New Approaches to Abdominal Aortic Aneurysm Rupture Risk Assessment
Engineering Insights With Clinical Gain

Timothy M. McGloughlin, Barry J. Doyle

Abstract—Abdominal aortic aneurysm (AAA) remains a significant cause of death in the developed world. Current treatment approaches rely heavily on the size of the aneurysm to decide on the most appropriate time for clinical intervention and treatment. However, in recent years, several alternative rupture risk indicators have been proposed. This brief review examines some of these new approaches to AAA rupture risk assessment, from both numeric and experimental aspects and also what the future may hold for AAA rupture risk. Although numerically predicted wall stress, finite element analysis rupture index, rupture potential index, severity parameter, and geometric factors, such as asymmetry, have all been developed and show promise in possibly helping to predict AAA rupture risk, validation of these tools remains a significant challenge. Validation of biomechanics-based rupture indicators may be feasible by combining in vitro modeling of realistic AAA analogues with both retrospective and prospective monitoring and modeling of AAA cases. Peak wall stress is arguably the primary result obtained from numeric analyses; however, as the majority of ruptures occur in the posterior and posterior-lateral regions, the role of posterior wall stress has also recently been highlighted as potentially significant. It is also known that wall stress alone is not enough to cause rupture, as wall strength plays an equal role. Therefore, should a biomechanics-based rupture risk be implemented? There have been some significant steps, both numerically and experimentally, toward answering this and other questions relating to AAA rupture risk prediction, yet regardless of the efforts that are under way in several laboratories, the introduction of a numerically predicted rupture risk parameter into the clinicians’ decision-making process may still be quite some time away. (Arterioscler Thromb Vasc Biol. 2010;30:00-00.)

Key Words: aneurysms ■ risk factors ■ experimental modeling ■ numerical modeling ■ review ■ rupture risk

Approximately 81 million people in the United States are currently living with one of the many forms of cardiovascular disease. Of this affected population, it is estimated that about 900,000 will die each year. Abdominal aortic aneurysm (AAA) is a dilation of the aorta beyond 50% of the normal vessel diameter, and it accounts for approximately 15,000 deaths per year in the United States.1 AAA rupture risk is typically determined by size, and it has been shown that in the 5 years following AAA diagnosis, rupture occurs in approximately 2% of AAAs less than 4 cm in diameter and in more than 25% of AAAs larger than 5 cm.2,3 Current clinical practice is to surgically repair large AAAs (diameter >5.5 cm) if the patient is fit for surgery or to regularly monitor (eg, every 6 months) smaller AAAs (diameter <5.5 cm) with ultrasound, with referral for surgery if the growth rate exceeds 1 cm/year or the diameter exceeds 5.5 cm.3 However, surgeons need to compare the risk of rupture with the risk of repair, as it has been reported that only 25% of AAAs rupture in a patient’s lifetime,4,5 and there can be serious complications with both open repair and endovascular aneurysm repair.

Recent research has cast doubt over the suitability of surgical repair based solely on the maximum diameter criterion.6–17 It is known that small AAAs can rupture and large AAAs can remain stable; therefore, many believe that factors other than size should be considered. Some interesting rupture risk parameters have recently emerged as alternatives to AAA size. AAA wall stress,7,8 vessel asymmetry,11 finite element analysis rupture index (FEARI),12 rupture potential index (RPI),9 severity parameter (SP),10 growth of intraluminal thrombus,18 and a method of determining AAA growth and rupture based on mathematical models19,20 have all been proposed as useful adjuncts to AAA size, yet all require extensive validation before they can be clinically accepted. Several of these newer approaches to rupture risk rely on biomechanics and numeric models to quantify the threat. In particular, finite element analysis (FEA) has been extensively used to determine the distribution of wall stress in the
aneurysm and has revealed some interesting correlations with both AAA asymmetry and AAA geometry. Overall AAA wall stress has been shown to be independent of maximum diameter, hence the general understanding that more than size alone should be considered in rupture risk evaluation. This article reviews some of the more recent advances in both numeric and experimental engineering methodologies used to investigate the possible rupture risk of patient-specific AAAs.

