial function can confound the results when data are analyzed with models that assume only a single hemodynamic variable is responsible. For instance, we have found that macroscopic shear stress and shear stress gradient are independent and interacting predictors of the expression of certain genes involved in atherosclerosis, and that different genes depend differently on these two variables.³⁴

Even so, compared to our understanding of hemodynamics, the interaction of the fluid dynamic environment with putative mechanosensors is much less well understood, as are the downstream effects of mechanotransducer activation. We leave the latter for the biologists, but the issue of transducer sensing and activation should be addressable through molecular mechanics, or possibly continuum, modeling. Calculations and controlled measurements of the response of mechanosensors to various hemodynamic stresses could indicate the most promising subjects for concomitant biological investigations.

Potential Applications

The potential applications of an understanding of the role of hemodynamics in atherogenesis are well appreciated by anyone who has written a grant on the subject to NIH in the last 40 years. Hemodynamic forces *in vivo* are not easily modified, but knowledge of the route by which they cause disease in conjunction with systemic risk factors can suggest rational interventions at the biological level.

The hemodynamic environment is mediated by vascular geometry, and geometric features that exacerbate atherogenic hemodynamics are indeed risk factors in their own right. Modern imaging techniques now allow us to simulate flows in patient specific geometries, and we could identify areas of adverse hemodynamics today if we confidently knew what to look for. Indeed, it now appears that we may be able to identify risky geometries simply from the vascular images, without requiring CFD. Factor analysis of geometric features coupled with flow

simulations in fifty carotid bifurcations has shown that the cases can be stratified with respect to the extent of low shear or long residence time simply on the basis of MRI-derived geometry. When we know for certain which mix of hemodynamic variables is the source of endothelial dysfunction, this kind of analysis will be able to identify individuals at risk through noninvasive imaging. These individuals can then be more aggressively managed to reduce the levels of controllable risk factors to which they are subject, such as hypercholesterolemia, hypertension, smoking, and metabolic syndrome.

Fluid–Structure Interactions in Biological Flows

In this section, we will review the state-of-the-art in FSI algorithm development for biological fluid dynamics concentrating upon the published work in the last decade in the area of arterial and valvular flow dynamics. The challenges that are present in the FSI analysis in these applications will be similar in other biological flow analysis as well with appropriate modifications. For example, the analysis of respiratory flow will require the analysis of compressible fluid flow while transport in the GI tract will require peristaltic flow dynamic analysis detailing the interaction between the intestinal wall and the food material that is being digested and transported along the GI tract.

FSI in Arterial Flows

With the several theories relating the local fluid-induced stresses with the initiation and development of atherosclerotic lesions in arterial sites of curvature and bifurcation,^{4,16,31} numerous experimental and computational studies have been published in the detailed fluid dynamic analysis in various arterial segments such as the carotid, coronary, and descending aorta. Initial studies were restricted to rigid wall models with regular geometry for these regions of interest. With the advent of high speed computers and various imaging modalities providing morphologically realistic three-dimensional geometry of the arterial segments, more realistic simulations have become a reality. Even though fluid dynamic simulations with the assumption of rigid arterial wall surfaces yield results that are reasonably accurate, there are several important considerations that require incorporating the arterial wall properties in the simulation: (1) the elastic nature of the wall will result in local deformations in the region of interest that will in turn alter the local fluid dynamics and hence the accurate determination of the local fluid-induced stresses on the intimal surfaces require such an analysis; (2) it can be anticipated that in addition to the local fluid-induced stresses, the stresses on the arterial wall will also play an important role in the arterial disease^{47,57}; and (3) Non-uniformity of material property in healthy tissue as well as material property alterations with the development of the atherosclerotic lesions at various stages need to be analyzed to understand the etiology, growth of the plaques and vulnerability for plaque rupture.

With the reconstruction of the 3D geometry at various times during a cardiac cycle, information on the position of the interface between blood and the soft tissue boundary can be realized. In a class of moving boundary analysis, the variation in the position of the interface can be specified as the fluid velocity at the boundary. One advantage of the moving boundary analysis is that the specification of realistic material properties for the soft tissue is not necessary, but no information on the deformation and stress on the soft tissue (such as the arterial wall) can be determined. As an example, the three-dimensional geometry of the coronary arterial segments at various times in a cardiac cycle have been obtained from a fusion of angiographic and intravascular ultrasound images.^{44,45,49} In the first study, the wall were considered rigid, but in a subsequent analysis translation, rotation, and geometric alterations in the arterial segment during a cardiac cycle were specified as moving boundary conditions in a detailed fluid dynamic analysis. The arterial wall was not modeled in this analysis and hence no information on the stress distribution on the wall is obtained. Peskin pioneered an immersed boundary method for the analysis of the interaction of the ventricular walls and heart valve

leaflets with the surrounding fluid.^{41–43} In this method, the forces exerted by the soft tissue on the fluid interface were incorporated in the fluid governing equations as an additional source term. Once again, the actual material properties of the soft tissue need not be specified in such an analysis and the stress distribution on the soft tissue cannot be computed.

