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Viewpoint

Towards More Personalized Surgical Indications for Thoracic Aortic Dilatation: Are We There Yet?

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ABSTRACT

Thoracic aortic aneurysms remain an important cause of death in the general population. The key to improving patient prognosis with thoracic aortic dilatation lies in early identification and tailored management strategies. Advances in the understanding of the molecular mechanisms of aneurysm formation, the natural history of disease, and clinical risk factors have led to significant improvements in patient management and overall outcomes. In the past decade, identification of the genetic basis of disease, together with wider availability of molecular testing, ushered in a new era for a tailored approach to the management of patients with thoracic aortic aneurysms. In this viewpoint, we explore these various iterative steps and future challenges.

RÉSUMÉ

L'anévrisme aortique thoracique demeure une importante cause de mortalité dans la population générale. Un dépistage précoce et une prise en charge personnalisée constituent des éléments clés pour améliorer le pronostic des patients atteints d'une dilatation anévrismale. Les progrès réalisés dans la compréhension des mécanismes moléculaires liés à la formation des anévrismes de même que l'histoire naturelle de la maladie et la connaissance des facteurs de mauvais pronostic ont permis d'améliorer de manière significative la prise en charge des patients et les issues cliniques de la maladie. Au cours de la dernière décennie, la découverte d'un lien génétique associé à la maladie et la plus grande disponibilité des tests de dépistage moléculaire ont permis d'offrir aux patients une prise en charge d'autant plus personnalisée. Dans cet article, nous explorons cette démarche itérative et des défis à venir dans le traitement des anévrismes aortiques thoraciques.

Thoracic aortic aneurysms remain an important cause of death in the general population. This is because aneurysms are mostly asymptomatic until an acute aortic event occurs and requires emergency surgery, which still carries a significant risk of mortality (15%-20% in most series).[1] Therefore, the key to improving patient prognosis with thoracic aortic aneurysms lies in early identification and tailored management strategies.

It has long been recognized that the larger the aortic diameter, the higher the risk of dissection, rupture, or sudden death. Longitudinal cohort studies of patients with dilated thoracic aortas further enhanced our understanding of the behaviour of enlarged aortas. The largest such cohort from the Yale group helped establish a hinge point (60 mm) at which the risk of an acute aortic event in the ascending aorta significantly increased.[2] In addition, these cohort studies highlighted an important point: approximately 20% of patients with nonsyndromic thoracic aortic aneurysms have an affected family member, which suggests a genetic component.[3] On the basis of these findings, recommendations were set to prophylactically replace the ascending aorta according to size criteria (>55 mm).[4] Although this marked a significant incremental step towards improvement of patient outcomes, several limitations remained. Recent studies have shown that ascending aortic diameter at the time of dissection is not an accurate reflection of predissection diameters; when dissection occurs, the aorta significantly increases in diameter.[5,6] Therefore any size criteria on the basis of the diameter of a dissected aorta are difficult to extrapolate to nondissected aortas. Indeed, a large proportion of patients with acute type A dissections (up to 2/3) have aortic dissections with aortic diameters <55 mm.[6,7] It was therefore clear that the sensitivity of a "one size fits all" approach was not robust enough to predict events, and more refinement in the criteria was necessary to offer better treatment options for each individual patient.

Further clinical modifiers were therefore studied and included in the decision-making process as markers of poor prognosis, such as longstanding hypertension, rate of progression of aortic dimensions, bicuspid aortic valve, and a family history of dissection or rupture.[4,8,9] Nevertheless, clinical modifiers also lack absolute sensitivity and specificity.

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For instance, bicuspid aortic valves were thought to be a predictor of poor outcomes in patients with moderately dilated aortas (>45 mm), with an increased risk of long-term mortality and acute aortic events.[10] Although aortic diameters in that study were only intraoperative visual approximations of aortic dimensions, it nonetheless resulted in reduced surgical thresholds for ascending aortic replacement to 45 mm in patients undergoing surgery for another indication, according to the 2006 American College of Cardiology (ACC)/American Heart Association (AHA) valvular guidelines.[11] However, thorough analysis of the natural history of patients with bicuspid aortic valves on the basis of longitudinal population-wide studies suggested otherwise, with an overall risk of aortic dissection of <0.5 cases per 100 patient-years. Of 416 individuals with functional bicuspid valves followed over 16 years in Olmsted county, only 2 cases of aortic dissection were reported.[12] Although this amounts to a high relative risk compared with the general population (8 times higher), the absolute incidence of aortic dissection remains very low. Similarly, a large cohort study of 642 patients with bicuspid aortic valves followed over 9 years in Toronto (10% of aortic sinuses >40 mm at baseline) showed a low absolute incidence of aortic dissection (5 patients or 0.1% per patient-year of follow-up).[13] In addition, overall long-term survival in both studies was similar to the general population.[12,13] These data led to a more conservative revision of the guidelines in their most recent iteration.[14,15] This illustrates the limitations of clinical modifiers when they are derived from patients in the numerator (ie, those in whom events occur) vs in the denominator (ie, the global population).[16] Caution needs to be the guiding principle to avoid subjecting otherwise healthy individuals to unnecessary treatments with an inherent risk of morbidity and mortality.

