≥ *Review Article* ≤

The Obsolete Maximum Diameter Criterion, the Evident Role of Biomechanical (Pressure) Indices, the New Role of Hemodynamic (Flow) Indices, and the Multi-Modal Approach to the Rupture Risk Assessment of Abdominal Aortic Aneurysms

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Although the therapeutic management of abdominal aortic aneurysms (AAAs) is currently based on the maximum diameter criterion, this has often proved inaccurate and misleading. Conversely, the biomechanical approach, which takes into account the pressure-induced wall stress exerted at every point throughout the aneurysmal surface, has been proven superior in predicting the rupture risk of AAAs, and its value is being increasingly recognized among physicians. More recently, hemodynamic indices, such as flow-induced wall shear stresses, have been indicated as potentially significant determinants of AAA natural history. Ultimately, a statistical model that takes into account all these factors may be relevant for making a sound prediction of the rupture risk of aneurysms and optimizing the management of these patients.

Keywords: abdominal aortic aneurysm, wall stress, shear stress, hemodynamics

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Introduction

Abdominal aortic aneurysm (AAA) is a disease of the elderly, which poses a significant risk for life and well-being in the aging population of the developed world.[1–3] An aneurysm is a balloon-like dilatation of a vessel that exceeds the maximum diameter of the adjacent normal artery by 50%. The abdominal aorta is the most common site of aneurysms in humans.[1,2] The feared complication of this condition is rupture, which despite significant progress in therapeutic modalities and interventions, is still accompanied by a striking overall mortality of 80%, although certain therapeutic algorithms have been proposed to result in better outcomes.[4–6] Accordingly, in the literature, a considerable effort has been made to identify the risk markers that indicate a high rupture potential and pinpoint the cases in need for elective treatment. The latter is accompanied by a periprocedural mortality rate of 1%–3%, which is in profound opposition with that of ruptured AAAs.[7–9] By contrast, these risks may be higher in compromised patients, reaching approximately 10% in specific subgroups of subjects.[10,11] Therefore, a meticulous estimation of rupture risk and a subsequent detailed weighing of possible procedural risks are fundamental to determining the optimal therapeutic management on a patient-specific basis. We have reviewed the current status, summarized recent advances, with a special interest in biomechanic and hemodynamic variables, and discussed future perspectives for the rupture risk estimation of AAAs.

Decision Making: Current Approach and Limitations

Current guidelines for the treatment of AAAs are solely dependent on the maximum diameter and growth rate criteria, and the global thresholds of 55 mm and 10 mm/year, respectively, are considered to indicate the need for intervention.[1,2,12] Nevertheless, it is now well understood

that this approach has several limitations and frequently leads to diagnostic failures and inaccuracies in the management of these patients.[13,14] Specifically, according to a contemporary systematic review, rupture rates for small AAAs under the threshold for surgical repair reached 1.61 ruptures per 100 person-years.[15] Furthermore, in a more recent report, Laine et al. examined a large cohort of ruptured AAAs and indicated that a remarkable 5.6% of men and 11.5% of women presented a maximum diameter of <55 mm and <52 mm, respectively, which are the thresholds for intervention, according to the European guidelines.[16] The law of Laplace, which is usually pointed out as the theoretical basis for the maximum diameter criterion, cannot be applied to evaluate the stresses exerted on the AAA walls for several reasons. Specifically, the AAA geometry does not involve a simple cylinder or sphere with a single value of radius and curvature, for which the Law of Laplace would be valid.[17] On the contrary, AAAs always present as complex shapes with major and minor curvatures that contribute to a mosaic of wall stress distribution throughout the aneurysmal surface.[17,18] Moreover, wall stress alone is insufficient to predict AAA rupture because this represents material failure that occurs when mechanical stress exceeds wall strength. Moreover, according to the biomechanical approach, rupture depends on the pinpoint comparison of strength and stress throughout the aneurysmal surface.