FSI simulations have seen rapid progress in the simulation of arterial fluid dynamics and heart valve dynamics in the last decade. The general requirements for realistic FSI simulations include:

1. Morphologically realistic three-dimensional geometry of the region of interest obtained from several imaging modalities such as ultrasound, CT, angiographic, and MR imaging modalities. Rapid advances have been made in the acquisition and processing of the images in order to reconstruct the complex three-dimensional geometry. These efforts have resulted in the development of patient-specific models for simulations in regions with arterial lesions.⁴⁶
2. Realistic non-linear anisotropic material properties for the healthy and diseased arterial wall segments (or heart valve leaflets) for the accurate depiction of the response of the wall segments to the fluid stresses. Simulations have generally considered blood as an incompressible fluid with Newtonian flow behavior or some simulations including the shear-thinning rheological models.
3. Appropriate coupling of the fluid and structural flow solver for accurate transfer of local deformation and forces at the fluid–solid interfaces.
4. Validation of the FSI algorithm developed with appropriate experimental or computational analysis for specific applications.

In the last decade, a number of studies employing FSI analysis in the arterial circulation have been reported in the literature. The geometry for the arterial segment of interest for these studies has been obtained with various imaging modalities including MR images^{25,55,56,67} and bi-plane angiograms.²⁴ Even though it is possible to employ morphologically realistic patient-specific 3D geometry, it is not possible to obtain patient-specific material property data in the analysis. The analyses have generally employed incremental elastic moduli for the arterial wall based on the measured deformation with the pulse pressure load⁶⁷ or based on non-linear regression fit to pressure-diameter inflation tests.⁶⁵ Shell elements that couple membrane and bending strains are employed in the analysis that includes geometric non-linearity. The FSI analysis is generally performed with commercial codes for the flow dynamic and structural analysis solvers with a user-written code for the coupling at the interface. Tang *et al.* have employed the FSI analysis for the dynamic analyses of human carotid artery atherosclerotic plaque dynamics.^{52–56} These studies have been employed to obtain a correlation between the local fluid dynamic effects on plaque progression, as well as stress distribution on the plaques and potential for plaque rupture. The three-dimensional geometry of the plaque is obtained from MR images while the material property for the arterial wall and the various plaque components were assumed to be hyperelastic, isotropic, incompressible, and homogeneous. These studies have resulted in the development of a local maximum stress hypothesis and a computational plaque vulnerability index for plaque rupture prediction,^{54,55} as well as the relationship between wall shear stress and plaque progression.⁵³ These studies have also suggested that FSI analysis is more important in the dynamic analysis of advanced plaques compared to those for healthy arteries or for the early lesions.⁶⁴

FSI analyses have also been employed to study the effect of compliance mismatch on intimal hyperplasia formation at the anastomotic sites of bypass grafts,³⁷ with compliance mismatch in stent implants,⁵⁸ and wall stress analysis in a stented aneurysm.³⁸ Bluestein *et al.*² employed a FSI analysis to predict the plaque vulnerability in the presence of microcalcifications and

suggested that such calcified spots may increase local stress concentrations by propagating stresses developing around it to vulnerable regions of the fibrous cap. Bluestein *et al.*³ and Rissland *et al.*⁴⁶ have reported on FSI analysis on patient specific abdominal aortic aneurysm models and have indicated the importance of including the intraluminal thrombus as well as the anisotropic material behavior of the aneurysmic wall in the simulations for the prediction of risk of rupture. Taylor and coworkers¹⁴ present a coupled momentum method for the analysis of the interaction between the vessel wall and the blood in three-dimensional deformable models for arteries. The vessel wall is considered as a linear membrane enhanced with transverse shear with the equations of deformation of the vessel walls at the variational level being specified as boundary condition for the fluid domain. The emphasis in this approach is the detailed analysis of the fluid pressure and shear forces at the boundaries applied to idealized carotid artery stenosis model as well as for patient specific models of the abdominal aorta including various arterial branches and the iliac bifurcation. This method of analysis has been extended to be coupled with the growth and remodeling of disease progression in arteries.¹³

