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Review Paper

Severity of Coronary Artery Disease linked to Lipoprotein-a in Aortic Valve Sclerosis

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ABSTRACT

Calcific aortic valve disease is the most common valvular heart disease in the Western world, and its prevalence is increasing. Aortic valve sclerosis (AVS) was formerly thought to be a natural degenerative process linked with ageing. As a result, clinicians typically considered the frequent and well-known mild, basal ejection murmur of aortic sclerosis to be of little or no clinical importance.AVS has been the subject of both clinical and animal research during the last decade. Despite the fact that AVS has emerged as a biomarker for cardiovascular risk, a meta-analysis of prospective studies found that plasma lipoprotein-a Lp(a) concentration is an independent risk factor for CHD in both men and women. Several studies have shown that Lp(a) is a distinct risk factor for cardiovascular disease. Previous research has found a link between Lp(a) levels and preclinical atherosclerosis, such as angiographic coronary atherosclerosis, ultrasonographic intima-media wall thickening, and calcification in the extracoronary arteries. Previous research has suggested that serum Lp(a) levels are positively linked with the occurrence of cardiovascular disease, implying that Lp(a) might be one of the independent risk factors for aortic valve sclerosis.

Aortic valve sclerosis

Calcific aortic valve disease is the most common valvular heart disease in the Western world, and its prevalence is increasing.Aortic valve sclerosis (AVS) was formerly thought to be a natural degenerative process linked with ageing.As a result, clinicians typically considered the frequent and well-known mild, basal ejection murmur of aortic sclerosis to be of little or no clinical importance.AVS has been the subject of both clinical and animal research during the last decade. In 1997, AVS emerged as a biomarker for cardiovascular risk, eventually leading to aortic stenosis in 16% of people. [(1)]

It is a slowly progressing condition with a clinical spectrum ranging from moderate valve thickening without restriction of blood flow, known as aortic sclerosis, to severe calcification with restricted leaflet mobility, known as aortic stenosis. This mechanism was formerly considered to be "degenerative" due to time-dependent wear-and-tear of the leaflets with passive calcium accumulation.There is now convincing histological and clinical evidence that calcific valve disease is an active disease process with lipoprotein accumulation, persistent inflammation, and active leaflet calcification, similar to atherosclerosis.

The overlap in clinical characteristics associated with calcific valve disease and atherosclerosis, as well as the association between the severity of coronary artery and aortic valve calcification, provide credence to the idea of a common disease process. [(2)]

Risk Factors for coronary artery disease

Aortic sclerosis and coronary disease share numerous risk factors, including male gender, older age group, cigarette use, diabetes mellitus, hypercholesterolemia, hypertension, hyperparathyroidism, renal illness, reduced bone density, and metabolic syndrome, according to several lines of evidence.

The role of elevated C-reactive protein (CRP) as a risk factor for aortic stenosis is debatable.Several investigations have found a link between aortic sclerosis and higher CRP levelsHowever, a recent prospective research comprising 5621 patients followed for 5 years and employing echocardiography and CRP measures found no link between CRP and the development of aortic sclerosis.Furthermore, being Caucasian and short in stature were found to be associated with the development of aortic sclerosis. [(3,4)]

Inflammation and lipoproteins

Mechanical stress causes endothelial dysfunction over time, which is subsequently exacerbated by an inflammatory cell infiltration composed of both T-lymphocytes and macrophages. Through adhesion molecules, monocytes enter the endothelium and develop into macrophages. [5] .These inflammatory cells upregulate inflammatory cytokines, transforming growth factor, and interleukin after entering the endothelium, all of which operate on valvular fibroblasts and promote cellular proliferation, extracellular matrix remodeling, and local calcification. Extracellular lipid deposition is found in tiny regions of the subendothelial region inside each valve leaflet, causing displacement of the elastic lamina and expansion into neighbouringfibrosa. [6] .

When LDL enters the subendothelial layer, it undergoes oxidative alteration and is then consumed by macrophages to form foam cells. Aortic sclerosis has been linked to high levels of plasma asymmetric dimethyl-arginine, a sign of endothelial dysfunction, according to research. [7]and that nitric oxide (NO) has a role in preventing valve calcification[8].Aortic sclerosis has been linked to NO resistance in platelets, which explains why individuals with aortic sclerosis have a higher risk of thrombosis. [9].

