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SPECIAL ISSUE - REVIEW

Cardiovascular disease management: the need for better diagnostics

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Abstract Current diagnostic testing for cardiovascular pathology usually rests on either physiological or anatomic measurement. Multiple tests must then be combined to arrive at a conclusion regarding treatment of a specific pathology. Much of the diagnostic decisions currently made are based on rough estimates of outcomes, often derived from gross anatomic observations or extrapolation of physical laws. Thus, intervention for carotid and coronary disease is based on estimates of diameter stenosis, despite data to suggest that plaque character and lesion anatomy are important determinants of outcome. Similarly, abdominal aortic aneurysm (AAA) intervention is based on maximal aneurysm diameter without regard for arterial wall composition or individual aneurysm geometry. In other words, our current diagnostic tests do not reflect the sophistication of our current knowledge of vascular disease. Using a multimodal approach, computer modeling has the potential to predict clinical outcomes based on a variety of factors including arterial wall composition, surface anatomy and hemodynamic forces. We term this more sophisticated approach "patient specific diagnostics", in which the computer models are reconstructed from patient specific clinical visualizing modalities, and material properties are extracted from experimental measurements of specimens and incorporated into the modeling using advanced material models (including nonlinear anisotropic models) and performed as dynamic simulations using the FSI (fluid structure interaction) approach. Such an approach is sorely needed to improve the effectiveness of interventions. This article will review ongoing work in "patient specific diagnostics" in the areas of carotid, coronary and aneurismal disease. We will also suggest how this approach may be applicable to management of aortic dissection. New diagnostic methods should allow better patient selection, targeted intervention and modeling of the results of different therapies.

Keywords Cardiovascular diagnostic testing · Fluid structure interactions

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1 Introduction

Cardiovascular pathology is the leading cause of death and disability in the Western world. Three major manifestations of this are myocardial infarction, stroke, and death from rupture of aortic aneurysm (AA). The anatomic conditions that lead to these problems (coronary and carotid atherosclerosis, aneurismal dilation of the aorta) are present in a presymptomatic state to varying degrees in the majority of the Western population over age 50. Progression of these lesions can lead to the unpredictable onset of symptoms that can be catastrophic and often irreversible. Current diagnostic tests [cardiac stress tests, computed tomographic (CT) angiography, magnetic resonance angiography, and duplex ultrasound] can identify the existence of these pathologies with a high degree of sensitivity, but are not specific enough to identify patients at high risk for disease progression or sudden occurrence of stroke, heart attack, or death. As a consequence, many interventions for coronary

atherosclerosis, abdominal AA (AAA), and carotid stenosis are prophylactic. This approach requires that asymptomatic patients be subjected to interventions (with associated morbidity) to prevent events that may never occur, rather than to treat symptoms. For example, while coronary revascularization is widely performed around the world, it has only been proven to reduce mortality in a subset of patients with severe ischemia [38]. Over 75% of patients who undergo carotid endarterectomy are asymptomatic, and it is estimated that 19 procedures have to be performed to prevent one stroke [2] in neurologically asymptomatic patients with carotid stenosis. Similar considerations arise in the case of intervention for AA.

While we understand that certain features (e.g., aneurysm diameter, luminal irregularity, plaque composition, luminal stenosis) are related to the development of symptoms in various atherosclerotic disease states, our level of knowledge is currently insufficient to analyze the multiple factors and their complex interactions which cause specific lesions to become symptomatic. One may safely assume that the interaction of local hemodynamic forces with lesion geometry and anatomy is of great importance in this regard. Combining various topographic and anatomic features with real and theoretical hemodynamic conditions using computer based modeling provides a mechanism to investigate these potential interactions.

Such an approach can result in new diagnostic tests that will allow more specific identification of high-risk atherosclerotic or aneurismal lesions in a presymptomatic state. The ultimate goal of these efforts is to identify patients with lesions that require intensive therapy, to select therapy based on the lesions characteristics, and to monitor response to intervention. One can refer to this approach as "patient based diagnostics." The present article is not meant to provide an exhaustive review of the prior and current work in this area. Rather it is meant to be a clinical perspective on the shortcomings of current diagnostic tests for common vascular conditions, namely, carotid bifurcation stenosis, coronary atherosclerosis, aortic aneurysm, and aortic dissection, and to suggest some directions that might result in improved diagnostics and ultimately better patient management.

