European Journal of Humanities and Educational Advancements (EJHEA)
Available Online at: https://www.scholarzest.com
Vol. 5 No.09, September 2024
ISSN: 2660-5589

AORTIC VALVE SCLEROSIS: PHYSIOLOGICAL STUDY OF HEART VALVES

Qasim Hamadi Abid[1] ; Noor H. Alkharsan[2] ;, Huda Najh Al Baroody[3]
[1] Pathological analysis department, College of applied medical science, university of Karbala, Karbala, Iraq
[2]Pathological analysis department, College of applied medical science, university of Karbala, Karbala, Iraq
[3] Pathological analysis department, College of applied medical science, university of Karbala, Karbala, Iraq
Correspondence author: Qasim Hamadi Abid. Email: qassim.h@uokerbala.edu.iq. Phone number: 07803190036

Article history:
Received: June 10th 2024
Accepted: July 8th 2024

Abstract:
One important clinical condition that often presents asymptomatically in adult populations is aortic valve sclerosis (AVS). It negatively impacts the cardiovascular system as an early stage of aortic valve stenosis and a marker for cardiovascular disease.

Keywords: Aortic valve sclerosis, Atherosclerosis and Inflammation

INTRODUCTION

Given that a 70-year-old patient's aortic valve will have opened and closed over 25 million times at a heart rate of 70 beats per minute on average, it is not surprising that calcific aortic valve disease does not manifest clinically until later in life (Owens & Otto, 2009). In developed nations, the most common reason for heart valve replacement is still calcified aortic valve disease (CAVD) (Vinodh, et al., 2007). According to Sanchez and Mazzone (2006), From mild calcification and/or From severe calcified aortic stenosis to leaflet thickening without valve obstruction (commonly referred to as "aortic sclerosis"), CAVD is associated with a wide range of disorder severity. It was believed that time-dependent degradation and passive calcium deposition were involved in the "degenerative" trileaflets valve deterioration (Freeman and Otto, 2005). The disease's active processes, such as endothelium impairment, inflammation, and lipid infiltration, may, nevertheless, be comparable to those seen in atherosclerosis, according to the histopathologic and clinical data. (Agmon,et al.,2004;Freeman and Otto, 2005).). However, a number of clinical risk factors, such as age, gender, hypercholesterolemia, Chronic artery disease (CADD) has been associated with low-density lipoprotein (LDL) cholesterol, hypertension, diabetes, and smoking(Boon et al., 1997; Stewart et al., 1997). Atherosclerosis and CAVD share certain similarities, but they are not the same disease process. For instance, there is not a 1:1 correlation between aortic valve disease and significant CAD patients. According to Freeman & Otto (2005) and Goldbarg et al. (2007), On coronary angiography, Only roughly 50% of adults with calcified aortic stenosis exhibit luminal narrowing that is clinically meaningful.

ANATOMY OF THE HEART:

Inside the walls of the heart is a thin layer of cells called endothelium, or endothelial cells. This is the part of the cardiac chambers that is in contact with the blood. Situated in the chest (thorax), the muscular organ known as the heart is encircled by a fibrous sac called "the pericardium". The fluid within the sac acts as a lubricant as the heart beats (Kibble & Halsey 2009). The heart's myocardium, or cardiac muscle cells, make up the majority of the walls. In each half of the human heart, the atrioventricular (AV) valves are situated between the ventricle and the atrium. Blood can flow from the ventricle to the atrium with their help, but not the other way around. The right AV valve is known as the tricuspid valve, and the left AV valve is known as the mitral valve(Kibble & Halsey 2009).

