Medical Therapy of Aortic Aneurysms: A Pathophysiology-Based Approach

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Abstract: One of the critical points in the pathogenesis of aortic aneurysms (AAs) is the disruption of the balance between vascular extracellular matrix (ECM) deposition and degradation. AAs are common features in some genetically determined diseases of the connective tissue, such as Marfan and Ehlers-Danlos. Acquired factors determining an enhanced inflammatory state of the arterial wall also play a key role. Previous studies have determined the role of tumor growth factor β (TGF-β); as a principal mediator of the pathogenesis of the alterations of the arterial wall homeostasis in AAs. The medical management of any AA is mainly focused on the use of pharmacological agents that reduce hemodynamic stress of the aortic wall, since hypertension is the major risk factor for the enlargement and rupture of the AAs. However, this is far from being a comprehensive pathophysiology-based therapeutic approach. Drugs potentially able to reduce the release of TGF-β may play a role in the pathogenesis of the AAs. They work by improving matrix repair, decreasing the proteolytic pattern and inhibition of angiotensin-converting enzyme (ACE) as well as preventing angiotensin II-induced angiotensin type-1 receptor (AT1R) activation. A new pathophysiology-based therapeutic approach, involving the mechanisms leading to the rupture of the AAs, could represent an additional tool in combination with the current established antihypertensive therapy.

Keywords: Pathophysiology, medical therapy, aortic aneurysms, atherosclerosis, insulin resistance, metalloproteinases.

ABDOMINAL AORTIC ANEURYSMS (AAA)

AAAs are a permanent, segmental dilatation of the infradiaphragmatic aorta greater than 3 cm [1]. AAAs are usually discovered when non-invasive imaging is performed in a patient who is referred for a screening or incidentally detected when imaging is performed for unrelated purposes [2, 3]. The prevalence of AAA varies based on gender and presence of risk factors [4, 5]. Men are 5 times more likely to develop an AAA than women (prevalence of 1.3 to 8.9 % in men compared with 1.0% to 2.2 % in women) [6, 7] and do so approximately 10 years earlier in age than women [8].

The major recognized risk factors for AAA are cigarette smoking, atherosclerosis, advanced age, family history and hypertension [2, 9]. These conditions lead to vascular wall injury, inflammation and an imbalance between the synthesis and degradation of connective tissue proteins [10]. Pathologic studies of AAA demonstrate infiltration of macrophages, lymphocytes, and mast cells in the media and adventitia of the vessel wall [11, 12], with resultant secretion of proteases, chemokines, and growth factors that induce apoptosis of vascular smooth muscle cells (VSMCs) [13], activation of matrix metalloproteinases (MMPs) [14] and neovascularization [12].

Complications of AAA include compression of adjacent structures, causing chronic abdominal and back pain and formation of thrombi that can lead to distal embolization or acute occlusion [15]. The most serious complication of AAA is rupture, which is more likely to occur with an AAA that is $\geq$ 5.5 cm in diameter or rapidly increasing in size (i.e. expanding > 1 mm/year). Accordingly, elective AAA repair is recommended if either of these conditions is present. Conversely, medical therapy to prevent AAA enlargement is recommended for AAAs that are less than 5 cm in diameter and stable in size since they are unlikely to rupture. Unfortunately, the treatment strategies to prevent AAA enlargement and rupture are not well defined. This review will explore: (a) the pathophysiological mechanisms identified in the development and progression of AAA, and, (b) existing and novel therapeutic strategies that may be beneficial in AAA treatment.

THORACIC AORTA ANEURYSM (TAA)

The incidence of TAAs is increasing because of the improvements in screening and the advances in imaging. TAA typically occur in men in the 50-70 year range, and the average of age at time of diagnosis is usually older in women [16].

TAA affecting the ascending and arch aorta include degenerative aortic aneurysms (AAs) and AAs associated with

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