Angiotensin converting enzyme and extracellular matrix

The angiotensin converting enzyme (ACE) has been found in aortic sclerotic lesions.[10].Although part of this enzyme may be generated locally, there is evidence that the bulk of it is extracellular and co-localized with apolipoprotein B. During systole, the aortic valve is subjected to pulsatile repeated pressure and shear stress, whereas during diastole, it is subjected to cyclical stretch and turbulent shear stress. Endothelial cells and the matrix convey them to valve interstitial cells (VICs). [11], This causes cell proliferation, increased collagen deposition, apoptosis, and increased expression of cathepsin S and K.. Additionally, increasing cyclic stretch enhances the expression and activity of matrix metalloproteinase (MMP)-1, 2, and 9, while decreasing the expression and activity of cathepsin L and tissue inhibitor of metalloproteinase-1 (TIMP-1) [12] .

In individuals with aortic sclerosis and coronary artery disease, soluble vascular cell adhesion molecule-1 (VCAM-1) increases, while soluble intercellular adhesion molecule-1 (ICAM-1) and s-E selectin decrease. [13].There is also an increase in the expression of elastolyticcathepsins S, K, and V, as well as their inhibitor cystatin C. [14].The relationship between calcific aortic valve disease and an increase in endothelin-1 and endothelin-2.In aortic calcific disease, a receptor supports the findings of inflammation and fibrosis.[15] .

Diagnosis of AVS

Clinically, aortic valve sclerosis can be suspected during physical examination by the presence of a mild ejection systolic murmur in the aortic region, a normal split of the second heart sound, and a normal volume carotid pulse; echocardiography is the best way to confirm it. It is characterized echo- cardiographically by localized regions of valve thickening, generally in the leaflet center, with commissural sparing and normal leaflet movement.

Diffuse leaflet thickness does not indicate aortic sclerosis; rather, it implies typical ageing changes, a separate valve disease, or an imaging artifact..According to some, the severity of aortic valve sclerosis can be graded as follows: grade 1 = increased echo density; grade 2 = 3 mm thickening or calcific deposits; and grade 3 = same as grade 2 with mildly restricted motion of aortic leaflets and pressure gradient of 16 mmHg across the aortic valve. [16]

Aortic sclerosis may be associated with mitral annulus calcification (up to 50%) and coronary artery calcification, although seldom with aortic regurgitation. [17]

The absence of reliable techniques to measure the degree of sclerosis has been a key issue in the study of aortic sclerosis. In contrast to aortic stenosis, when velocity is increased through the aortic valve, Doppler measures are ineffective in aortic sclerosis.

The amount of calcification observed on the aortic leaflets in the short axis image on the echocardiography has been used to assess the degree of aortic sclerosis. Although echocardiography is the gold standard for detecting aortic valve sclerosis, it does not measure calcium. Electron-beam tomography may be the most suited imaging modality; this approach may quantify and sequentially monitor aortic valve calcification. The relevance of aortic valve bioprosthesis calcification and its association with cardiovascular events is unknown.

Clinical Outcomes in Adults With Aortic Sclerosis

Despite the fact that aortic sclerosis is clinically asymptomatic, its presence is related with higher morbidity and mortality, even when other cardiovascular risk factors are controlled for.Aortic sclerosis was linked with a 40% increase in the risk of myocardial infarction and a 50% increase in the risk of cardiovascular mortality in individuals with no prior diagnosis of coronary artery disease at study entrance in the Cardiovascular Health Study.[18]Similarly, those with aortic sclerosis had a 1.8-times greater probability of getting a new coronary incident in a prospective analysis of over 2000 older patients, with further investigations correlating these findings.[19] .The mechanism of aortic sclerosis-related poor outcomes is not completely understood.The valve lesion is unlikely to be the major cause since valve hemodynamics are normal or near normal, and the time course suggesting a connection of aortic sclerosis with adverse outcomes is brief in comparison to predicted hemodynamic progression rates.Furthermore, embolization of valve-related plaque or thrombus into the coronary arteries is improbable since no studies have shown that aortic sclerosis valve lesions are unstable or linked with thrombus development. [20,21]. Aortic sclerosis has been considered as a surrogate sign for either underlying

atherosclerotic disease or valvular dysfunction.[22]or some broader systemic activity, such as inflammation.[23]The cardiac catheterization laboratory, where up to 50% of patients with severe aortic stenosis undergoing preoperative assessment for valve replacement are identified with concomitant substantial coronary artery disease, provides supporting evidence for a surrogate marker for atherosclerosis. Another piece of evidence supporting this idea is the overlap in genetic polymorphisms linked with both disease processes. [24]

This relationship, however, cannot explain the reported adverse outcomes since not all patients with aortic stenosis develop coronary artery disease. Aortic sclerosis may be a proxy sign for a systemic inflammatory disease, as evidenced by connections to nonspecific indicators of inflammation such as serum homocysteine, C-reactive protein, and endothelial dysfunction. According to one study, this connection is reversible, with a reduction in blood C-reactive protein levels in individuals with aortic stenosis after valve replacement. [25]