HEART VALVES PHYSIOLOGY:

The AV valves are passively opened and closed by pressure differences across them. Blood can flow from the ventricle into the atrium when the valve is forced open, which happens when the blood pressure in the atrium is higher than that of the ventricle separating it from it. On the other hand, the AV valve between a contracting ventricle and its connected atrium is forced shut when the internal pressure of the contracting ventricle exceeds that of the atrium. Consequently, Blood travels into the aorta from the left ventricle and the pulmonary trunk from the right ventricle. Blood cannot be forced back into the atria as a result. The valves are joined to the ventricular walls' muscular projections, or "papillary muscles," by fibrous tissue. chordatendinae (Mihaljevic, et al.,2008). The aortic and pulmonary valves, which open from the left ventricle into the aorta and the right ventricle into the pulmonary trunk, are the locations of the semilunar valves. The papillary muscles only function to restrict valve movement and keep them from being

everted(Kibble & Halsey 2009). These valves function in a completely passive manner, much like AV valves; pressure differences across them control whether the valves are open or closed. When the ventricles are contracting, they allow blood to enter the arteries; however, when the ventricles are relaxing, they block blood flow in the opposite direction(Mihaljevic, et al.,2008).

GROSS ANATOMY THE AORTIC VALVE:

The aortic valve is the tricuspid valve that separates the aorta from the left ventricular outlet tract (LVOT) terminal segment. The left, right, and non-coronary semilunar cusps make up this structure. The area between the aorta and the leaflet margins is referred to as the "sinus of Valsalva," and it is within the expanded aortic sinuses where the cusps are attached. These sinuses are called the right, left, and because two of them give rise to coronary arteries, they are not coronary sinuses. However, these sinuses are rarely strictly right or left due to the oblique position of the aortic root(Anderson, et al., 1991).

Normally, the upper part of the sinus of origin is where the coronary artery ostia open, and commissures are the places where the aortic attachments of two neighboring cusps meet. The commissure aligns with the region of aortic valve-mitral valve continuity, separating the noncoronary and left coronary leaflets (Mihaljevic, et al., 2008). The fibrous aorto mitral curtain, a crucial anatomical landmark that directs the surgeon during root enlargement procedures, is located beneath this commissure. Calcification and the spread of infections are frequent occurrences along this curtain. The noncoronary leaflet is located to the right of this commissure, and the AV is directly attached to the right atrial wall (Mihaljevic et al., 2008).

THE NORMAL HISTOLOGY OF AORTIC VALVE:

The ventricularis, located on the ventricular side of the leaflet, is composed of radially aligned, elastin-rich fibers that are perpendicular to the leaflet margin. Collagen fibers and fibroblasts, the main constituents of the fibrosa, are arranged circumferentially, parallel to the leaflet margin, on the aortic side of the leaflet(Freeman & Otto, 2005). The spongiosa is a loose layer of connective tissue located at the base of the leaflet, situated between the ventricularis and the fibrosa. Tensile strength and pliability for decades of repeated motion are provided by these layers combined**(Freeman& Otto, 2005)**,

PATHOPHYSIOLOGICAL ASPECTS OF AVS:

Atherosclerosis:

Aortic valve sclerosis, or AVS, is a condition that is characterized by localized inflammation and the accumulation of plasma lipoproteins within the lesions. There are several similarities between it and atherosclerosis. Though it is distinct from atherosclerosis, aortic valve disease shares some similarities with the latter's initial lesions, consisting of subendothelial buildup of intracellular lipids and lipoproteins, disruption of the basement membrane, and T lymphocyte, foam, and nonfoam cell infiltration, as well as systemic and localized inflammation activation(Rajamannan & Otto, 2004).

However, calcification in AVS is more extensive than in atherosclerosis, and the disease's clinical manifestations are caused by fibrocalcific thickening (Rajamannan & Otto, 2004).

Comparison of endothelial function in healthy individual. Patients with aortic valve sclerosis (AVS) have increased intima-media thickness, which is indicative of early atherosclerotic vascular structural changes, and decreased endothelium-dependent, post-ischemic, flow-mediated dilatation (Rashidi et al., 2005). This strengthens and validates the theory linking AVS, atherosclerosis, and a higher chance of subsequent cardiovascular events in individuals with valve sclerosis (Diehl, et al., 2008).