Computational AAA Rupture Risk

The law of Laplace states that there is a linear relationship between diameter and wall stress and is often applied to AAA to calculate the mechanical stress acting on the vessel wall. However, the law of Laplace is based on cylindrical geometries, whereas AAAs are complex structures, and therefore the law fails to predict realistic wall stresses. Stringfellow et al applied FEA to the problem to determine wall stress and paved the way for the extensive research into numerically predicted AAA wall stress that is currently being performed. It was concluded in this article that FEA (and therefore computational modeling) is a versatile tool for use in the study of vascular mechanics and may be potentially more useful than size alone in determining the clinical significance of AAAs. That work, however, used idealized AAA models, whereas actual AAAs are typically highly irregular structures, and the wall stress is not evenly distributed. Since the late 1980s, the use of FEA has proven to be a very useful method in determining patient-specific AAA wall stress and has also been coupled with computational fluid dynamics to provide more accurate estimations of the AAA wall stress though fluid-structure interaction techniques. However, there are still mixed opinions as to the possibly insignificant increase in wall stress accuracy when using fluid-structure interaction compared with the very significant increase in computational time. The use of computational fluid dynamics has proven effective in analyzing the hemodynamics of AAAs and has resulted in a new tapered graft design that may help reduce the blood flow problems and biomechanical performance associated with traditional stent-graft designs.

Numerical modeling has repeatedly highlighted the pitfalls of solely using the diameter criterion. Fillingler et al demonstrated that peak wall stress may be a better indicator of rupture than diameter, and it has since been reported by several groups that equivalent diameter AAAs may have largely different rupture potentials. Also, it has previously been shown that AAA wall strength can vary significantly within a particular aneurysm, and therefore to fully understand the likelihood of rupture based on peak wall stress, the AAA wall strength must also be considered. A biomechanics-based rupture-prediction tool was recently developed by the authors, whereby FEA-computed peak wall stress is coupled with the wall strength of that region determined by mechanical testing. This method is termed the FEARI and is based on the definition of material failure; that is, an AAA will rupture when the local stress exceeds the local strength. The FEARI returns a simple rupture index by dividing the peak wall stress by the strength at that location with values close to 1, indicating a high rupture risk, and 0, indicating a low rupture risk (Figure 1). When FEARI results were compared between electively repaired (n=42) and ruptured (n=10) AAA cases, FEARI was significantly higher in the ruptured group (FEARI=1.01±0.43 vs 0.66±0.3, P=0.018). The FEARI predictive tool indicated that not all of the cases examined may have required surgical intervention and revealed that AAAs with similar diameters may have markedly different rupture potentials, therefore implying that maximum diameter is not a "one-size-fits-all" approach to AAA management. This approach relies on mechanical testing of AAA tissue and therefore is dependent on the accuracy of the mechanical test to represent patient-specific tissue strength. A significant limitation of this rupture index is the low numbers of tissue samples tested. The strength component of the model is based on published literature, specifically tensile test data obtained from 149 AAA tissue samples harvested from 69 patients. Mechanical data for AAA tissue are difficult to obtain, primarily because the majority of AAA cases are repaired using minimally invasive techniques, and therefore the abdomen is not opened. Also, excised tissue samples are usually harvested from the anterior regions of the AAA, as there are increased surgical complexity and risks associated with tissue removal from the posterior regions of the aneurysm. If a large, multicenter study could actively seek AAA tissue for mechanical testing, the population-based accuracy of the model could be further enhanced, thus improving the FEARI.

Another biomechanics-based rupture index has also been suggested and may be more clinically applicable than FEARI. The RPI, which was developed by the Vorp group at the University of Pittsburgh, uses a combination of experimental tensile testing and statistical modeling to predetermine the wall strength on a patient-specific basis, with wall stress then predicted using FEA. Although both FEARI and RPI are similar in their working hypotheses, RPI uses a more sophisticated technique to determine wall strength. The strength of AAA tissue is calculated using parameters such as age, sex, smoking status, family history of AAA, normalized diameter, and the maximum thickness of the intraluminal thrombus. RPI was reported to possibly identify high rupture risk AAAs a priori better than either diameter or peak wall stress alone (Figure 2). The potential of RPI to become a useful rupture-prediction tool may be significant, although the approach requires extensive validation before it can be considered in a clinical setting.

Kleinstreuer and Li have reported a novel rupture risk tool that incorporates 8 weighted biomechanical parameters that return a dimensionless SP. They reported that their SP may be clinically applicable and were able to show how the SP values of 3 different AAA cases available in literature were similar to the actual clinical decisions of either "waiting for repair" or "possible rupture." The same authors have also reported, in a separate publication, an equation that can predict the maximum wall stress of an AAA to within 9.5% of that computed using FEA. The 9.5% difference was obtained by applying their new equation to 10 different AAAs previously reported in the literature. This novel equation is an adaption of the law of Laplace, which takes into account geometric ratios and parameters, as well as the
maximum vessel diameter and the blood pressure of the patient. The accuracy of these 2 approaches reduces greatly with geometric complexities, and also these tools fail to comprehensively determine the likelihood of rupture. As with all computational tools, there is a need to determine the clinical feasibility of using such methods to assess rupture potential.