Recognition of the familial segregation of disease, combined with progress in genetic research techniques, marked a new chapter in the understanding and management of thoracic aortic pathologies. Indeed, after the discovery of the fibrillin gene and its role in Marfan syndrome,[17] growing mechanistic insight into the homeostasis of the aortic wall was achieved.[18] This led to identification of the important role of transforming growth factor beta (TGFβ) in the extracellular matrix, not only of blood vessels, but other organs such as the lungs, eyes, and bones, and thus explained some of the extracardiac manifestations of connective tissue disorders. With better characterization of the phenotypic expression of disease, a new chapter of genetic discoveries in the syndromic forms of disease mostly linked to proteins in the TGFβ signalling cascade were reported, and commonly termed Loeys-Dietz syndrome.[19,20] In addition, a number of genes responsible for smooth muscle cell activity within the aortic wall were also identified in familial forms of thoracic aortic aneurysms, such as the ACTA-2 gene (encoding for smooth muscle α-actin) and MYH11 (smooth muscle myosin).[21,22] To date, a growing number of genes have been linked to hereditary forms of aortic aneurysms, which only accounts for approximately 20% of the spectrum of familial forms of thoracic aortic aneurysms. With each gene discovery, more precise phenotypic characterization allows physicians to more accurately diagnose and differentiate seemingly similar conditions. Furthermore, various international collaborative efforts in the form of registries such as the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry or the Montalcino Aortic Consortium (MAC), contribute to enhance our understanding of the natural history of each condition on the basis of its genetic component. Accordingly, current ACC/AHA and Canadian Cardiovascular Society guidelines on the management of thoracic aortic disease have introduced the type of genetic mutation into the decision-making algorithm for surgical intervention, with different genes corresponding to different thresholds.[4,9] For instance, TGFβ-related aortopathies are thought to confer a higher risk of acute aortic events at smaller diameters, marking a sharp contrast in surgical indications between these patients and those with Marfan syndrome.[4,9]

We have thus entered a new era in the management of patients with thoracic aortic aneurysms, with the underlying genetic mutation becoming a central component. With decreasing costs, miniaturized equipment, faster turnover, and widespread availability of next-generation sequencing, the ability to rapidly confirm a suspected genetic diagnosis has reached new levels. In addition, advancements in digital technology have allowed integrating this complex knowledge into physician-friendly applications (eg, www.aorticsurgeryguidelines.com), in order to better tailor the management of individual patients while integrating the latest scientific practice guidelines (Fig. 1). Nevertheless, the enthusiasm for this new chapter in the management of patients with thoracic aortic disease has to be balanced against several outstanding issues. First, the yield for detection of variants in individuals with suspected connective tissue disorders or familial thoracic aortic aneurysms remains low on the basis of the currently identified genes (approximately 20%).[23] Furthermore, widespread genetic testing can result in a significant number of mutations of unknown significance, which can complicate rather than simplify patient management. Finally, the risks associated with widespread genetic testing from an ethical and practical perspective, ought to be taken into consideration. Indeed, the ethical implications can be complex and wide-ranging as discussed in this issue of the *Canadian Journal of Cardiology*. From a practical standpoint, caution is key: new syndromes are discovered through the extreme end of the clinical spectrum (ie, the more severely affected patients), therefore potentially driving more aggressive surgical recommendations. It is important to use caution in promoting treatment algorithms on the basis of a small numbers of patients. Indeed, the 2014 European Society of Cardiology guidelines on the diagnosis and treatment of aortic diseases do not distinguish between TGFβ-related aortopathies and Marfan syndrome, because of a lack of sound evidence in their view,[8] which is in contrast with current 2010 ACC/AHA and 2014 Canadian Cardiovascular Society guidelines, which both recommend early surgery (>40-42 mm in diameter) for patients with TGFβ-related aortopathies.[4,9] This has to be weighed against the risk of these surgeries, especially in centres with less expertise. In addition to surgical volumes, surgical risk should be personalized according to individual patient factors (extent of aortic involvement, previous surgeries, comorbidities, ventricular function, etc) and the potential for less invasive endovascular therapies, which might not only decrease the risk, but also influence the timing for intervention. It is therefore our role as