Biomechanical Approach: Role of Pressure-Induced Wall Stress

Subsequently, other tools have been developed to calculate the magnitude and distribution of wall stress and strength of the AAA wall. Finite element analysis (FEA) and fluid structure interaction (FSI) take into account the vessel geometry, boundary conditions, and arterial pressure and flow to provide a map of wall stresses.[19] FEA is a numerical method used to overcome the computational hazards due to the increased geometrical complexity of patient-specific AAAs. During this process, the three-dimensional AAA model is divided into a finite number of elements, and then, the behavior of each element or sub-region is examined. Given that these elements have a small size and simple geometric configuration, this is mostly straightforward. Subsequently, the whole system is resembled through the description of the behavior of all the elements taken together. During FEA, after being divided into a large number of finite elements, the AAA model is loaded with a uniform pressure, and a map of the displacement and wall stress distribution throughout the aneurysmal surface are obtained.[20] Despite the fact that most computational studies on AAAs use a uniform wall loading, this is actually not uniform because of the

presence of pulsatile blood flow. To deal with this phenomenon, FSI has been developed, during which a non-uniform pressure is applied to account for fluid dynamics and obtain a more realistic pressure distribution along the AAA surface. In general, the addition of blood flow is more realistic to structural analysis alone, but it requires increased computational time. Therefore, whether FSI improves simulations to such an extent that would justify the increased computational burden has not yet been definitively determined.[20] Several assumptions may hamper calculation and influence final values, but many studies have indicated the superiority of these indices compared with the simple two-dimensional maximum diameter criterion for differentiating between ruptured and non-ruptured AAAs and predicting high rupture risk over time.[21–25] In this regard, in a pioneer study published by Fillinger et al. in 2002, patient-specific AAA models were first used to indicate that peak wall stress (PWS) calculated in vivo was significantly higher in ruptured than in diameter-matched non-ruptured AAAs.[22] In a subsequent analysis, the same authors suggested that for AAAs under surveillance, PWS was a more sensitive marker of susceptibility to rupture than was maximum diameter. Specifically, PWS identified patients who later required emergent repair with a sensitivity of 94%, specificity of 81%, and overall accuracy of 85%, which were significantly better rates than those for the maximum diameter criterion using the widely accepted threshold of 5.5 cm (sensitivity: 81%, specificity: 70%, accuracy: 73%).[23] Other authors have reported similar outcomes, and a recently published meta-analysis of nine studies comparing 204 intact with 144 symptomatic or ruptured AAAs revealed that PWS was significantly higher in the latter group.[24] In addition to the abovementioned data, other biomechanical indices have been proposed to potentially advance rupture risk estimation. In this regard, the peak wall rupture index (PWRI) relates PWS to vessel wall strength and has been reported to most precisely distinguish between asymptomatic and symptomatic AAAs.[25] Specifically, mathematical models that enable us to non-invasively calculate wall strength distribution throughout the AAA surface similar to that of wall stress have been available since 2006.[26] Therefore, the integration of these indices into one variable that displays the pointwise comparison of stress and strength, or in other words, the stress/strength ratio for every point of the AAA surface, provides a distribution of the PWRI.

In this instance, stress refers to the pressure-induced, in-plane wall stress that displays the forces acting on the aneurysmal wall as a result of systemic pressurization. By contrast, wall shear stress (WSS) is the tangential force exerted by blood flow on the luminal surface, and its role during the evolution of AAAs had been typically considered unimportant for several reasons. First, AAAs almost

universally contain an intraluminal thrombus (ILT), which creates a barrier between the endothelial layer of the arterial wall and the flow-induced shear stress. Second, according to histologic data, AAAs are actually missing a recognizable intimal layer that would be subjective to the influence of shear stress. More importantly, the shear stresses acting on the AAA wall are orders of magnitude smaller than the in-plane wall stresses.[17]

