REVIEW ARTICLE

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Acute thoracic aorta dissection: unraveling the pathophysiology of a silent killer

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INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality in the world and, among them, aortic diseases stand out, especially atherosclerosis, aortic aneurysms (AA), aortic dissections (AD), and aortitis. Acute aortic dissection (AAD) has a bad prognosis and presents itself by a sudden laceration of the intima and media layers of the aorta and its pathophysiology is correlated with atherosclerosis, aging, and inflammatory diseases such as vasculitis, in addition to connective tissue diseases, such as Marfan and Ehlers–Danlos syndromes[1]. This study aims to shed light on the pathophysiology and diseases associated with AAD, such an aggressive and deadly vascular disease.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS OF THE AORTA

The aorta is the largest artery in the human body, in caliber and length, with the largest number of tributary vessels and the largest volume of blood transported. It starts at the sinotubular junction and is divided into thoracic and abdominal aorta, based on the aortic hiatus of the diaphragm[1]. It is divided into three layers, namely, intima, media, and adventitia. The intima is made up of the endothelium and simple squamous epithelial tissue that lines the inner surface of the vessel. Between the intima and the media, there is an internal elastic lamina that makes up the subintima layer (Figure 1).

The middle layer is mainly composed of concentric layers of leiomyocytes, smooth muscle cells (SMCs), organized according to the vessel's length helically. They are responsible for the rigidity and elasticity of the aortic wall. Between the SMCs, there are variable amounts of elastic fibers and lamellae, collagen reticular fibers, adhesive proteins, proteoglycans, and glycoproteins. SMCs are responsible for the production of these extracellular matrix (ECM) molecules[2-4]. This layer has a thinner external elastic lamina that separates it from the adventitia. The amount of elastic laminae in the media layer plays an important role in energy conservation, regularization, and maintenance of blood flow at a constant value, preventing distension and loss of arterial anatomy. This elastic effect prevents the loss of kinetic energy in the blood, according to the determinations imposed by the Bernoulli equation, thus maintaining the total energy of the system.

Elastin and collagen are the main structural proteins of the middle layer, providing elasticity and tensile strength, respectively. Both proteins are stabilized by covalent cross-links and their formation is mediated by the enzyme lysyl oxidase (LOX). Cross-linking of tropoelastin monomers by LOX forms elastin molecules that cross-link with microfibrils to form elastic fibers and desmosines. In collagen cross-linking, pyridinoline is formed. Pyridinoline and desmosine stabilize, the cross-links of collagen and elastin, respectively[5,6] (Figure 2).

Finally, the tunica adventitia consists of loose connective tissue rich in collagen fibers, fibrocytes, and fibroblasts. This layer includes the *vasa vasorum*, responsible for the vascularization of the outermost layers of the aorta, in addition to the *nervi vasorum*, that promotes the contraction of SMCs through the noradrenergic action and lymphatic vessels for aortic self-regulation and metabolism[2-6].

THORACIC AORTIC DISSECTION

Diseases affecting the thoracic aorta can be categorized into acute or chronic. The most common are aneurysms, dissections, acute aortic syndrome (AAS), connective tissue diseases, and vasculitis. Among the causes of AAS, there is thoracic aortic dissection (TAD), which stands out for its high morbidity