2 Carotid bifurcation stenosis and stroke

Stroke is one of the most common vascular pathologies encountered in Westernized man. Stroke is the third leading cause of death, behind myocardial infarction and cancer and the leading cause of long-term disability in the US. There are about 700,000 strokes and 150,000 deaths attributable to stroke annually in the US [31]. Approximately 30% of strokes are due to stenosis at the common carotid bifurcation [31]. Treatment of carotid bifurcation stenosis by endarterectomy or, more recently, angioplasty with stent placement has been shown to be effective in stroke prevention, and is associated with low morbidity and mortality [1, 6, 12, 13]. As a consequence, treatment of carotid bifurcation stenosis is one of the most common vascular interventions currently performed, with >160,000 procedures performed annually in the US. Equally significant, 75–80% of these procedures (>120,000 annually) are performed on asymptomatic patients; specifically, to prevent rather than treat symptoms. The clinical decision to perform carotid revascularization in neurologically asymptomatic patients is made on the basis of maximal diameter stenosis of the lesion. Unfortunately, diameter stenosis is not a robust discriminator of which lesions will and will not develop symptoms, and the majority of severe lesions will remain asymptomatic [13]. While multiple prospective randomized trials have proven carotid endarterectomy effective in preventing stroke in patients with "severe" (>70%) diameter stenosis of the carotid artery, efficacy depends on a low complication rate (<3% for asymptomatic patients), which allows the procedure to be performed somewhat indiscriminately. These same data indicate that 19 carotid endarterectomies must be performed to prevent one stroke, or that about 90% of these procedures are "unnecessary" [32].

A second important issue in carotid disease is the risk of progression from "minor" or "moderate" bifurcation stenosis to "severe" stenosis. Since less than "severe" carotid bifurcation stenoses are rarely associated with symptoms; detection of lesions that are likely to progress over time and, therefore, should be serially monitored, is a matter of clinical importance. Several natural history studies address this issue [27, 30]. Plaque progression is dependent on a number of atherosclerotic risk factors, including smoking, dyslipidemia, and hypertension, although the relationship is multifactorial. Similarly, progression is related to the initial degree of stenosis; that is, "moderate plaques" are more likely to progress than "mild plaques".

Plaque characteristics and surface character have been shown to improve the predictive ability of diameter stenosis to identify patients at risk for stroke. It has been known for many years that irregular or "ulcerated" surfaces are more likely to result in embolization and neurological symptoms than are smooth plaques [22]. "Soft" or "echo lucent" plaque (consisting of a lipid core and intramural hemorrhage) has been correlated with an increased propensity for neurological symptoms [10, 16, 25]. The thickness of the "fibrous cap" over the plaque is also felt to be important in identifying lesions that will become symptomatic [19]. It is equally likely that plaque composition and surface character will influence the progression or regression of carotid bifurcation stenoses, and

in fact treatment with lipid lowering agents has been related to changes in carotid plaque morphology [20]. Significant work has been done, primarily in the coronary circulation, investigating the role of hemodynamic forces on atherosclerotic plaque stability. Shear stress [9, 34] and blood pressure [8] have both been shown to relate to plaque stability and rupture. Conversely, plaque composition and topography can impact local stress concentrations and influence remodeling [15, 28].

Like other investigators, we have performed studies on the influence of plaque composition on the shear stress of idealized arterial stenoses (Fig. 1). In this model, the stresses developing within the vessel wall and the various components of the lesion are computed using the FSI approach with careful characterization of the properties of the various plaque components material properties. Specifically, the modeling was aimed at investigating the effects of calcified inclusions on the plaque stability. Our simulations demonstrate significant influence of calcification spots embedded within the plaque's fibrous cap on stresses developing within the wall, with stress concentration propagating around a calcified inclusion and a significant increase in the hoop stresses that indicate increased vulnerability to plaque rupture [3]. This specific analysis was carried out in simple streamlined models of coronary stenoses with smooth plaque. However, our goal is to adapt these techniques to irregular patient specific coronary and carotid bifurcation lesions (such as the IVUS reconstructed patient specific coronary lesion simulation depicted in Fig. 2). Detailed anatomic information of wall composition, vessel tortuosity, and lumen topography can be obtained using ultrasound techniques. In the coronary circulation, this requires intravascular ultrasound, which is an invasive technique at the time of coronary angiography. We have performed some preliminary analyses on coronary lesions (Fig. 2), but the ability to follow the course of a specific lesion over time is limited. However, at the carotid bifurcation, data can be derived percutaneously and serial measurements with long-term follow-up is possible. Using Duplex technology, real-time hemodynamic and anatomic information can be obtained at various points in the vessel, including different parts of the plaque. This capability opens the potential to develop a lesion-specific estimate of the propensity for embolization or progression. Since observations can be repeated over time and correlated to clinical developments, the validity of our models