New Role of Flow-Induced Shear Stress

Conversely, recent data that have improved our understanding of AAA development and rupture suggest an alternative role of shear stresses. Initially, studies on intracranial aneurysms postulated that a significant relationship exists between the regions of low WSS and those where thrombus deposition was observed to occur in vivo.[27] Despite the fact that the pathophysiology of intracranial aneurysms is far different from that of AAAs and a direct link between these two entities should not be implied in any way, these findings could have motivated research toward identifying the possible relationships between hemodynamic conditions and thrombus formation in AAAs as well. Consequently, emerging data revealed that in AAAs, shear stresses have a significant negative correlation with ILT accumulation, resulting in an increased thrombus deposition in the portions of the aneurysm sac where the shear stress was minimum.[28] Moreover, in longitudinal studies that take into account the initial and final states of the AAA, low WSS was observed at regions where the ILT subsequently accumulated.[29] Another hemodynamic parameter would be the relative residence time (RRT), which reflects the residence time of blood near the aortic wall. This takes into account not only the magnitude of WSS but also the variation of the WSS vector in time. Because pulsatility gives rise to flow reversal, RRT includes information about both the WSS value and change of direction and thus overcomes the difficulties that arise when each of these variables is examined seldomly.[29,30] This variable has been shown to be positively related to ILT accumulation, providing grounds for the theoretical concept that proximal recirculation zones at the neck of the aneurysm promote the activation of platelets, which then adhere to sites of low WSS at the distal portion of the sac, initiating the cascade that ultimately results in ILT deposition.[31] More importantly, the rate of ILT accumulation has been reported to be the same as that of aneurysm enlargement. Furthermore, a comparison between AAAs with and without a thrombus showed that the former group exhibited lower values of WSS and higher values of AAA expansion, implying that low WSS may promote not only ILT accumulation but also AAA growth.[32]

In fact, a deleterious role of ILT involving the promotion of aortic wall degeneration, inflammation, and weakening has been proposed by several published reports. Data from histologic studies have suggested that ILT thickness may be associated with vascular smooth muscle cell apoptosis and elastin degradation, as well as high metalloproteinase concentrations in the underlying wall, and in this regard, the presence and amount of thrombus can affect arterial wall integrity.[33] Other studies have indicated that the aneurysm wall under a thrombus layer was not only thinner but also contained fewer elastin fibers, which were mostly fragmented. Moreover, it contained fewer smooth muscle cells and more apoptotic nuclei. Aortic walls not covered with ILT presented a dense collagenous matrix with differentiated smooth muscle cells, whereas those covered with ILT contained de-differentiated apoptotic cells.[34] Additionally, aortic walls covered with a thick layer of ILT have been shown to be hypoxic and therefore subject to neovascularization and inflammation. These factors have been related to wall weakening and a higher susceptibility to rupture.[35] Other researchers have used computational modeling and FEA in longitudinal studies to indicate a negative effect of ILT in the natural history of AAAs. Speelman et al. illustrated that AAAs with a higher amount of thrombi experience a lower PWS and a significantly higher growth rate.[36] Further insight has been provided by a recent study that evaluated the regional growth of AAAs using an automatic method to slice the AAA surface orthogonally along the centerline to obtain 100 cross-sections with correspondence to the initial and follow-up states. This demonstrated that the regional growth rate was dependent on the local baseline diameter and local ILT thickness, in addition to the local wall stress level in segments not covered by ILT. In segments covered with a thick ILT layer, the wall stress did not affect the growth rate.[37] According to the abovementioned data, wall weakening due to the presence of a thrombus may play a more imminent role during AAA growth than does the stress acting on the wall. It should be acknowledged that these studies used growth rate as a surrogate marker for the risk of rupture. Despite the fact that the growth rate does not necessarily mirror the actual rupture risk in every AAA, data in the literature have indicated a significant relation between these variables.[38] Moreover, rapid growth is currently included in the guidelines for the management of AAAs as an indication for interventional treatment.[1,2]

Taking into account these findings, a significant role of WSS in the natural history of AAAs, mainly through its influence on the pattern of ILT deposition and distribution, has started to become evident. Ultimately, it has been recently suggested that the hemodynamic parameters of WSS may be significant predictors for AAA rupture risk in a multivariate analysis. A contemporary study reported

significant associations between these indices and outcomes categorized as non-aneurysmal, AAA, or ruptured AAA, indicating an important role of these parameters for the evaluation of AAA rupture risk.[39]