Furthermore, research on aortic valve tissues obtained during surgical intervention has demonstrated that, in comparison to normal valves, diseased aortic valves express a greater number of endothelial markers and von Willebrand factor. These findings provide additional evidence for the link between endothelial dysfunction and the advancement of calcified aortic valve disease (CAVD) (Parolari et al., 2009).Based on clinical research, increased levels of the endothelial dysfunction marker symmetric dimethylarginine (ADMA) in the plasma that manifests at some stage during the disease's clinical course, are linked to advanced CAVD. It takes nitric oxide (NO) to stop valve calcification from developing(Ngo, et al., 2009).

LIPID METABOLISM:

One of the conventional risk factors for atherosclerosis, abnormalities in lipid metabolism, has been linked to calcific aortic valve disease (CAVD). Otto et al. (1994) suggested that lipid metabolism and CAVD might be related. Neutral lipids, both extracellular and intracellular, are present in high concentrations in diseased aortic valves but not in healthy valves

Numerous studies, including O'Brien et al. (2002), which clearly demonstrated that circulating lipids could penetrate aortic valve leaflets and, as a result, have local effects in the aortic valve interstitium, bolster the notion that lipid metabolism and AVS are closely related. Furthermore, in sclerotic aortic valves, Apolipoprotein B and circulating low-density lipoprotein co-localize with the angiotensin converting enzyme. This discovery implies the concentration of the angiotensin converting enzyme in aortic lesions could be caused by plasma lipoprotein retention. LRP5, or The cell-surface receptor known as low-density lipoprotein receptor related protein is a member of the low-density lipoprotein receptor-related protein family. It participates in a number of biological functions, such as retinoid uptake, neuronal

migration, and lipid metabolism. Another way that lipid metabolism and AVS are related is through the process of aortic valve mesenchymal myofibroblasts differentiating into osteoblasts, which is where LRP5 comes into play(Caira, et al., 2006).

INFLAMMATION:

It has been known for more than ten years that aortic valve "early lesions" are marked by inflammatory characteristics; T lymphocytes and macrophages have been found, and monocytes use adhesion molecules to penetrate the endothelium layer and mature into macrophages. There is intense extracellular matrix remodeling occurring in the subendothelium and fibrosa in tandem with the formation of neovessels. This combination of inflammation mediators and matrix remodeling strongly suggests a rational role for inflammation during the course of aortic valve disease (Freeman & Otto, 2005). These areas see the release of proinflammatory cytokines by activated T cells, including interleukin-1ß and transforming growth factor-ß1.

OXIDATIVE STRESS:

Early atherosclerotic and aberrant oxidative stress conditions set off the myofibroblast cell's calcification process activation. It has been shown that high concentrations of the valve's calcified and peri-calcific areas, superoxide and hydrogen peroxide cause severely calcified aortic valves to exhibit increased oxidative stress. Moreover, the manifestation and functionality of catalase and other antioxidant enzymes decline in tandem with the rise in reactive oxygen species. It is still unclear how the processes driving elevated oxidative stress in aortic valve disease are different from those driving atherosclerosis, but cyclic stretch, cell proliferation, and cardiovascular risk factors all activate these cells to change into calcifying phenotypes(Rajamannan, et al., 2003).

INFECTION:

In addition to being suggested as potential causes or promoters of coronary heart disease, infectious agents have sparked interest as potential sources of CAVD. Chlamydia pneumoniae is a particularly interesting case. The majority of studies discovered that Chlamydia pneumoniae was more common in aortic valve disease than in healthy aortic valves, despite contradicting data(Juvonen et al., 1997). According to recent research by Bratos-Perez et al. (2008), A significant proportion of surgically removed severely stenotic aortic valves (48/75, 64%) provide proof that self-replicating calcifying nanoparticles, also known as nanobacteria, are present, which proliferate over time when cultivated in the appropriate media. These nanobacteria have previously been detected in Human calcific valves or vessels, abdominal aortic aneurysms, and carotid disease; they may represent novel pathogens that are presently under investigation. However, more proof is required to definitively establish the involvement of these agents in CAVD or any other infectious agent that might be involved.