FSI and Heart Valve Dynamics

In the case of arterial flow analysis described above, the range of motion of the arterial wall due to the pulse pressure is generally of the order of about ten percent during a cardiac cycle. Generally, the arbitrary Lagrangian–Eulerian (ALE) method has been successfully employed in the FSI analyses of arterial flow dynamics. On the other hand, application of FSI analysis in both native and prosthetic heart valve dynamics results in relatively large motion of the leaflets in a cardiac cycle and hence the geometry of the flow domain changes significantly during a cardiac cycle. In such analyses, mesh adaptation is difficult without loss of mesh quality or without changing the mesh topology in employing the ALE method.

In the last decade, number of publications has appeared in the literature on the development of FSI analysis for heart valve dynamics. In the case of mechanical heart valve dynamics, leaflets of tilting disc or bileaflet valves are made from pyrolytic carbon, a relatively hard material compared to the biological valve leaflets. Moreover, in the analysis of mechanical valve dynamics, the effect of flow-induced stresses on formed elements such as the red blood cells and platelets are of more interest in improving our understanding of the initiation and development of thrombus, still a major complication with these implants. Hence the leaflet material are considered as rigid in such an analysis and the motion of the leaflets in response to the external forces (fluid pressure, shear, and gravitational effects) can be computed using the governing equations of rotational motion³⁰ of the disc. The motion of the leaflets changes the shape of the flow domain and hence affects the local flow dynamics. During the opening phase and with the leaflets in the fully open position, flow rate past the valve are relatively large and hence turbulent flow can be anticipated particularly during the decelerating part of the systole in the region distal to the leaflets. Hence turbulent flow modeling has been of interest particularly in the analysis of systolic flow past the aortic valves. During the mechanical valve closing phase, large pressure gradients have been demonstrated across the leaflets especially during the final stages of valve closure and leaflet rebound. During this stage, the fluid is forced through the relatively small gaps between the leaflet edge and the valve housing or through the hinge mechanism in the case of bi-leaflet valves. Accurate resolution of flows in this region requires local mesh refinement in order to compute the velocity profiles and shear stresses in the clearance gap.³⁰ In this study, a two-dimensional FSI analysis was employed to analyze the local fluid dynamics in the gap between the leaflet edge and the valve housing as well as in the gap between the two leaflets during the closing phase of a bi-leaflet valve. The simulations were validated by comparing the position of the leaflets during valve closure with experimental data for the same valve model. The results showed the presence of large velocity magnitudes and relatively large shear stresses in the peripheral gap at the instant of valve closure. Based on particles modeled as platelets being subjected to high shear stresses in the

passage through the clearance gap and subsequent large residence time of ‘activated’ platelets in the region of the disc, this study suggested a potential mechanism for thrombus deposition in the vicinity of the leaflets that are observed with implanted mechanical valves. In order to accurately resolve the flows in a full three-dimensional model that includes the details of the hinge mechanism for the leaflet motion during the opening and closing phases, such codes need to be parallelized and the simulation performed using multiple processors. Dumont *et al.*^{10,11} have reported on the validation of a 3D FSI analysis for mechanical valve dynamics and have compared the hemodynamic and thrombogenic performances of the recessed hinge and open pivot bi-leaflet mechanical valve models. The flow solver employed a commercial package and a structural solver for the leaflet dynamics in this simulation. The leaflet position was adjusted using a stabilizing subiteration scheme based on the numerical derivative of the moment on the leaflet.¹¹ The study concentrated on the flow distal to the leaflet in the open and closed positions in order to compute the shear stress distribution and platelet activation parameter based on the integral of the shear stress and particle residence time. Laminar flow was assumed for the flow past the valve during the valve opening phase in this study even though turbulent flow has been demonstrated past mechanical valves during this part of the valve function.