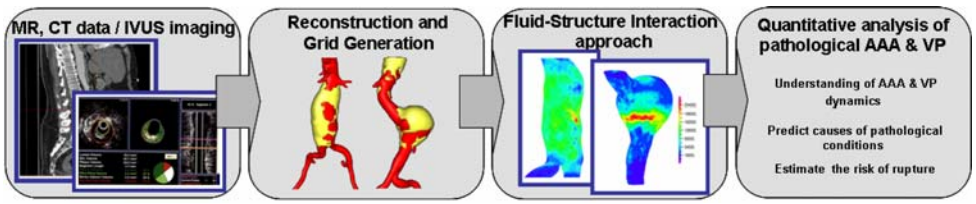

Fig. 1 The "patient specific diagnostics" approach is composed of four major steps. Collection of medical data using novel imaging modalities such as computed tomography (CT), magnetic resonance (MR), and intravascular ultrasound (IVUS) imaging. Accurate delineation of the pathological structures of interest and introduction of these three-dimensional patient specific structures to grid generators. The third step is to solve the fluid structure interaction (FSI) problem predicting flow and pressure field inside the lumen and the stress and displacement interaction with the anisotropic wall tissue. This approach can address open questions of the pathology, predict the causes, and estimate the risk of rupture

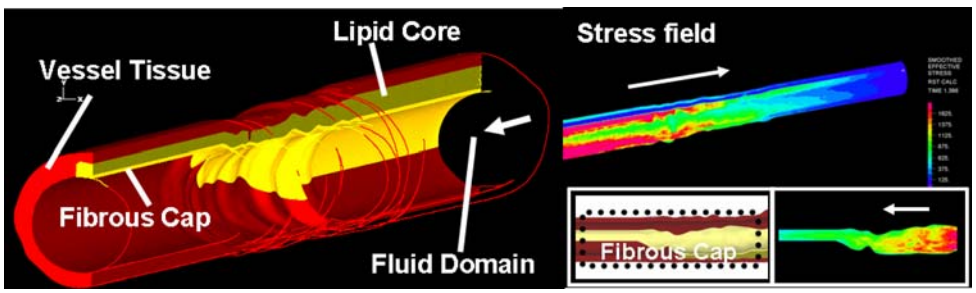

Fig. 2 Using the IVUS modality, a patient-based model of vulnerable plaque (VP) was reconstructed containing essential structures of a pathological coronary vessel. The patient-based VP includes a *lipid core*, a *fibrous cap* with 65-μm thickness, vessel wall with anisotropic properties, and the blood lumen. The results of FSI patient-based simulations show stress concentration developing within the fibrous cap around the plaque's lipid core. This increase of the stress concentration at the proximal side of the fibrous cap indicates an increase of the VP risk of rupture. *On the left*, the complete model is shown containing the basic structures of the pathological coronary vessel. *On the right*, the stress field is presented at the peak of the systole. The detail shows the stresses on the thin fibrous gap region. The *arrows* in the figure represent the flow direction

can be correlated with measurable changes in plaque character and clinical outcomes. The implications for characterizing the many asymptomatic lesions encountered in the atherosclerotic patients are significant. We are currently undertaking such preliminary studies. We have already incorporated in our modeling sophisticated anisotropic material models that take into account fiber orientation within the vessel wall, and fitted the model dynamic behavior to published experimental data of specimens that were tested with biaxial stretching. While these specimens are not necessarily patient specific, they significantly improve our ability to more faithfully characterize the plaque properties and bring the FSI models closer to the clinical domain.

3 Coronary artery disease

Coronary artery disease, characterized as stenosis by atherosclerotic plaque, is the leading cause of cardiovascular disease and death in the Western hemisphere, accounting for almost one in four deaths annually in the US. It remains the major cause of sudden and premature death among American adults aged 35 or greater [24]. Diagnosis and evaluation of coronary artery disease has traditionally been based on evidence of ischemia either at rest or after cardiac stress. Modalities to detect ischemia include electrocardiography, echocardiography, and cardiac nuclear perfusion scans. While these studies identify global or regional ischemia, they must be combined with angiographic studies, catheter-based coronary angiography and, more recently, thin-sliced gated CT coronary angiography, to pinpoint lesions that require treatment. This approach requires sequential rather than real-time evaluation; that is, physiologic imaging followed by anatomic definition of lesions. Decisions to intervene on a specific anatomic lesion are based on two-dimensional measurements of anatomic stenosis, as is the case with carotid angiography.

Aside from the fact that significant inter- and even intra-observer variability exists in the determination of degree of stenosis in coronary lesions (>10%), the hemodynamic consequences of an individual coronary lesion are the result of multiple factors. Such factors include the diameter of stenosis, length of stenotic segment, character of the lesion, and degree of collateral circulation. Although it may be a relatively straightforward decision to treat a 90% diameter stenosis or occlusion in a major epicardial artery, the decisions regarding more moderate lesions are more difficult, and the results less uniform. It is known that many moderate stenoses may result in ischemia, either from progression of unstable plaque or because of inadequate collateral circulation. Nonetheless, a policy of routine intervention in all moderately stenotic lesions, just as treatment of all carotid stenoses >60%, will result in significant overtreatment with unnecessary increases in both health care costs and procedural morbidity. New diagnostic modalities that combine anatomic and physiologic measurements in real time have the potential to increase the specificity with which lesions requiring intervention can be identified.

