Risk prediction for abdominal aortic aneurysm: One size does not necessarily fit all

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INTRODUCTION

Affecting as many as 3 million people per year, abdominal aortic aneurysm (AAA) is the 10th leading killer in the USA.¹ In AAA, the aorta enlarges gradually over time until one day, it suddenly ruptures. Unfortunately, given reported mortality rates as high as 81% in patients who suffer acute rupture, death is almost a certainty. Unlike ischemic heart disease (IHD), which produces chest pain to alert patients to seek medical attention, AAA provides no warning signs. Thus, the identification of patients requires physicians to screen those at risk with anatomical imaging. Like IHD, the diagnosis of AAA needs to evolve from merely looking at the size of the lumen to incorporating more advanced techniques including molecular imaging, as reviewed by Gandhi et al, in this issue of the Journal,² genomic information, and machine learning. Only then can we bring more personalized diagnostic strategies to those individuals who may not fit the current risk stratification paradigms. Early detection will enable the implementation of appropriate measures such as smoking cessation, healthy lifestyle behavioral changes, and disease-altering medications (i.e., statins and beta blockers), all of which may delay the need for surgical intervention and prevent rupture.³

A POTENTIAL OVER-RELIANCE ON ABDOMINAL AORTIC SIZE FOR DIAGNOSIS AND MANAGEMENT

For better or worse, screening and management of AAA relies on the measurement of the size of the abdominal aorta.^{3,4} Based on epidemiological studies, the risk of rupture is consistently determined by the AAA size. Five years after the initial diagnosis of AAA, smaller AAAs (< 4 cm in diameter) have a 2% rupture risk in contrast to larger AAAs (> 5 cm), which have greater than 25% rupture risk. If initial screening results in detection of an AAA, defined by dilation of the aorta by more than 1.5 times its normal size at the level of the renal arteries (e.g., typically > 3 cm in diameter), serial monitoring is performed to detect aggressive growth (> 1 cm/year) or the attainment of an absolute diameter > 5.5 cm, both of which trigger surgical intervention.⁴

While this simplistic approach may yield better provider execution, several factors question the suitability of this strategy. First, anatomical thresholds for one subgroup may not be applicable to all groups. Women, for example, have faster growing aneurysms,^{5,6} rupture at smaller diameters,⁷ and have three- to four-fold higher risk of rupture than men.⁸ These data suggest that currently defined anatomical thresholds may not accurately predict risk and may potentially underdiagnose disease in women. Notably, the most recent recommendations for AAA management are largely based on randomized controlled trials that recruited primarily Caucasian men between the ages of 65 and 75 years.^{4,9-12} Because findings from these trials may not be generalizable to women, older adults, and other racial/ethnic groups, the application of current management guidelines may not be appropriate in women as well as other subgroups. Inclusion of these groups in future clinical trials is critical to better understand how we can impact the natural history of AAA in all patients

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Figure 1. Schematic of the integration of multiple parameters to better screen and monitor patients at risk for rupture. These measures include the electronic health record (EHR) that incorporates clinical risk factors, ultrasound (US), and computed tomography (CT) that enable anatomical imaging, positron emission tomography (PET) that facilitates the imaging of biological processes, genetic information that includes genetic variants that confer risk, and machine learning that allows for the rapid, automated screening of images for incidental aneurysms.

who may be at risk. Second, while the addition of the surgical criteria to treat AAAs with “aggressive growth regardless of size” may incorporate other risk factors such as genetic predisposition,¹³ biomechanical factors (e.g., abdominal aortic wall stress, vessel asymmetry),¹⁴ and lesion complexity (e.g., the presence and absence of thrombus¹⁵), these recommendations may not reflect the impact of these individual factors, which may differ at the patient level. Finally, in the era of precision medicine, it seems remiss if we continue to ignore how advances in imaging, genomic, and proteomic strategies, and machine learning can help us better identify those at risk and timely schedule their interventions.

ADDING MOLECULAR IMAGING MAY PAVE THE WAY FOR MORE PERSONALIZED CARE

Akin to adding fractional flow reserve to extend information available from the anatomical “lumino-grams” provided by left heart catheterization,¹⁶ imaging biological processes known to contribute to AAA pathogenesis may further enhance risk stratification

and identify those patients who may most benefit from surgical intervention. Gandhi et al² in this issue of the journal provide a comprehensive review of the application of radiotracers to image biological processes that have been shown to contribute to AAA including calcification, proliferation, angiogenesis, and inflammation.¹⁷ Importantly, Gandhi et al² highlight the barriers to clinical translation such as the cost for the manufacturing of novel tracers, existing regulatory hurdles, and the need to perform extensive testing to validate clinical efficacy. As a result, the majority of studies performed in humans have used F¹⁸-FDG, despite its known lack of disease-specific activity and variable efficacy results.² Importantly, the authors suggest some of these difficulties could be mitigated by “repurposing” agents that have already been evaluated in cancer patients. Notable agents undergoing preliminary clinical testing in patients with AAA that have been used to image the aforementioned biological processes in cancer include the calcification marker F¹⁸-NaF¹⁸ and the inflammatory chemokine receptor Cu⁶⁴-DOTA-ECL1i (NIH-CCR2 AAA study),¹⁹ which have been previously evaluated in preclinical models and ex vivo human AAA tissue.

Additional validation studies including randomized control trials in patients with AAA, however, are needed to determine whether adding molecular imaging by PET complements anatomical imaging.

LOOKING TO THE FUTURE APPLICATION OF “OMIC” TECHNOLOGIES AND MACHINE LEARNING IN AAA MANAGEMENT

Advances in technology have enabled us to measure and integrate multiple parameters in a single subject. From the electronic health record (EHR) to imaging scans to the genome, reams of data can potentially be used to improve the diagnosis and treatment of patients with AAA. Recently Li et al²⁰ developed a machine-learning framework that combined the electronic health record and personal genome to identify patients at risk for developing AAA. By integrating both the EHR and genomic data, the predictive accuracy, based on the receiver operating curve analysis, increased to 0.803 from 0.69 to 0.775, respectively, for EHR and genome information alone. Similarly, others have used deep learning models to provide individualized and automated assessments of abdominal aorta size as well as to detect the presence of thrombus and calcification, which are also features associated with increased rupture. While these software can certainly be used to track patients who already have AAA, they can also be applied to any image that includes the abdominal aorta to find incidental AAAs. Because the overall low adoption rate of screening worldwide,⁴ machine learning to detect AAAs in all imaging scans that include the abdominal aorta may improve the overall detection of AAA in asymptomatic individuals. In the future, one can envision a multifaceted approach for each individual patient that includes the integration of the EHR, -omic technologies, as well as anatomical and molecular imaging to identify patients at highest risk for the development of AAA and its complications (Figure 1).

Declarations

Disclosures

The authors have nothing to disclose.

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