The major problems associated with the native aortic and mitral valves and also biological prostheses are leaflet calcification and structural failure. Hence in the analysis of biological leaflet valve dynamics, the complex deformation of the leaflets during a cardiac cycle and the in-plane and bending stress distribution is of primary interest in relating the effect of mechanical stresses on valvular pathology. In order for a realistic simulation of the leaflet dynamics, non-linear anisotropic material property specification becomes necessary. Quasi-static⁵⁰ and dynamic^{17,26–28} finite element analysis with tissue valve leaflets have been performed in order to determine the in-plane and bending stress distribution on the leaflets and provide reasonable estimate of the stresses developed on the leaflets during its function. However, the analysis is based on the application of a uniform pressure loading on the surface of the leaflets. The effect of local pressure and shear stresses on the complex leaflet deformation can only be determined through a FSI analysis. In the case of tissue heart valves with relatively thin leaflets, a time scale disparity is present with the leaflet structure responding about 40 times faster than the fluid⁶⁰ and hence there is a need for an implicit or strongly coupled method of analysis in the analysis of tissue heart valve dynamics. de Hart *et al.*^{6,7} employed a fictitious domain method for the analysis of the interaction of the leaflets with the fluid. However, dynamic analysis with physiologically realistic Reynolds numbers has not been achieved with this method due to numerical instabilities with large Reynolds number flows. In addition, the accuracy of the fictitious domain method in the treatment of the interface is lower and hence its usefulness in the computation of the detailed stress distribution on the leaflets, of interest with tissue valve dynamics, is limited.¹⁰ Kunzelman *et al.*³² have reported on the dynamic analysis of the mitral valve dynamics using the FSI analysis. Anisotropic material property was specified for the leaflets while the fluid was assumed to be compressible employing an artificial compressibility approach. The bulk modulus for blood was modified by several orders of magnitude for computational efficiency and once again, physiologically realistic Reynolds numbers were not achieved. In general, the FSI analysis of particularly biological leaflet valve dynamics have been limited to non-physiological flow regime and inadequate grid resolutions. Vigmostad⁶⁰ has reported on an FSI analysis that overcomes the difficulties detailed above. A fixed Cartesian grid flow solver is employed in this analysis to avoid re-meshing due to large deformations of the leaflets. The solid interfaces in the computational domain are identified by a sharp interface level-set technique. The solid boundaries can move freely in the computational domain without mesh distortion and this method can be successfully applied for both thin and volumetric embedded objects in a unified fashion. Experimentally determined non-linear material property for pericardial valve leaflets was specified in this analysis that is currently restricted to two-dimensional analysis. The solutions have been successfully obtained for physiologically

realistic flow conditions overcoming the limitations of the previous analyses. Extension of this code for three-dimensional analysis and validation with appropriate experimental data is currently underway with code parallelization and the use of multiple processors.

Future Directions

Rapid advances are being made within the last decade on the FSI analysis of biological flows and further advances can be anticipated in the near future. With the advances in imaging techniques, patient-specific geometrical specifications are employed aiming toward real-time analysis for surgical and interventional applications. Even though morphologically realistic geometry can be obtained from the images, it is impractical to anticipate specifications of patient-specific material properties in the analysis. One alternative is to determine the range of material property variations for healthy specimens and for pathological specimens from experimental studies for use in such analyses. In the case of applications of such analyses in the presence of atherosclerotic plaques (lipidous, fibrous, and calcified plaque components) or aneurysmal segments, local variations in material property can be anticipated. Techniques such as ultrasound elastography^{8,9} may prove to be useful in the specification of patient-specific plaque component material description in the analysis for plaque rupture prediction. More recently, Liang *et al.*^{39,40} have employed intravascular ultrasound image registration technique to measure the strain tensor across the arterial wall cross-section throughout the cardiac cycle and such data may prove very useful in validating the FSI simulations in arterial dynamics. In the case of FSI analysis of valve dynamics, further advances in the development of FSI algorithm with strong coupling between the solid–fluid interfaces is necessary for realistic 3D dynamic simulation of healthy, pathological, and prosthetic valve functions. Even if FSI analysis from commercial packages are employed in which validation of the codes have been performed, it is important for independent validation of the results of the analysis with either experimental data or prior published results in the application of such analyses for complex biological flow phenomena.

The FSI analyses for biological applications have also been generally restricted to the organ level and a correlation is obtained between regions of high stresses (in the solid or fluid domain) and the pathologies. However, the changes in the normal biological function are affected at the cellular and sub-cellular level. In order to couple the mechanics at the organ level to pathological alterations at the cellular/sub-cellular level, multi-scale simulation algorithm development also is of vital importance. Such an integrated approach in bio-mechanics holds promise to serve as a paradigm for clinical applications of fundamental mechanics.¹

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Abbreviations

ALE	Arbitrary Lagrangian–Eulerian
CFD	Computational fluid dynamics
CT	Computed tomography
FSI	Fluid–structure interaction
LDL	Low-density lipoprotein
MMP	Matrix metalloproteinase
MR	Magnetic resonance
MRI	Magnetic resonance imaging
Ox-LDL	Oxidized low-density lipoprotein
3D	Three-dimensional