However, further research contradicts the apparent link between inflammatory indicators and calcific aortic valve disease. After controlling for age, gender, and smoking history in a recent prospective clinical cohort analysis of 381 patients, numerous indicators of inflammation, including blood counts, fibrinogen, and Chlamydia pneumoniaeseropositivity, were not related with aortic sclerosis.[25]

Despite histopathologic evidence supporting a disease model of leaflet endothelial damage with local inflammatory alterations and leaflet remodeling, as well as evidence of an unfavorable risk associated with aortic sclerosis, a definite connection to a systemic inflammatory state has yet to be shown.Endothelial dysfunction, genetic polymorphisms, or another unidentified cause are other plausible explanations for the elevated cardiovascular risk linked with aortic sclerosis.

Lipoproteins and cardiovascular disease

Elevated plasma levels of low density lipoprotein (LDL) and low levels of high density lipoprotein (HDL) represent a significant risk of cardiovascular disease development.[26]. Saturated fat consumption and sedentary lifestyle have been linked to around 31% of coronary heart disease and 11% of stroke in people. The Framingham Heart Study and other research indicate that [27], Cigarette smoking of any amount, elevated blood pressure, elevated serum total cholesterol and low-density lipoprotein cholesterol (LDL-C), low serum high-density lipoprotein cholesterol (HDL-C), diabetes mellitus, and advancing age are the major and independent risk factors for coronary heart disease (CHD). Recently, Patrick and Uzick published a review. [28]Levels of circulating homocysteine, fibrinogen, C-reactive protein (CRP), endogenous tissue plasminogen-activator type I, lipoprotein(a), factor VII, and specific infections such as Chlamydia pneumonia were identified as novel risk factors for CHD.

These investigations demonstrated that an individual's overall risk is the sum of all significant risk variables. Conditional risk factors and predisposing risk factors are the other variables that contribute to the overall risk of CHD. Although the conditional risk variables are associated with an elevated risk of CHD, their causal, independent, and quantitative contributions to CHD are not fully proven. The independent risk variables are exacerbated by the predisposing risk factors.

The American Heart Association has recognized two of these risk factors as significant risk factors: obesity and physical inactivity (AHA) [27]. Obesity's negative consequences are exacerbated when it manifests as abdominal obesity, an indication of insulin resistance. These risk factors are present prior to the clinical presentation of coronary atherosclerotic disorders. The therapeutic importance of these risk assessments is to identify high-risk patients who need to be monitored, motivate patients to adhere to risk-reduction therapy, and adjust the amount of risk-reduction effort necessary in potential patients..[28]

Lp(a) and atherosclerosis

Nonetheless, a meta-analysis of prospective studies found that plasma Lp(a) concentration is an independent risk factor for coronary heart disease in both men and women. Lp(a) was recently established as a predictor of CHD risk in the Prospective Epidemiological Study of Myocardial Infarction (PRIME), a cohort study that included 9133 men from France and Northern Ireland with no history of CHD or use of hypolipidemic medications. [29]. Atherosclerosis has been shown to be a major pathogenic component in the occurrence and progression of aortic valve sclerosis.[30,31].Lipoproteins in the blood (a)

Lp(a) is an independent macromolecular lipoprotein that consists of a Lp(a) with a high degree of homology and specific antigenicity, which plays a pivotal role in the incidence and development of atherosclerosis and thrombosis through the underling mechanism of interfering lipid metabolism and fibrinolytic system, which is significantly different from the metabolic pathways of alternans. Several studies have shown that Lp(a) is most likely an independent risk factor for cardiovascular disease. [32]. Previous research has shown that Lp(a) levels are associated to preclinical atherosclerosis, particularly angiographic coronary atherosclerosis.[33], Extracoronary artery ultrasonographic intima-media wall thickening and calcification[34]. Previous research has suggested that serum Lp(a) levels are positively linked with the occurrence of cardiovascular disease, implying that Lp(a) might be one of the independent risk factors for aortic valve sclerosis. [35,36]. However, the link between Lp(a) levels and aortic valve sclerosis remains a mystery. The clinical outcomes of blood lipid and coronary angiography were retrospectively analyzed for 8 consecutive years in a study of 1260 hospitalized patients with aortic valve sclerosis, with the goal of evaluating the diagnostic value of serum Lp(a) and its association with the severity of aortic valve sclerosis in the elderly population. Apo lipoprotein (a) [apo(a)] is a hydrophilic glycoprotein with striking similarity to plasminogen. [36].It inhibits tissue-type plasminogen activator in a competitive manner.[37-39]It inhibits tissue-type

plasminogen activator in a competitive manner.[40]. It inhibits tissue-type plasminogen activator in a competitive manner.[40]The protein Lp(a) has been proposed as a link between the atherosclerotic and thrombotic features of coronary artery disease (CAD). Lp(a) levels are highly heritable. [41], and it has been shown [42]Lp(a) has been postulated as a connection between the atherosclerotic and thrombotic aspects of coronary artery disease (CAD).