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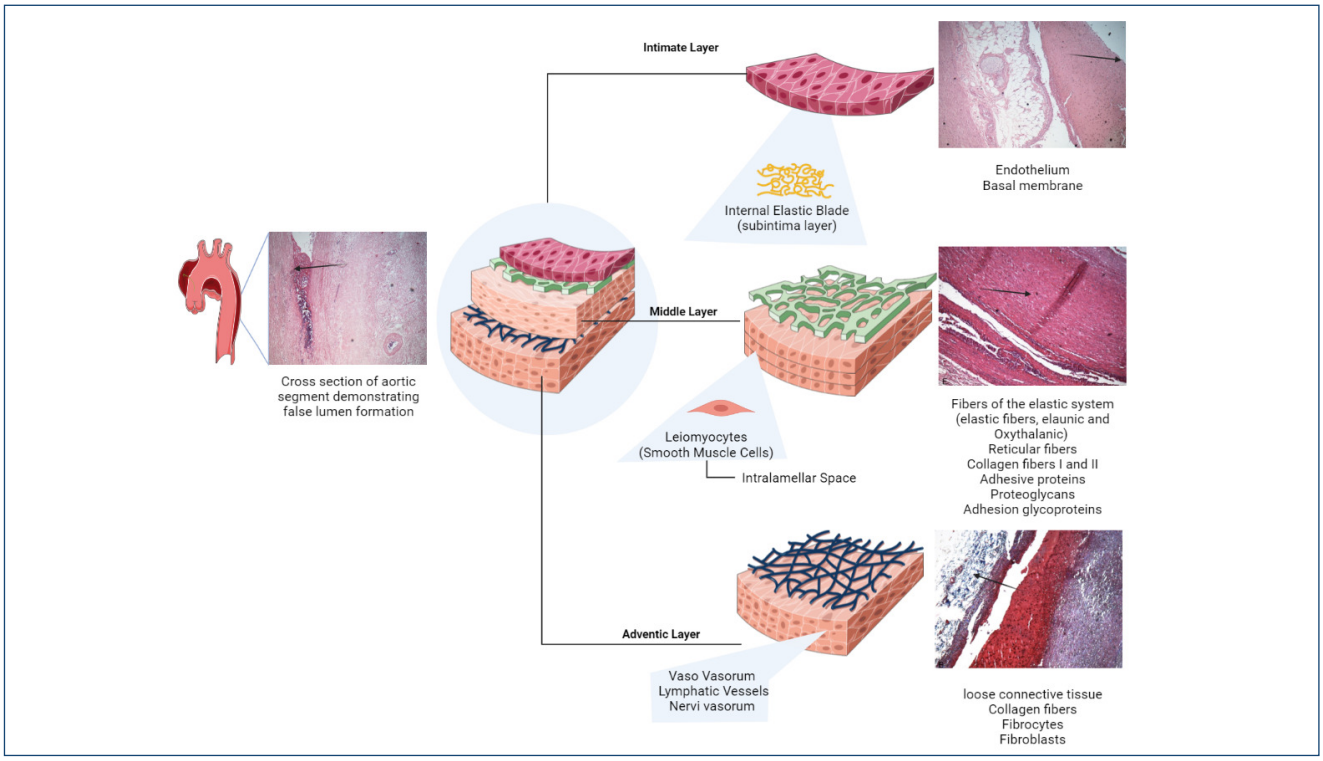

Figure 1. Schematic of a cross-section of aortic segment demonstrating the formation of the false lumen, the layers that make up the artery wall and its main structural components. Light microscopy images stained with hematoxylin and eosin were obtained from Professor Tenório et al. (2017)[5].

and mortality. Despite the differences in the pathophysiology of these diseases, systemic arterial hypertension (SAH) and atherosclerosis are the main participants involved in the pathogenesis of TAD, and SAH, in particular, is its greatest risk factor[7-9].

Thoracic aortic dissection begins with sudden lacerations and continuity breaks in the intima and media layers of the aorta. This rupture allows pulsatile blood to penetrate the medial layer and cause it to separate along the length of the vessel. This leads to the formation of a second channel, called the false lumen, leading to the relative thinning of the adventitial layer. Due to the mechanics of the injury, there is an accumulation of inflammatory cells throughout the aorta, which generates fragility of the architecture, dilation, and rupture. These changes can lead to disturbances in blood flow from the arteries tributary to the aorta, leading to multiple organ injuries secondary to TAD, and subsequently, high mortality[9-13].

THE IMPORTANCE OF ATHEROSCLEROSIS IN THE PATHOGENESIS OF THORACIC AORTIC DISSECTION

The accumulation of cholesterol and fat in the arteries accelerates collagen and elastin degradation, thus compromising the strength, structure, and elasticity of the aortic wall[5,6]. Atherosclerotic plaque formation is mediated by the immune system and significantly contributes to TAD. The first step in atherosclerosis is endothelial damage caused by sustained high

