Working hypothesis

Aortic valve: do its nervous and contractile elements have any role?

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Recent knowledge on aortic valve physiology and its cellular and ultrastructural characteristics lead us to believe that the opening and closing mechanism is not only the result of the different pressures between the aorta and left ventricle but it is also a function of the interaction between elastic forces acting on a complex structure such as the valve. The latter consists of cells with muscular properties and of some elements capable of dynamically modifying their properties. These cells, which can regenerate themselves, seem to be closely related to nerve endings whose exact function at the valvular level is yet to be defined.

The aim of this paper was to review the most recent literature on the aortic valve nervous and ultrastructural properties as they are related to the physiological and pathophysiological patterns.

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The aortic root is that segment of the left ventricular outflow tract which supports the leaflets of the aortic valve, delineated by the sinotubular ridge superiorly and the bases of the valve leaflets inferiorly[1]. The semilunar insertion of the aortic leaflets forms the hemodynamic junction between the left ventricle and the aorta and delimitates proximally the three sinuses of Valsalva. These are almost symmetrical bulges named according to the coronary arteries arising from them. The wall of the sinuses is mainly aortic wall and only in the proximal part of the right and left sinuses is there an increasing component of ventricular musculature. Below the leaflet insertions, there are three interleaflet triangles, whose apexes form the commissures. The triangle between the non-coronary leaflet and the left coronary leaflet forms part of the aorto-mitral curtain while the triangle between the non-coronary leaflet and the right coronary leaflet is in the membranous part of the septum[2].

The anterior wall of the left outflow tract is formed by the muscular and membranous interventricular septa, while the subaortic curtain and the posterior wall are formed by the anterior leaflet of the mitral valve[3].

The valve leaflets, the sinuses, the annulus and the sinotubular junction are an anatomical unity that acts as a single hemodynamic system. It moves spatially and changes its shape and size as a function of the different phases of the cardiac cycle. The entire aortic root moves downwards towards the left ventricle during systole[3]. The opening and closing mechanism of the aortic valve is not only determined by the differences in pressure or by the ejected blood flux into the aortic root at each systole, but it is in strict relation with the dynamic and composite structure of the aortic root[4-7].

A normal aortic valve opens before the onset of aortic blood flow with a stellate orifice and no flow or pressure gradient across the valve is needed to initiate its aperture[5,8,9]. The second phase of valve movement is a rapid opening with a maximal orifice when the aortic flow reaches about 75% of its maximum value. During the opening phase, the aortic orifice changes its stellate shape into a round, intermediate and triangular shape[10]. The tension stored in the valve cusps, together with the vortices in the sinuses, leads to an initial slow phase of valve closure when the flow is still increasing during early systole[11]. The last phase of valve movement is rapid end-systolic valve closure, which is completed by back flow of the blood during diastole.

The complex physiology of the aortic root is influenced by aortic root pathology and alterations in left ventricular contractility. Stenotic valves are characterized by a

slower opening movement with a maximum area attained later in systole[10], at mid-deceleration[12]. Aortic stenosis is not a fixed obstruction to blood and stenotic valve dynamics is related to the progressive increase in the force required for valve opening during ejection. Flow-dependent or pseudo-aortic stenosis can lead to misdiagnose significant aortic stenosis[12-14]. Correct management of patients with aortic stenosis, left ventricular dysfunction and low gradients is strictly related to dobutamine echocardiography referring patients with stenosis and a preserved contractile reserve to surgery whilst conservatively managing those with pseudo-stenosis[15-17]. Increasing degrees of leaflet calcifications decrease the flow-dependent orifice enlargement reserve, thus explaining the clinical differences observed between patients with similar aortic stenosis and left ventricular function[12,13].

The mechanisms at the basis of aortic leaflet physiology and pathophysiology are not completely clear. Most experimental studies demonstrate that the movements of the aortic leaflets depend only on the flow and on the elastic and mechanical properties of the aortic root[5,8,10,18], thus excluding an active role of the aortic leaflets.