More than 3 decades ago, Darling et al reported that 82% of AAA ruptures occur along the posterior and posterolateral wall. As the majority of ruptures occur in the posterior regions, the wall stress acting on these regions may have clinical relevance. This hypothesis encouraged research into the influences on posterior wall stress, and it was found that the asymmetry of the AAA is strongly related to the posterior wall stress distribution. In that report, the authors developed a simple method of measuring AAA asymmetry and observed that inflection points, which are regions where the curvature changes from concave to convex, were deemed to be the likely regions of peak or high wall stress, observations that have been noted in other studies. The work postulated that asymmetry could become a useful addition to diameter in determining AAA severity. Others have also recently examined the role of geometry on AAA wall stress by measuring the tortuosity instead of the asymmetry in 19 patient-specific cases. In that study, the authors conclude that diameter does statistically influence peak wall stress but that tortuosity may also affect wall stress. Although clinicians do consider AAA geometry when determining the likelihood of rupture, they may often be interpreting the geometry with endovascular aneurysm repair in mind rather than in relation to the effect on wall stress. Geometry plays a vital role in wall stress distributions, and the results of a patient-specific stress analysis may serve as useful decision aides for the clinician.

Experimental validation of biomechanical approaches to rupture assessment may be possible through the use of the experimental methodologies developed and reported previously. It is now possible to create patient-specific rubber AAA models that are nonuniform in wall strength similar to the in vivo situation. These models can then be studied using the rupture technique reported by the authors. Identifying the rupture locations of these experimental models and comparing them with the numerically predicted rupture site using biomechanical models may help toward in vitro validation. Preclinical validation, however, is difficult to achieve and significantly more costly. Retrospective clinical validation may be made possible by predicting the rupture threat using the proposed biomechanics-based indicator and applying this model to AAAs that have previously ruptured. By comparing the rupture prediction with the
actual clinical outcomes, it may be possible to show that certain ruptured AAAs have significantly higher rupture risk indices compared with electively repaired and monitored cases.

It may also be possible to prospectively validate these tools by monitoring the biomechanics-based rupture threat in patients who are followed over time. Suitable candidates who could be included are patients who have small AAAs (diameter <5 cm) and are regularly monitored for AAA enlargement, patients who refuse surgery, and those patients who are high risk and advised against surgical intervention. This cohort could be followed until their AAA either ruptures or becomes symptomatic. Biomechanical rupture risk models could be calculated at every time point using the CT images, and values could be compared over time. Rupture indicators could be inspected for correlation with growth patterns and clinical events and may ultimately work toward the clinical validation of these new tools.

There are of course some limitations to the clinical validation strategies of these biomechanical rupture risk parameters. Firstly, clinicians will always feel that large AAAs should be treated if the patient is fit for surgery. Large AAAs are an obvious clinical concern, with statistics placing them in the high-risk category, regardless of biomechanical indices. Conservative management of these cases could possibly result in fatal circumstances, and therefore biomechanical parameters should always be used in conjunction with not only AAA size but also, and possibly more importantly, clinical judgment. Computational rupture risk indices may be reserved for small to medium-sized AAAs where regular monitoring is involved before ever being considered for large AAAs.

**Experimental AAA Rupture Risk**

Experimental methodologies do not receive the same attention as numeric techniques in relation to AAA rupture risk, partially because of the labor intensity of manufacturing patient-specific AAA models, performing experiments, and ensuring significance of results through repetition and accuracy. Numeric modeling, on the other hand, is relatively quick to perform, and changes can be easily incorporated into models through parameter-based modeling packages. Nonetheless, computationally determined rupture-prediction must be thoroughly validated before clinical acceptance and for such an approach to demonstrate the level of robustness needed for clinical adoption. It is at this stage that experimental AAA rupture risk may play a key role. To facilitate validation of numeric models, it is now possible to create patient-specific experimental AAA models by rapid prototyping or injection molding with the latter technique shown to create repeatable anatomically correct benchtop models for a variety of in vitro modeling applications. To develop accurate representations of the AAA wall, a technique has been reported that can manufacture silicone AAA models with random or controlled material properties, with methods in place to nondestructively assess these material properties. It has also recently been demonstrated that the intraluminal thrombus, which may significantly influence the rupture site, can be included in experimental models. These benchtop AAA analogues can be used to determine rupture locations and validate numerically predicted burst sites.