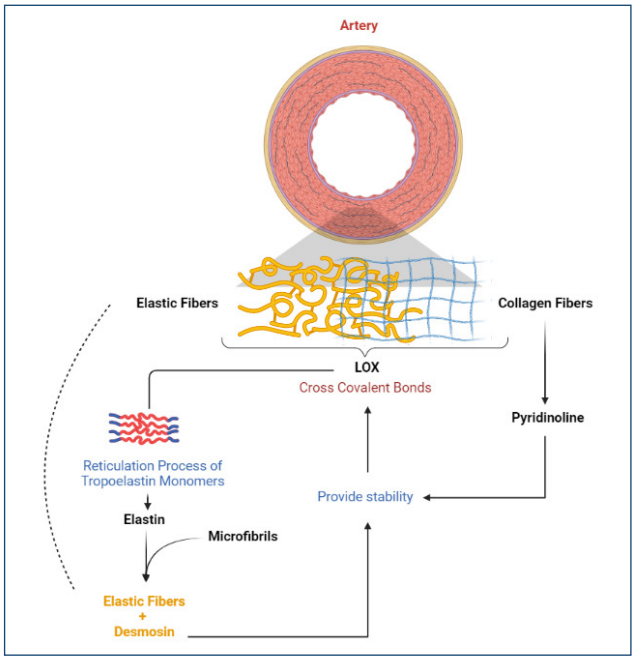

Figure 2. Middle tunic cross-linking process to provide elasticity and tensile strength. LOX: lysyl oxidase.

blood pressure, smoking, alcohol, and obesity. The endothelium is activated by the expression of adhesion molecules, in addition to high levels of interferon alpha and beta that are generated after activation of the Toll-like receptor 9. T cells produce pro-inflammatory mediators, such as interferon gamma (IFN-γ), which favors the adhesion of monocytes to the endothelium and their migration to the intimal layer, leading to a local inflammatory action[12-15].

Adherent monocytes to the intimal layer migrate to the subendothelial space in response to locally produced chemotactic molecules and differentiate into macrophages and foam cells. Macrophages are a rich source of growth-regulating molecules and cytokines that act as the main mediator of cell migration and proliferation. Due to this intense inflammatory reaction, there is activation of pro-apoptotic receptors in SMCs that are present after the subintima layer, so that there is a rupture of the interlaminar layer of elastin fibers. Apoptosis of SMCs and the consequent destruction of the ECM in the aortic wall are accompanied by an increase in the degree of inflammation. Several cytokines and chemokines that promote the recruitment of inflammatory cells to the aortic wall, such as tumor necrosis factor A (TNF-A), interferon gamma (IFN-γ), transforming growth factor-beta (TGF-β), metalloproteinases (MMPs)-1, MMP-9, and MMP-12, interleukin (IL)-1, IL-2, IL-6, and IL-8, can be found in the aortic wall. The presence of T lymphocytes, macrophages, mast cells, and neutrophils in the aortic wall evidences the stimulation of cell migration and its local harmful effect. This suggests that inflammation participates in the pathogenesis of TAD by regulating aortic wall homeostasis. T lymphocytes and macrophages can be found diffusely along the medial layer, in focal accumulations between the layers of SMCs, and within the wall of the vasa vasorum, suggesting its possible migration from the adventitia to the media of the aortic wall. These inflammatory cells are potential sources of proteases that can degrade the ECM and lead to aortic wall weakening, called tunica media degeneration[13-18].

Furthermore, TGF-β and MMPs promote aggregation of reactive oxygen species (ROS) or nitrogen intermediates, which induce apoptosis of SMCs and contribute to the degradation of interlaminar fibers. Recent studies have identified a number of molecular mechanisms that interact with the TGF-β pathway, including miR-29b, SMAD, activator protein-1 (AP-1), nicotinamide adenine phosphate oxidase-4 dinucleotide, and the mTOR pathway. They can lead to accelerated degradation of elastin and collagen fibers resulting in vascular wall weakness. In contrast, the increased expression and disordered collagen deposition may correspond to a slow repairing and pro-fibrotic process triggered by the fragmentation and depletion of elastic fibers. This fibrosis can also be due to an increase in the expression and release of growth factors that can culminate in an increase in collagen and consequent increase in arterial stiffness (Figure 3)[13-25].