One of these modalities is intravascular ultrasound (IVUS). This technology, which integrates an ultrasound probe on the tip of a diagnostic catheter used during coronary angiography, allows analysis of coronary plaque composition. Analysis similar to that described above for carotid atheroma can be performed, including plaque composition (calcium, lipid, fibrous tissue, and thrombus), lumen contour, lesion length, and thickness of the fibrous cap covering the plaque. Combining anatomic and hemodynamic data should allow one to identify coronary plaques associated with increased risk of rupture or expansion due to intraplaque hemorrhage. Such lesions can be selected for treatment, while lesions with less potential risk may be observed unless they produce distal ischemia. While IVUS is of great potential importance, its invasive nature limits the ability to perform serial measurements of specific lesions. Rather the investigator must rely on global measurements of ischemia or clinical outcomes, neither of which can be confidently attributed to changes in a specific anatomic location. Clinical correlations and proof of concept will be more difficult to establish in the coronary circulation than at the carotid bifurcation.

A second catheter-based technology measures pressure and flow proximal and distal to a coronary stenosis at the time of coronary angiography [17]. The purpose of this technology is to detect the hemodynamically significant changes associated with a specific coronary lesion. A pressure transducer or a Doppler flow probe is placed on the tip of a coronary wire, and measurements of pressure and flow (Doppler velocity) are made at baseline and after hyperemia induced with adenosine. In normal coronary arteries, flow will increase by three- to five-fold after infusion of a vasodilator, and pressure will not drop significantly. When a hemodynamically significant stenosis is present, the flow increase with vasodilators is reduced, the drop in distal perfusion pressure exaggerated, and a Doppler velocity elevation occurs distal to the stenosis.

Three indices are derived from measurements of pressure, flow, and Doppler velocity proximal and distal to a stenosis: coronary flow reserve (CFR), fractional flow reserve (FFR), and hyperemic stenosis resistance (HSR) [35, 37]. CFR is expressed as the ratio of flow at maximal hyperemia to flow at baseline. It is a summed response of both epicardial and microcirculatory resistance. CFR is normally in the range of 2.7–5.0 and decreases as the severity of stenosis increases. CFR depends on multiple factors, including contractility, preload, and heart rate. Because of this, and the fact that it

reflects a sum of both epicardial and microcirculatory resistance, it cannot be used as the sole measure of a specific lesion's hemodynamic significance. However, a CFR of >2.0 is predictive of normal myocardial perfusion. This measure is most suited to evaluate the state of the microcirculation in the presence of non-obstructed coronary arteries. FFR, which is the ratio of flow with stenosis to flow without stenosis at maximal hyperemia, is independent of changes in heart rate or central hemodynamics. Practically, FFR is calculated by the ratio of pressure proximal and distal to a specific stenosis after infusion of adenosine to achieve maximum hyperemia. It is a highly reproducible measurement, and is independent of gender, hypertension, or diabetes. The normal value for FFR is 1.0 and ratios of >0.8 are correlated with absence of inducible ischemia with a sensitivity of 90%. Furthermore, FFR can be calculated separately for coronary artery, myocardial and collateral flow compartments. HSR is calculated by dividing the difference between the proximal pressure (P_a) and the pressure distal (P_d) to the stenosis at maximal hyperemia by the mean velocity (mV) at hyperemia (i.e., $P_a - P_d$/mV). Like FFR, this measure is independent of baseline hemodynamic conditions. The normal value for this ratio is 0.0. HSR is useful in evaluating lesions before and after interventions (percutaneous transluminal coronary angioplasty), and is most useful when the results of CFR and FFR are discordant [35, 37].

This technology of velocity and pressure measurements using a coronary wire at the time of angiography is most useful in evaluating "moderate" lesions of borderline hemodynamic significance (i.e., 40–60%), long lesions, and multiple diffuse stenoses [21]. The technology has been applied to identify lesions for intervention, check the success of intervention, and determine which of multiple lesions should be targeted for therapy. Clinical trials have shown that using the indices derived from this technique can predict which "borderline" lesions require intervention to allow targeted therapy and, in addition, can predict long-term outcome after intervention [21].

4 Aortic aneurysm disease and rupture

Aneurismal dilation of the aorta occurs in 2–4% of males over the age of 65 in the Western world. The disease is increased in patients who have evidence of coronary, carotid, or peripheral vascular disease, a history of smoking, or a family history of aneurismal disease [39]. Recently, routine ultrasound surveillance screening for abdominal aortic aneurysm has been recommended for males over the age of 65 and selected high-risk females [33]. The major morbidity of aneurismal disease is rupture, which is associated with mortality rates of 50–75%. Prophylactic intervention to prevent aneurysm rupture is recommended for patients whose annual risk of rupture exceeds the risk of operation (2–5%). Rupture risk is generally correlated to maximal aneurysm diameter; consequently, this parameter has been used to determine the need for intervention. Current recommendations, based on prospective studies, indicate that aneurysms should be repaired when the maximal diameter exceeds 5.0–5.5 cm [18, 23]. However, as is the case with other atherosclerotic conditions, the development of symptoms (in this case rupture of the aneurysm) is multifactorial, and an absolute correlation between size and risk of rupture is impossible to obtain [14]. Important variables expected to influence rupture risk include the configuration of the aneurysm (fusiform vs. saccular), the size of the normal adjacent aorta, vessel tortuosity, and the presence or absence of thrombus and calcium.