Multimodal Approach to Rupture Risk Estimation of AAAs

Moreover, the inclusion of other parameters derived from different pathophysiological fields (biomechanical, hemodynamic, demographic, and the widely used maximum diameter criterion) in one prediction model takes the rupture risk estimation process a step forward because it is in accordance with the etiology and natural history of AAAs. Admittedly, demographic, morphometric, biomechanic, and biological characteristics related to rupture risk have been identified by several studies to advance rupture risk assessment, but these characteristics are unlikely to individually capture the multi-factorial pathology of AAA formation and evolution and accurately predict the rupture risk. Therefore, the different categories of risk markers could have a complementary role to each other, and their integration in one statistical model would probably achieve a more complete picture of the aneurysm state and improve the rupture risk estimation.

In this regard, we previously examined a cohort of small AAAs in a surveillance program that analyzed a total of 24 characteristics across five categories (morphometric, thrombus-related, biomechanical, biological, and demographic).[40] Regarding morphometric characteristics, a total of 10 indices were examined (maximum/neck/normalized diameter, AAA length/surface/volume, saccular index = maximum diameter/AAA length, aorta-neck and neck-AAA angulation, and tortuosity). Based on biomechanical analysis, aortic aneurysms with an aspect ratio (vertical/horizontal) of <1 were defined as "saccular" aneurysms because these presented a drastic increase in the stress exerted on the arterial wall.[41] Thrombus-related variables included absolute and relative ILT volumes, maximum thickness, and the asymmetric thrombus deposition index, which has been recently introduced to quantify the eccentric deposition of ILT.[42] The biomechanic parameters included the PWS value and location and PWRI. Finally, demographic information included age, sex, and family history of AAA, and biologic factors involved platelet counts, creatinine levels, and cholesterol levels. Statistical analysis was performed in WEKA, which is an open-source machine-learning software used for data mining.[43] The highest ranked attributes were selected with chi-square statistics, and a J48 decision tree algorithm with ten-fold cross-validation was used to develop a model based on the data. The decision-tree analysis demonstrated that the AAA growth rate (slow or rapid)

could be predicted with an accuracy of 76.5%, based on the thrombus eccentric deposition in the sac, its relative volume, and the neck-AAA angulation.[40] In the same context, Raut et al. proposed a classification scheme to differentiate between ruptured and non-ruptured AAAs using geometric features, which resulted in a model with 86.6% accuracy.[44] The length of the sac, surface area, tortuosity, and the ratio of ILT to total aneurysm volume represented the nodes of the decision tree and were therefore the significant determinants of outcome. More recently, the Florence Risk Score of AAA rupture has been proposed to sufficiently differentiate between ruptured AAAs, non-ruptured AAAs, and non-aneurysmal aortas, and it takes into account the maximum diameter, presence of diabetes, and hemodynamic indices.[39] This represents an attempt to create a comprehensive scoring system for grading the risk of AAA rupture in individual patients using a combination of predictors. Therefore, a multimodal approach is needed for AAA assessment, and data from the abovementioned studies could be a step toward this end.[39] A multidisciplinary approach to the diagnosis and management of AAAs could be advanced and implemented in clinical practice after being tested in a large patient cohort and found to include additional risk markers.

Conclusion

The therapeutic management of AAAs is currently based on the maximum diameter criterion, which has limitations and may lead to therapeutic inaccuracies. The calculation of wall stress and strength through computational modeling has advanced rupture risk estimation, offering a more biomechanically sound prediction. Moreover, it is only recently that the role of flow-induced shear stress in the formation and the development of AAAs has started to become evident. Finally, a multi-factorial approach taking into account several variables that could be implicated in AAA progression seems appealing to achieve more accurate patient-specific rupture risk estimation because this approach is in accordance with the pathophysiology of aneurysmal disease.

Funding

Disclosure Statement

The authors declare that there is no conflict of interest.

Author Contributions

Study conception: NK, CI
Literature search: NK, KT
Manuscript preparation: NK, KT
Critical revision: CI
Final approval: NK, KT, CI

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