Experimental rupture modeling was initiated with idealized AAA geometries and progressed to include realistic cases. This seminal work used high-speed photography to capture the rupture site and showed that AAAs rupture at inflection points and not at regions of maximum diameter. Similar observations have been reported throughout numeric studies in the literature, which have shown that inflection points exhibit higher wall stresses than the maximum diameter regions. Each experimental model was imaged using CT before testing to generate accurate numeric reconstructions for validation purposes using previously reported 3D reconstruction techniques and the commercially available software Mimics (Materialise). Rupture occurred at the location of numerically predicted peak wall stress in 80% of cases and at high, but not peak, stress regions in 10% of cases. These sites were also shown to be regions of complex gaussian surface curvature and correlated well with the stress patterns observed using photoelastic stress analysis on the same geometry. Good agreement was found among FEA-predicted wall stress, experimental rupture site, numerically predicted surface curvature, and experimental wall stress (Figure 3). The remaining 10% of models examined in this study had defects in the AAA wall, which shifted the rupture location away from regions of elevated wall stress to that of the defect. Wall defects are also likely to affect rupture location in vivo, as it was shown that the location of peak wall stress is not the rupture site in the presence of aortic blebs. The methods and techniques reviewed here represent some of the more significant steps in assessing AAA rupture in vitro, an area of research that, as mentioned previously, receives minor attention.

**The Future of AAA Rupture Risk**

AAA rupture threat is currently the subject of intensive research, with many aiming to prove that numeric models,
and ultimately a biomechanics-based approach to rupture prediction, may have clinical relevance. As the volume of reports highlighting the inadequacies of the maximum diameter criterion grow, clinicians may become more aware of the ease with which alternative rupture risk parameters can be incorporated into the decision-making process. Several of the recently proposed risk indicators may be useful additional tools for the clinician and complement the current use of maximum diameter and growth rate. These new tools can return recommendations in as little as a few hours after medical imaging, depending on the tool used and the facilities available. Validation of numeric models, in particular FEA, has been performed in terms of quantitative wall stress correlations using idealized geometries and also qualitatively by correlating rupture locations and regions of curvature. However, the limitations of numeric modeling should be noted. An important limitation of FEA is that the approach does not take into account the hemodynamics of the situation, which can affect the forces exerted on the aortic wall. In recent years, many researchers have favored a fluid-structure interaction approach to aneurysm modeling yet the significant increase in computational time compared with the relatively small increase in wall stress accuracy remains in question. There are, however, many drawbacks to patient-specific numeric wall stress predictions that are applicable to all approaches. Aortic wall thickness still remains elusive from traditional CT and MRI images. Numeric modeling relies heavily on the assumed wall thickness of the model and is believed to be intrinsically related to the wall stress. Many researchers use a uniform wall thickness ranging from 1.5 to 2 mm, but it was shown that decreasing the wall thickness by 25% results in a 20% increase in peak wall stress and vice versa. It is also known that AAA wall thickness in vivo is nonuniform, ranging from 0.23 to 4.26 mm; therefore, in terms of patient-specific rupture-prediction, it is beneficial to incorporate nonuniform wall thickness into numeric models also. A reliable and robust method to extract wall thickness data from CT images is desirable and would significantly improve the current use of numeric modeling in AAA rupture assessment. Martufi et al recently described a method to determine wall thickness from CT images; however, the approach is yet to be validated. Arguably the most significant limitation of numeric modeling today is the inability to translate these approaches to the clinic. In a recent article, Neal and Kerckhoffs report on the current progress in patient-specific modeling and conclude that the incorporation of patient-specific modeling into the workflow of the clinician will require, among other things, regulatory approval by the relevant bodies, such as the US Food and Drug Administration. This represents another significant barrier to incorporating numeric modeling into everyday AAA clinical assessment; however, this barrier should not deter researchers from investigating the problem and developing new exciting ways to quantify rupture risk.