GENOMICS:

Numerous genomic investigations have evaluated the potential correlation between genetic factors, primarily related to atherosclerosis and bone metabolism, and calcific aortic valve disease (CAVD) (Parolari et al., 2009).Regarding atherosclerosis, Avakian et al. (2001) The frequency of AI and apolipoprotein E in aortic stenosis patients was assessed, and the results were inconsistent with previous research suggesting a potential connection between the development of aortic valve disease and lipid metabolism(Parolari et al., 2009).

The evaluation of genetic polymorphism of the vitamin D receptor, which predicts either bone mineral mass or density, has been used to study the genomics of bone metabolism. The B allele is linked to increased levels of parathormones, a propensity for more rapid bone loss as one ages, and decreased calcium absorption, is more frequently found in patients with aortic valve stenosis. These findings suggest that the profile of bone metabolism that encourages calcium mobilization from bone may contribute to calcification of the aortic valve(Ortlepp et al., 2001).

Replicative senescence is a nondividing state that occurs after a certain age. that somatic cells go through along with particular morphological and cellular alterations, such as the shortening of telomeres during cell replication (Goldbarg et al., 2007).Senescent cells with shorter telomeres may be present in aortic valve cusps, which require continuous cell turnover due to their constant mechanical stress. Research has shown that in elderly patients, calcific aortic disease is positively correlated with shorter leukocyte telomere length (Goldbarg, et al., 2007).

Moreover, some alpha estrogen receptor polymorphisms may have an impact on the aortic valve calcification process. These polymorphisms may be associated with the frequency of calcification of the aortic valve in women who have gone through menopause, most likely due to high cholesterol(Nordstrom, et al., 2003).

Thus far, research suggests that the development of aortic valve disease is solely caused by polymorphisms in bone metabolism; the roles of genomics related to lipid metabolism and cell cycle regulation are yet unknown(Parolari et al., 2009).

Bone metabolism:

Nonetheless, Microscopic calcification coexists with areas of lipoprotein accumulation and inflammatory cell infiltration in aortic sclerosis. Active calcification plays a major role in the leaflet stiffness of severe aortic stenosis and is noticeable at an early stage of the disease(Freeman & Otto, 2005). It has been shown that osteopontin is expressed by macrophages, a protein required for the development of bones. There is a correlation between the location and degree of valvular calcification and the expression of osteopontin mRNA(Freeman & Otto, 2005). A nidus for early calcification, matrix vesicles are released by valvular fibroblasts in response to stimulation from oxidized low-density lipoprotein (LDL). Furthermore, calcific nodules have been linked to certain valvular myofibroblasts with an osteoblast

phenotype; in vitro, these myofibroblasts have been demonstrated to form calcific nodules at a higher rate when growth factor-ß1 is transformed and exposed to oxidized lipids(Rajamannan, et al., 2003).

CONCLUSION:

Aortic sclerosis is linked to a high-risk clinical profile in adults with AVS who do not have stenosis or other overt valvular disease. This includes older age, hypertension, smoking, ischemic heart disease, chronic renal failure, higher total cholesterol, higher LDL, lower HDL, higher serum calcium, and serum phosphate, as well as preclinical CVD echocardiographic findings, including increased blood flow velocity across the aortic valve, abnormal left ventricular geometry (thickened posterior wall and interventricular septum), decreased ejection fraction (EF%), and enlarged left atrium combined with diastolic dysfunction, aortic regurgitation, mitral annular calcification, and aortic root calcifications, all of which may worsen the prognosis associated with aortic valve sclerosis.

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