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EDITORIAL COMMENT

Three-dimensional transesophageal echocardiography – An added value tool for the assessment of aortic plaques in ischemic stroke

Ecocardiografia transesofágica 3D – uma ferramenta de valor acrescentado para a avaliação de placas aórticas no acidente vascular cerebral isquémico

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Cardiac embolism accounts for approximately one third of all cases of ischemic stroke. Paradoxical embolism and embolism from the thoracic aorta, particularly of its atheroma contents, lead to the additional cases of stroke and systemic embolism.[1]

Aortic plaques typically start developing during childhood and early adulthood. In these early stages, they are often clinically silent and contain both intra and extracellular lipid deposits. However, in advanced stages, plaques become more complex and undergo progressive changes from atheroma to fibroatheroma, which includes a fibrous cap around a lipidic core. Plaque growth, in size and complexity, is also associated with neoangiogenesis and activation of metalloproteinases, which lead to the development of a network of incompetent vessels and surface plaque ulceration. These phenomena are intrinsic to the concept of plaque vulnerability and are responsible for the increased risk of intraplaque hemorrhage and thromboembolic events.

Echocardiography is a widely used tool for the assessment of stroke etiology, both in at-risk patients and for secondary prevention. This technique allows the identification of cardiovascular sources of thromboembolism, assess the risk of recurrence, and guiding therapy in an individual patient. Thus, echocardiography plays an important role not only in the diagnosis, but also in the prevention and treatment of cardiovascular sources of embolism.

The detection, characterization, and quantification of aortic plaques can be accomplished by transesophageal echocardiography (TEE), computed tomography (CT), or magnetic resonance imaging (MRI). There are several plaque grading systems using a variety of parameters, such as plaque thickness, surface characteristics and presence of mobile components. Details of plaque grading systems are presented in the most recent guidelines on aortic disease.[2]

Transesophageal echocardiography is the imaging modality of choice for diagnosing aortic atheromas. This real-time imaging method provides higher-resolution images compared to transthoracic echocardiogram (TTE) and has good interobserver reproducibility. TEE studies have reported

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that the extent of atherosclerosis in the aortic arch and thoracic descending aorta is a strong and independent risk factor for ischemic stroke.[1,3] The association is particularly robust when the plaques are thick and complex in nature. Racial differences have been reported in ischemic stroke patients, not explained by other risk factors, which may be related with plaque burden and complexity in the thoracic aorta.[4] The prevalence of aortic atheromas on TEE is variable according to the population. In an American community-based TEE study, aortic atheromas were present in 51% of people over 45 years, being of complex structure in 7.6% of cases.[5]

Computed tomography studies have reported that the extent of aortic calcification predicts cardiovascular death and all-cause mortality. Calcified atheromatous lesions are readily detected and quantified on conventional CT, with calcium scores providing incremental value for prediction of stroke risk. MRI studies have reported that aortic wall thickness may also predict adverse cardiovascular events.[6] However, these imaging modalities are relatively insensitive for the detection of aortic plaques and are limited in assessing plaque characteristics. Non-obstructive general angioscopy is a novel but invasive method for evaluating atherosclerotic plaques in the aorta.[6] Imaging of the thoracic aorta can directly visualize atheromatous lesions, which have been consistently associated with the risk of ischemic stroke.

Nuclear imaging studies might also prove to have a role in the risk assessment of these patients. In a recent study, Fletcher et al. showed that thoracic 18F-sodium fluoride (^{18}F-NaF) positron emission tomography could improve the identification of patients at the highest risk of ischemic stroke. In patients with established cardiovascular disease, thoracic aortic ^{18}F-NaF activity is associated with the progression of atherosclerosis and future ischemic stroke. Arterial ^{18}F-NaF activity identifies areas of atherosclerotic disease prone to clinically significant progression and atherothrombotic events.[7]