Recently, attention has been focused on the relationship between the aortic valve physiological behavior and its structural components in order to understand the ultrastructural basis of aortic physiology[8,18,19]. In diastole[19] the valvular leaflets are subjected to a higher stress rotation that occurs in a limited area of the leaflet itself. It was thought to be related to the leaflet ultrastructure whose main component is represented by a semi-fluid matrix enclosed between two fibrous tissue plates. This matrix is deformable and is mainly composed of collagen fibers and sugar complexes – glycosaminoglycans synthesized and secreted with a higher turnover by fibroblasts.

During the cardiac cycle, the leaflet attachment to the aortic wall can modify its matrix status thanks to modifications in the hydration of the glycosaminoglycans that also allows it to absorb the different leaflet pressure stress[19].

The alterations or loss in extracellular macromolecular components could modify the structural and functional integrity[8,18,19] of the aortic valve, probably also modulating its calcific degeneration[20-22]. So, the cellular viability and the preservation of the collagen framework and intercellular matrix components seem to guarantee the long-term heart valve function by playing a role in the prevention of matrix mineralization[20-22]. In fact, the collagen network provides the major structural basis for long-term performance[22] and the cellular matrix is the main component of the stress area on the aortic leaflets. Several studies[8,19,23-31] on the interstitial cusp matrix and valvular innervation[26-31] suggest that the valve has contractile properties involved in the aortic valvular opening and closing mechanisms. There is a rearrangement process of the structure of the aortic valvular leaflets which is modulated by the cellular components present in the extracellular matrix[19]. Its responsiveness is essential to the vitality and duration of valvular cusps. Nevertheless, it is not yet clear whether these cells, defined as fibroblasts, myofibroblasts, fibrocytes or stromal cells[29-31], have contractile characteristics and/or syncytial ability or both. However, both the presence of smooth muscle cells in the aortic cusps as well as their function are still being studied. Using different substances it has been found that there is a contractile capacity at the cusp level; by means of electron microscopy it has been possible to detect, in aortic valve interstitial cell cultures, the presence of a cytoskeleton and of contractile proteins specific for smooth muscles[29-31]. The function of these has not yet been well defined. During systole the aortic valve cusps go through an initial rapid shifting phase[4,5] – "rapid opening phase" – and always maintain a constant time and speed equal to an average of 82% of the total shifting during opening. The rapid opening phase following the initial leaflet opening phase is independent of the blood flux and pressure gradient.

Kawano et al.[26] found nervous fibers positive to acetylcholinesterase arranged on the ventricular side of the semilunar aortic cusps. These form a plexus that is localized in the basal two thirds of the valvular leaflet. These innervations start off as ventricular subendocardial and aortic adventitia. The presence of sensorial and autonomic innervations on normal aortic cusps is very surprising since it leads to the assumption of a neuronal component of the functional valve control[25]. In animals, endothelin, noradrenaline and adrenaline induce concentration-dependent contraction of the aortic leaflets[32] while electrical stimulation and noradrenaline increase the tension in the mitral valve leaflets[33]. Nervous fibromuscular elements might be able to determine, depending on the amount of pressure detected by the receptors on the aortic root, a change in the elastic modulus of the aortic wall and, consequently, the possibility that valvular leaflets start their opening movement a few milliseconds before systolic ventricular ejection. In this manner, they could prevent the direct impact of the blood mass with the ventricular surface of the valvular leaflets themselves. An even more interesting hypothesis is that regarding the possibility of contractile properties, at least in the rapid valve opening phase, which would reduce stress on the valvular leaflets during the first phase of blood ejection.

The new studies on aortic valve physiology and on the role of the contractile elements present in the aortic valve leaflets lead us to believe that the aortic valve is a composite structure capable of changing its elastic modulus as a function of stress. More studies are required for a better understanding of the role of valvular nerves and its association with the mechanisms of cardiac aortic valve disease. This would also allow us to evaluate how the different aortic valve surgical techniques may modify cardiovascular function.

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