Advances in medical imaging have enabled several new approaches to be examined in relation to the better understanding of AAAs. A recent study by Tierney et al has explored the feasibility of using acoustic radiation force impulse imaging, which was developed at Duke University, to examine AAA mechanical properties. An artificially induced AAA model was analyzed using the acoustic radiation force impulse technique to study the effects of AAA on vascular elastic pathology. The mechanical changes produced in the artificially induced aneurysm were found to be detectable using acoustic radiation force impulse imaging. The technique was then further applied in another study to determine patient-specific AAA tissue strength using a previously diagnosed AAA patient. This preliminary investigation revealed that it was possible to excite the diseased aortic wall. However, at these realistic aortic depths, there are challenges in generating sufficient radiation forces to measurably displace this tissue. The technique appears to hold promise in determining patient-specific AAA material properties but requires further investigation. The application of
positron-emission tomography and CT to AAA assessment has gained interest recently after a preliminary investigation by Sakalihasan et al in 2002. It was demonstrated in 5 patients that high levels of 18F-fluorodeoxyglucose uptake in the AAA wall are associated with FEA-predicted wall stress (Figure 4). If indeed metabolic activity can be definitively correlated to wall stress in a much larger cohort of patients, positron-emission tomography–CT could become a useful tool in AAA assessment. Speelman et al recently examined the relationship between circulating biomarkers and FEA-predicted wall stress. That study analyzed matrix metalloproteinase-9, tissue inhibitor of the metalloproteinases-1, α1-antitrypsin, and C-reactive protein, all of which are biomarkers that are believed to reflect inflammation and degeneration in the AAA wall and influence AAA growth. The article reported, however, that there was no correlation between FEA-predicted wall stress and biomarker concentrations. Clearly there is a need to investigate these hypotheses further, in larger cohorts, to determine clinical applicability.

The contribution of MRI in assessing cardiovascular disease is also becoming evident. Not only can MRI provide flexible medical imaging without the significant radiation problems associated with CT, but it can also quantify blood velocities with quantitative magnetic resonance flow imaging using phase-contrast magnetic resonance angiography. However, although phase-contrast magnetic resonance angiography is accurate in measuring velocities of the blood, the approach cannot measure wall shear stress and is therefore most powerful when used as a precursor for computational models to provide useful inlet and outlet boundary conditions. It has recently been suggested that the inlet boundary condition may have important implications in cerebral aneurysm growth and also causes variations in skewness and recirculation of flow throughout AAAs. Dynamic imaging has also played a significant role in advancing AAA assessment. Much effort has focused on the effects of reconstruction and smoothing of computational models derived from both CT and MRI datasets, yet the requirement of smoothing is almost eliminated when reconstructions are based on more advanced forms of dynamic imaging techniques. CT scanners such as the Aquilion ONE 320-slice CT (Toshiba America Medical Systems Inc) are now capable of capturing entire organs in a fraction of a second, thus reducing exposure to radiation (which is thought to cause as many deaths per year as AAA rupture: ≈15,000 deaths) and creating 3D reconstructions of exquisite detail and accuracy. Numeric models derived from advanced dynamic imaging modalities may be one step closer to achieving a standardized platform from which numeric models can be developed, an important step if clinical approval of patient-specific modeling is desired.

There is a clear need to revisit and revise the current rupture risk parameters. Some useful adjuncts to AAA size have recently emerged, and with further validation, they may...
become clinically feasible. Biomechanical aspects of AAA rupture are important\footnote{1} and may improve the current approach to AAA assessment if models can be rigorously validated and if key opinion leaders can be convinced of the benefits. In a 2006 survey\footnote{2} of 392 vascular surgeons, more than 92\% of clinicians use maximum diameter and growth rate to determine surgical intervention, as is the standard current practice. Nineteen percent of clinicians were not aware that the biomechanics of the problem may be influential in rupture risk, and an additional 69\% were aware of biomechanics-based rupture risk but were not familiar with the approach.

Although there are some potential parameters that, once fully validated and tested, could readily be implemented into the clinical toolkit, it will be quite some time before use of these tools becomes common practice. However, with research efforts continuously striving to accurately understand AAA rupture risk on a patient-specific basis, the gap between experimental research and clinically feasible rupture risk tools is becoming smaller by the day.

Acknowledgments
We acknowledge Prof David Vorp at the University of Pittsburgh, not only for his role in our AAA research efforts but also for his contribution to the field of AAA biomechanics. We also acknowledge the Department of Vascular Surgery at the HSE Midwestern Regional Hospital, Limerick, Ireland, in particular Eamon Kavanagh, Prof Pierce Grace, Dr Peter Coyle, and Paul Burke.

Sources of Funding
This work was funded in part by Irish Research Council for Science, Engineering and Technology grant R2/2004/SP008 and by US National Heart Lung and Blood Institute grant R01 HL060670.

Disclosures
None.

References
55. Redberg RF. Cancer risks and radiation exposure from computed tomographic scans: how can we be sure that the benefits outweigh the risks? Arch Intern Med. 2009;169(22):2049–2050.
New Approaches to Abdominal Aortic Aneurysm Rupture Risk Assessment. Engineering Insights With Clinical Gain
Timothy M. McGloughlin and Barry J. Doyle

Arterioscler Thromb Vasc Biol. published online May 27, 2010; Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved. Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2010/05/27/ATVBAHA.110.204529.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/