Editorial

Predictions and insights for the abdominal aortic aneurysm

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Comment on: MA3RS Study Investigators. Aortic Wall Inflammation Predicts Abdominal Aortic Aneurysm Expansion, Rupture, and Need for Surgical Repair. Circulation 2017;136:787-97.

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Modern vascular surgery imposes its principal preventive role worldwide, by focusing on two arterial diseases, carotid artery stenosis and aortic aneurysms. Both vascular disorders may result in a debilitating or life-threatening situation. There is a tremendous scientific interest about the vulnerable asymptomatic plaques and the aortic aneurysm with imminent risk of rupture; thousands of scientific hours have been consumed in order to identify which asymptomatic carotid plaque is the potent source of emboli for an ischemic stroke, as well as to detect which aortic aneurysm is going to rupture. In an attempt to draw a universal cut-off line for asymptomatic diseases, the degree of carotid stenosis remains an acceptable criterion for the carotid disease, although the intervention in an asymptomatic carotid stenosis is often debated by many investigators. Similarly, for aortic aneurysms, the maximum diameter of the aneurysm along with the aneurysm growth rate still define globally accepted thresholds for intervention (1).

Nevertheless, many factors associated either with the carotid disease, or with the aneurismal aorta, are being investigated and with parallel assessment of the risks, aim at fine-tuning a personalized indication for surgery, certainly before the manifestation of the sound complications from both diseases. This endeavor consists of an intense hunting for the so-called markers, as paraclinical indices of the altered physiology; the ideal marker must be highly proportional to the process of the disease or has to reflect specific conditions with major clinical impact, such as aneurysm expansion or rupture (2). If the markers of such a quality exist, and if they can be identified by current modalities, they may alter the contemporary recommendations concerning the intervention indications, by precisely predicting a forthcoming disaster. Like in all scientific fields, following the initial related and crosschecking evidences, a hypothesis is built and through observational, or experimental studies, expectations for important reliable markers are hopefully created.

In particular, for the abdominal aortic aneurysm (AAA), with an incidence of more than 3–5% in general population, we have only a scarce bit of information about the true pathophysiology of an aortic dilatation. There is no doubt that an aneurysm is a disease mainly of the tunica media (and the adventitia) of the artery, that finally obeys to the simplified law of Laplace (bubble law) and ruptures. As 95% of all the aortic aneurysms are infrarenal, investigations are focused on this entity, trying to reveal the causes for this nature's predilection with lethal consequences (dilatation-expansion, and rupture with >90% mortality).

The two poles for an aortic aneurysm pathology are: the disease of the proper aortic wall, and the stress acted on the wall; they both contribute in a rupture, that occurs at the weakest site of the aortic wall with/or where the most intense wall stress is exerted. The weakness of the infrarenal aortic wall is determined by several factors such as genes, elastin/collagen imbalance, relative lack of vasa vasorum, metalloproteinase activity, pathogenic microorganism presence (e.g., Chlamydia) which impacts immune activity, and inflammation (3,4). The aortic wall undergoes a continuous dynamic remodeling in order to withstand, and promote the cardiac pulse wave and as a response to injury;

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aging with a subsequent gene regulation derangement results in a diseased aortic wall leading to an aneurysm formation; gene erratic regulation is obvious in patients with connective tissue disorders where due to the aortic wall disease, aneurysms are present in young age; the incidence of inherited aneurysm formation due to familial gene disorders is up to 20% for first order relatives. Aortic wall deterioration may be induced by atherosclerosis, but the latter is rather a coincidence than a determining factor for infrarenal aortic dilatation, though wall ischemic changes due to vasa vasorum occlusion in obstructive arteriopathy have been observed.