Whereas routine TEE in all stroke patients is not recommended, guidelines consistently encourage echocardiography as the gold standard imaging modality in patients with suspected embolic stroke and inconspicuous neurovascular imaging. This is of particular importance for patients with no contraindication for anticoagulation, where imaging has a role for defining treatment. With TEE, the heart is not masked by extracardiac structures such as bones and lung tissue. In many echocardiography laboratories, evaluation for a source of embolism is the most common indication for TEE. Proximity of the esophagus and the aorta enables TEE to be the ultrasound technique of choice in thoracic aorta assessment and provides high-resolution images of the entire artery (excluding a small distal portion near the innominate artery). TEE and TTE should be used in a complementary manner since they allow a holistic study of cardiac and vascular structures.[3]

Standard TTE and TEE are useful but yield better results when additional imaging techniques are performed. These include, but are not limited to, high-frequency and fundamental imaging, off-axis and nonstandard views, multiplane plans and three dimensional (3D) imaging, and the use of contrast (both agitated saline and transpulmonary microbubble contrast agents). 3D and multiplane imaging has opened echocardiography to new paths of assessing cardiac structure and function. Although standard two dimensional (2D) imaging is still overwhelmingly used, 3D and multiplane imaging can highlight areas often missed or overlooked as well as specify areas of interest when it comes to sources of cardiac, aortic, and pulmonary emboli.[2]

Modeling atherosclerosis in genetically modified animals is currently the mainstream in atherosclerotic research. The animal models available to date can simulate all stages of plaque development, providing an opportunity to study the pathogenesis of lesion formation, mechanisms of plaque vulnerability and regression and, therefore, evaluation of new therapeutics and imaging techniques. A good understanding of the similarities and differences between the animal models and human disease is important for the effective extrapolation of data for the translational application.[8]

A better understanding of atheromatous disease and its treatment is of utmost importance in the field of health economics, since the costs associated with atherosclerotic cardiovascular disease are significant and increasing. Despite clinical attempts to mitigate risk factors, the progression of atherosclerosis and atherothrombosis is still the cause of one in four deaths. To overcome this, besides modification of lifestyles, more successful methods are required to improve diagnosis, drug delivery, achieve high therapeutic efficacy and reduce side effects. Advances in the biotechnology for targeted therapy using peptides and recombinant proteins, as well as nanotechnology for therapeutic-loaded nanomedicine platforms, are attracting major interest.[9]

Embolic stroke of undetermined source accounts for 23–40% of all strokes. Although aorta atheromas and patent foramen ovale are more frequently seen in patients with cryptogenic stroke, a pathogenic link needs to be further clarified. Cryptogenic stroke represents a diagnostic challenge which makes it difficult to implement a suitable prevention strategy.[10]

In a cross-sectional community-based study, Aparicio et al. discovered that plaques in the descending aorta are associated with accelerated brain aging. These data highlight the potential implications of incidentally identified subclinical aortic atherosclerosis and question whether targeted intervention in these high-risk individuals can modulate cognitive decline.[11]

Appropriate research is important and enables therapy to target the underlying cause of the index stroke. Diagnostic investigation of suspected cases of embolic stroke of undetermined source, particularly with advanced diagnostic techniques, should be guided and chosen in accordance with patient characteristics at the time of clinical presentation, in a cost-effectiveness perspective.

In this issue, Rodrigues et al.[12] demonstrates, in a study involving 78 consecutive patients with embolic stroke, that the diagnosis of a complex plaque was improved with 3D TEE compared to 2D TEE based on plaque morphology analysis and on the ulcerations detection. The results of this study may open a new perspective in 2D/3D TEE use as a standard imaging method for the study of cryptogenic stroke patients, enabling better characterization of atherosclerotic plaques and their embolic potential.

In addition, these new techniques may contribute to the ongoing discussion on the role of imaging in the prevention

of embolization during endovascular procedures, especially those with arterial access such as transcatheter aortic valve implantation candidates.[13]

The thoracic aorta is an essential structure to be considered in the study of patients with embolic stroke. Whenever a TEE study is indicated, the complementary use of 3D imaging may represent an added value with implications for etiological diagnosis and adaptation of an individualized therapeutic strategy.

Conflicts of interest

The author has no conflicts of interest to declare.

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