The ability to estimate the rate of aneurysm progression is also of great clinical importance. As is the case with carotid stenosis, initial aneurysm size is a major determinant of progression, with average aneurysm expansion rates of about 10% diameter per year [33, 39]. However, individual patient risk factors, vessel angulation, and hemodynamic forces undoubtedly influence this process. In Figs. 3 and 4, two different aneurysm configurations are displayed. It is easy to imagine that each of these configurations would have a different risk of rupture or progression, even though the absolute diameter may not differ dramatically.

Fillinger et al. [7, 36] have studied the impact of wall stress on aneurysm rupture and progression, using 3D CT reconstructions and static modeling of stresses developing within the aneurismal wall. Their analysis has focused primarily on how these stresses related to diameter. We have used a more advanced FSI modeling approach to determine both wall shear stresses and von Mises' wall stresses in aneurysms of differing configurations, both with and without thrombus [4]. Complex flow trajectories within the AAA lumen indicated a putative mechanism for the formation and growth of the intraluminal thrombus (ILT). The resulting magnitude and location of the peak wall stresses was dependent on the shape of the AAA. Out data suggest that while thrombus does not significantly change the location of maximal stress in the aneurysm, the presence of thrombus within the AAA may reduce some of the stress on the wall. Accordingly, inclusion of ILT in stress analysis of AAA is important and will likely increase the accuracy of predicting the risk of AAA rupture. We have recently performed additional dynamic fluid structure interaction (FSI) numerical studies using anisotropic specimen based material models, where patient specific 3D geometries were reconstructed from CT scans (Fig. 3).

We have additionally incorporated wall calcification into our models [29]. Our simulations clearly indicate that isotropic hyperelastic models that are widely used even in the more sophisticated FSI simulations underpredict the

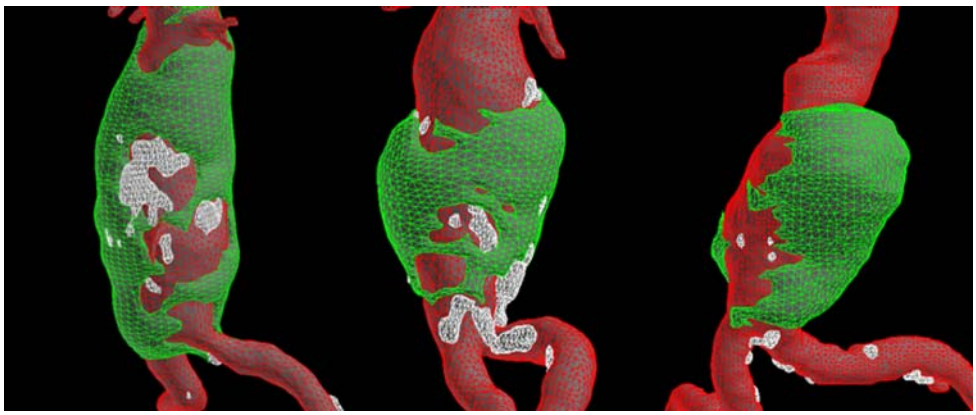

Fig. 3 Three different triangulated volumes of abdominal aortic aneurysm configurations are displayed. The intraluminal thrombus (ILT) and lumen volumes are presented with *green* and *red colors*, respectively. The *white structures* represent the wall calcifications (color in online version)