In addition to the aortic wall weaknesses, the shape of the aorta is an important parameter involved in aortic dilatation or expansion, as the blood, an incompressible fluid, propelled by cardiac thrust, interacts strongly with a tortuous aortic wall. In the 1830, Chelius in his *Handbook of Surgery*, postulates that arterial curves promote aneurysm formation (5). Newer studies state that there is an anisotropic energy distribution inside the aorta, in longitudinal and in transverse direction (2); it also seems that the aorta firstly elongates and then dilates (6). Peak wall stresses in 3D models estimated by finite element analysis, can explain the rupture in specific aortic loci as a phenomenon not necessarily dependent exclusively on local diameter or wall thickness. Additionally, the firm ring outside the inter-renal aortic portion combined with the aortic pulse counterwave from the aortic bifurcation expose the contained infrarenal aortic section to a forceful fluid-structure interaction. This reflective wave is amplified, and it strains the wall with a greater intensity in case of aortic-common iliac surface area mismatch, and in augmented aortic stiffness. The aortic wall, already defected or not, reacts in this new increased tension, with an increase of the surface (enlargement), to ameliorate the local exerted pressure; this process leads to the ongoing expansion in an equilibrium of horror between wall tension (depended from the diameter) and matrix components of remodeling; that is the reason we meet enormous aneurysms without rupture. When the destabilizing components like the metalloproteases (MMPs) dominate over their inhibitors (TIMMPs), down regulation of the structural components takes place, resulting in a decreased wall strength, and the aortic wall ruptures. Body size and habitus, male gender, epidemiological risk factors like smoking, chronic obstructive pulmonary disease (COPD), benign prostatic hyperplasia (BPH), and other, act in combination inflicting wall injury, or to expand or promote a rupture of the AAA (7). This multifactorial synergy obviously transmits signals through a biochemical pathway. The detection of such biomarkers in the plasma (MMPs) currently it is not very promising, and the markers are not anatomically specific for a certain diseased section of the vasculature. However, due to the present advanced imaging capabilities with an excellent resolution and diminution of study time, the combination of the imaging findings with specific molecular metabolic activity shines light on a long route to prediction for AAAs (8-10). This is currently attempted with positron emission tomography (PET), with fusion techniques with computed tomography (CT) or magnetic resonance imaging (MRI), and recently by using ultra small superparamagnetic particles of iron oxide (USPIOs) with an MRI scan (11,12). A convenient metabolic pathway, which is evident in the aortic wall, is inflammation where infiltration of the tunica media by lymphocytes and macrophages has been histologically proven. The activity of macrophages may be revealed, using cell-specific PET tracers such as 18F-fluorodeoxyglucose (18F-FDG) which is a glucose analogue or others, however imaging of AAA is accompanied by a low specificity due to its multifactorial nature; thus, this method is not recommended for a routine use on clinical basis (12,13). Recent data from a well-designed prospective multicenter study, the MA3RS with a cohort of 342 patients with AAAs >4.0 cm and a follow-up of two years concluded that USPIO-enhanced MRI can predict the rate of aneurysm growth and clinical outcome, but this modality cannot be accepted as an independent predictor of aneurysm expansion or clinical outcomes in a model incorporating known clinical factors; the authors of MA3RS study state that USPIO enhancement appeared to be greater in those with emergent AAA related events, including aortic aneurysm rupture although this has to be supported by more studies (14). However, MA3RS study, by establishing a reliable method to detect at least one metabolic pathway in AAAs, opens a field for medical treatment of aortic wall inflammation through molecular vectoring, and most importantly, through USPIO-enhanced MRI the result of the respective medical treatment can be assessed. Additionally, as the use of USPIO is not associated with the risk of nephrogenic sclerosis like gadolinium, and due to its long-lasting blood pool enhancement, it may be used in MR studies that require detailed and/or long-lasting vessel imaging like MR angiography, though it can provoke immune reactions.

In a holistic approach, every single study concerning the physiology of AAAs is welcome; in clinical praxis prediction

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is required for the individualization of treatment. However, the scientific challenge for AAAs is, following an early detection of an aorta with a propensity for dilatation or with a small aneurysm—U/S studies consist a realistic method—to identify with the proper detecting molecules all the metabolic pathways of the disease, by tracking alterations in molecular level at the microenvironment of the aortic tissue (15). Then, by using the same detectors as vectors, or through other medical solutions, we have to modify the aortic wall by remodeling and enhancing the up regulation of the strengthening matrix components, with the aim to interrupt and reverse this hostile biological irregularity at an early stage. Until then, we need early predictors to tell us when to use with safety, our open or endovascular mechanical solutions (16), in the hope that we change the natural history of the disease.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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