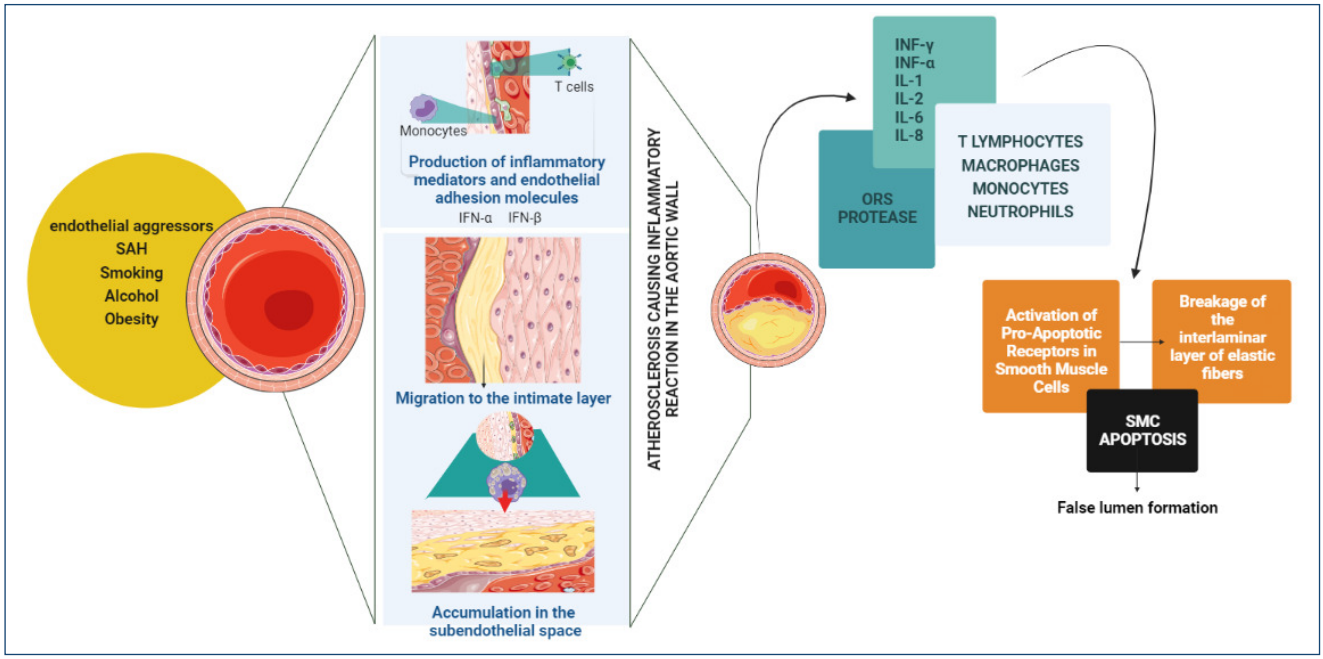

Figure 3. Atherosclerotic mechanism in the pathogenesis of thoracic aortic dissection. SAH: systemic arterial hypertension; IFN: interferon; IL: interleukin; ROS: reactive oxygen species; SMC: smooth muscle cell.

AORTIC DISEASES ASSOCIATED WITH THE DEVELOPMENT OF THORACIC AORTIC DISSECTION

Aneurysms, annuloaortic ectasia, aortic arch hypoplasia, coarctation, arteritis, vasculitis, bicuspid aortic valve, and genetic diseases that affect connective tissue, such as Turner, Marfan, Loeys–Dietz, and Ehlers–Danlos syndromes, are diseases involved in the development of TAD. These connective tissue disorders lead to aortopathies through overstimulation of TGF-β activity in the ascending aorta. However, only 20% of all TAD cases are due to syndromes. Consequently, non-syndromic TAD comprises the majority of cases and can be divided into familial, in which one or more family members have the disease, and non-familial. Interestingly, in cases of syndromic and non-syndromic TAD, often only one gene seems to be responsible for the pathophysiological mechanism of the disease. This creates the potential for early detection and preventive treatment, in contrast to diseases that have complex multigenetic and pathophysiological origins, such as atherosclerosis[18-26].

CONCLUSIONS

Thoracic aortic dissection is a clinical condition with high morbidity and mortality and is strongly related to aging, SAH, atherosclerosis, and connective tissue diseases. The absence of early predictors and screening methods are limiting factors in the treatment and control of damage caused by this disease. Therefore, it is urgent to carry out studies that aim at elucidating the pathophysiology and mechanisms, which are still obscure, that result in the development and validation of biomarkers.

AUTHORS' CONTRIBUTIONS

RM: Conceptualization, Methodology, Writing – review & editing. **CRN:** Conceptualization, Writing – review & editing. **JHAPF:** Writing – review & editing. **PPT:** Conceptualization, Supervision, Methodology, Writing – review & editing.

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