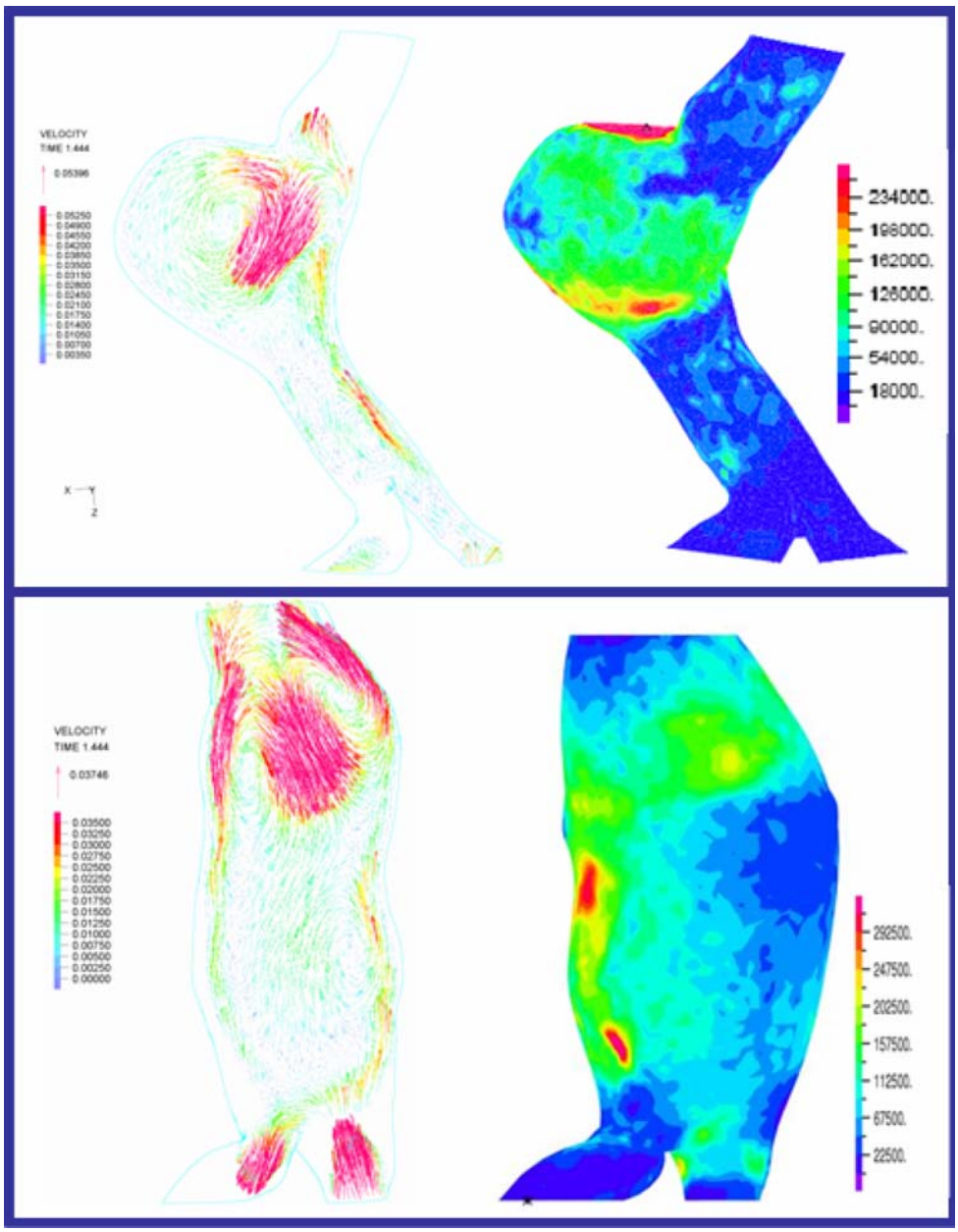

Fig. 4 Two representative FSI studies of a saccular aneurysm (*top*) and a fusiform aneurysm (*bottom*). The velocity field in the lumen and the stress field on the wall at peak systolic pressure are presented for both aneurysms. The maximum stress was 414.3 kPa, and the minimum stress was 217.0 kPa for the fusiform aneurysm using an anisotropic material formulation. The maximum stress was 272.1 kPa and the minimum stress was 166.4 kPa for the saccular aneurysm using an anisotropic material formulation. More details for these FSI simulations can be found elsewhere (P. Rissland et al. [29])

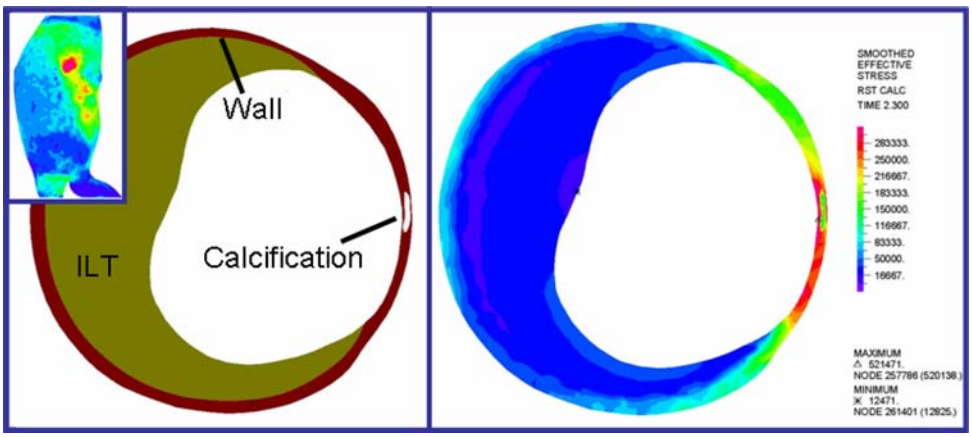

Fig. 5 The figure presents a cross-sectional area of the patient specific abdominal aortic aneurysm (AAA) shown in the detail on the *top left corner*. The modeled AAA is composed of the thin tissue wall with estimated thickness of 2 mm, *red* in the *left* figure. The ILT is presented in *yellow*, and the calcification embedded in the wall is *colored white*. On the *right side*, the stresses extracted from the FSI patient-based approach are presented. It is observed that the stress is very high in the area of the calcified spot, and has its lowest value in the ILT. This simulation predicted a peak stress of 0.65 MPa versus the simulation without the embedded calcification in which the peak stress was 0.5 MPa, representing a 30% increase of the peak stress (color in online version)

stresses developing within the aneurismal wall, as compared to those predicted by anisotropic models. Thus they may underpredict the AAA risk of rupture. While efforts carried out by us and by several groups are still in a nascent stage, and necessarily many complex aspects may need to be excluded to make the modeling feasible, they still hold a great promise for evaluating a variety of patient specific variables in a model designed to depict the progression of the disease; by predicting the risk of expansion and rupture of a particular aneurysm and by helping the clinician to determine whether a surgical intervention is warranted. Further, these models may be used to determine the influence of a variety of potential interventions, from tight blood pressure control to the placement of endovascular grafts, on aneurysm growth and remodeling.

There are a number of problems which are associated with the current modeling techniques. These include difficulty of accurately determining wall thickness, the mechanical properties of the arterial wall and underlying thrombus, and problems associated with estimating the effect of wall calcification on wall distensibility and strength. Modeling efforts to date have for the most part been based on idealized models which assume uniform properties of the aneurysm wall, even though it is clear that this is not the case. Since aneurismal disease is an intrinsically degenerative process, wall thickness is likely to vary considerably from one aneurysm to another and indeed within given areas of a single aneurysm. Wall thickness is difficult to measure with precision given the limits of resolution associated with current imaging techniques. Similarly, since aneurismal degeneration involves disruption and degradation of the elastic lamellae, one cannot extrapolate the elastic properties of normal arterial wall to the aneurismal condition. Compounding this is the patchy distribution of calcium throughout the aneurysm wall and indeed within the thrombus at times. Finally, the composition of intraluminal thrombus is known to vary from aneurysm to aneurysm and within one aneurysm from one location to another. While these issues are daunting when viewed collectively, some approaches are available to address them. The issue of wall thickness may be difficult to resolve but with the exception of inflammatory aneurysms differences may not be great. Gated imaging techniques, comparing changes in lumen, wall and thrombus between systole and diastole may allow estimates of "distensibility" of both the wall and thrombus. Such measures may be the best that can be done to estimate in vivo mechanical properties of the arterial wall. For the present, efforts are limited to idealized models which study broader issues of the relationship of intraluminal thrombus, arterial tortuosity and calcification to shear and wall stress. Fortunately, there is much work to be done to answer even these broad questions (Fig. 5).

5 Aortic dissection

A third important clinical area is that of aortic dissection. Aortic dissection has an incidence of approximately 1 in 10,000 populations per annum, and is increased in older age groups [11]. There is good reason to believe that the condition is under-reported. An aortic dissection occurs when the tunica media of the artery is disrupted, and the arterial wall splits through the media. Under conditions of flowing blood, this may progress distally for an unpredictable length of aorta until there is either rupture through

the adventitia of the vessel or "re-entry" into the true lumen of the vessel by a more distal intimal "re-entry tear." This condition results in a complex pathology in which different pressures are present in the "true" and "false" lumina which may result in true lumen compression and occlusion of aortic branches. The mortality of this condition is high, with major complications including rupture and end-organ ischemia. Some authors estimate that mortality increases at the rate of 1% per hour once the diagnosis or aortic dissection is made [7]. Both medical and surgical treatments remain associated with significant short- and long-term complications. Recent introduction of endovascular stent grafts offered some hope of reducing the complication rates of surgical intervention, but a prospective randomized trial of endovascular grafts versus medical management failed to show significant benefit of a routine surgical approach [5, 26].

Treatment of aortic dissection is an ideal place for patient specific diagnostic image analysis. Such analysis would take into consideration the unique aortic geometries defined by the location of the dissection, site of the original entry tear, length of the lesion, and relative size of the true and false lumina. In addition, such modeling could evaluate the efficacy of medical management such as beta blockade on lesion progression. While we have not as yet engaged in efforts to study this process, it is an ideal area for future investigation.

6 Conclusions

Cardiovascular diseases are one of the most common pathologies encountered in our modern world. Cardiovascular pathology is widespread, particularly in an aging western population. In the majority of cases, lesions remain asymptomatic for long periods of time until they result in sudden and often catastrophic events such as stroke, myocardial infarction and hemorrhage. Current therapeutic decisions are often made based on the desire to prevent symptoms from occurring rather than to treat symptoms themselves. The current approach, which often identifies and treats lesions at an asymptomatic stage, is insufficiently specific. Furthermore, current cardiovascular diagnostics are usually unidimensional, i.e., either anatomic, hemodynamic or occasionally physiologic. As such, each diagnostic modality provides only one perspective of a complex and dynamic process. Disease progression and the development of symptomatic conditions both depend on a dynamic interplay of forces including vessel wall geometry, systemic and local flow conditions, collateral circulation and arterial wall composition. Many current diagnostic methods lack the specificity and sophistication to readily integrate these data into real-time decision making algorithms. The combination of anatomic and hemodynamic information combined with the use of computer generated modeling offers the potential for lesion-specific therapeutic decisions, i.e., "patient specific diagnostics". These models may also provide the basis to test various existing and new treatment algorithms for the prevention and treatment of cardiovascular disease.

This discussion has centered on the potential use of new technology to refine diagnosis of lesions. We have not discussed the role of these techniques in studying the pathophysiology of atherosclerotic disease and modeling the effects of treatment. Computer models may help define the effects of specific operative and non-operative interventions on disease progression. Some of the techniques mentioned above are already being used to evaluate the success of coronary angioplasty. It is easy to imagine computer modeling applied to predict the response of peripheral vascular lesions to placement of open or covered stents. The relative propensity for different morphologies to remodel after intervention is an area ready for investigation. In a similar manner, these technologies offer the future prospect of predicting the effect of altering plaque characteristics or hemodynamic conditions on the progression or regression of disease. It may be possible in the future to target specific lesions for specific interventions such as lipid lowering therapy, antihypertensive therapy, angioplasty, stent placement or operative intervention. While this may seem fanciful at the present time, it is not at all out of the realm of possibility in the not too distant future.

New diagnostics will need to incorporate the characteristics of the diseased arterial wall (thrombus, lipid core, calcification, elasticity), and account for hemodynamic forces that influence the lesions microenvironment. Developing diagnostic algorithms which predict individual lesion instability and progression will allow targeted therapy based on the individual lesion in question. Use of these diagnostics after intervention would allow assessment of the interventions effectiveness of lesion risk.

Current clinical management of cardiovascular pathology is based on relatively sensitive but non-specific diagnostic testing. While this allows detection of a larger number of patients with disease, it also results in overtreatment of many patients who are and may remain asymptomatic. Furthermore, therapeutic decisions are made based on data which markedly oversimplify a complex and dynamic process of disease. Diagnostics which incorporate and integrate a greater amount of the diverse factors controlling the processes associated with cardiovascular disease will provide increased specificity for more targeted and appropriate therapy in the future.

The approaches discussed in this article are aimed at predicting theoretical behavior of atherosclerotic lesions

using certain assumptions under idealized conditions. While these efforts may provide potential novel insights into the pathophysiology of atherosclerotic processes and identify mechanisms for treatment, their conclusions must be tested empirically.

Determining the ultimate utility of this approach will require prospective correlation both with clinical outcomes and changes in lesions over time, since they are designed to predict future events in presymptomatic lesions. Longitudinal clinical and anatomic correlations are essential. This is most easily done in the areas of carotid bifurcation atherosclerosis and progression of aneurismal disease. These two clinical conditions are widely prevalent in a presymptomatic condition in the older population and both are amenable to repeated non-invasive imaging over time. Follow-up of these lesions in their presymptomatic state is common and accepted medical practice. While aortic dissection is somewhat less common, regular medical follow-up is recommended for most distal ("Type B") dissections and non-invasive imaging with CT or MR techniques is the current standard of care. While the need for better diagnostics in the coronary circulation is equally important, the ability to obtain similar longitudinal data in the coronary circulation presents a greater challenge.

We envision a patient-based diagnostic tool to integrate medical imaging, e.g., CT and Doppler ultrasound, with cutting edge numerical modeling to, e.g., accurately predict the risk of rupture in AAA. This will provide clinicians and surgeons with a refined diagnostic and decision toolkit to determine the need for a surgical intervention. The clinical endpoint will be achieved with a fully integrated system of imaging/modeling to depict the pathology and quantify its mechanical properties under hemodynamic conditions. With the maturing of this technology, the clinician will obtain within a few hours a fully dynamic and quantitative depiction of the pathology. Furthermore, it will be capable of predicting changes in vascular pathologies resulting from alternate therapeutic interventions for individual patients, pointing to preferred approaches. This innovative methodology will have a major impact on the clinical treatment of patients with occlusive and aneurismal cardiovascular diseases, by determining the need for elective surgery, evaluating alternative therapies, improving the surgical outcomes, and reducing mortality rates and ensuing healthcare costs.

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