Levels of Lp(a) are strongly heritable. A history of prior myocardial infarction is also associated with elevated plasma Lp(a) (MI) [43,44]A history of prior myocardial infarction is also associated with elevated plasma Lp(a) (MI) [45-48].Nonetheless, there is still some ambiguity about the relationship between plasma Lp(a) and angiographically defined CAD.

Some investigations have found a link between plasma Lp(a) levels and the severity of angiographic illness. [49-54], but others have failed to confirm these findings [56]. This debate may be fueled by a paucity of data on clinical status and coronary risk factors in much such research.

Furthermore, women have frequently been underrepresented, restricting the possibility of analyzing potentially significant gender disparities. In one research, plasma Lp(a) levels were evaluated in a sequential series of well-characterized white men and women having coronary angiography for the evaluation of chest pain compatible with chronic stable angina. This method allowed for a thorough examination of the relationship between Lp(a) levels, CAD severity, and other clinical factors in men and women.

Lp(a) and AVS linked to CAD

Lipoprotein(a) is considered a causal risk factor for ischemic Cardiovascular disease [57].A genome-wide association research recently discovered a genetic variation (rs10455872 SNP) in the LPA gene locus, regulating plasma levels of Lp(a), as linked with aortic valve calcium and sclerosis (AVS) [57].

In Western countries, the most prevalent heart valve problem requiring treatment is calcific aortic valve disease. It is projected that 2% to 7% of the population over the age of 65 would be affected. [58]. Previously thought to be a passive, degenerative condition in which the valve degenerates with age due to calcium accumulation, it is becoming clear that disease progression is a regulated process that shares risk factors with atherosclerotic cardiovascular disease, such as elevated cholesterol levels, hypertension, smoking, and diabetes mellitus. [59,60]. Furthermore, congenital aortic valve abnormalities, such as bicuspid valve shape, which may be present in 50% of individuals with severe AVS, are major risk factors.[61]However, despite certain common risk factors with atherosclerotic disease, there is currently no effective way to prevent aortic valve disease development, and aortic valve replacement, which is expensive and linked with perioperative mortality, remains the sole therapeutic option. It is believed that identifying causative risk factors would lead to possibilities for prevention.

Lp(a) consists of a cholesterol-laden low-density lipoprotein particle bound to a plasminogen like glycoprotein, apolipoprotein(a) [62]. Lp(a) promotes atherosclerotic stenosis, and possibly thrombosis, and has been hypothesized to contribute to wound healing [63].,Each of these explanations might account for a connection with AVS. Plasma levels of Lp(a) are largely influenced by variations in the LPA gene, which codes for apolipoprotein (a). The kringle IV type 2 (KIV-2) repeat polymorphism in the LPA gene determines the size of the expressed apolipoprotein (a), the size of which corresponds inversely with Lp(a) levels. [64].

A new discovery in a general population context was found in a prospective study of 77,680 people that showed a dose-dependent higher risk of AVS in those with elevated Lp(a) levels. Persons with Lp(a) levels over the 90th percentile had a twofold to threefold higher risk of AVS compared to those in the lowest fifth of the concentration range, with similar findings in women and men separately.. Furthermore, the confirmed association of LPA rs10455872 minor allele carrier status with an increased risk of AVS, combined with our instrumental variable analysis results that included information on three LPA genetic variants (all associated with lipoprotein[a] levels), suggests that the association may be causal. Lp(a) is an emerging risk factor for ischemic cardiovascular disease [65], where data from in vitro, animal, and large genetic studies of LPA gene variants [65] provide evidence for a causal role in promoting atherosclerotic stenosis, and possibly also thrombosis at extreme Lp(a) levels. Lp(a) has been proposed to have a role in wound healing (64), where it may bind to fibrin via its apolipoprotein(a) component, perhaps blocking fibrinolysis and limiting bleeding, and transport cholesterol via its low-density lipoprotein component to areas of tissue repair. Data indicating preferential accumulation of Lp(a) at areas of tissue damage and healing corroborate this notion. [64, 65].

Both Lp(a)-mediated mechanisms involved in normophysiological phenomena such as wound healing and pathophysiological manifestations such as atherosclerotic stenosis may explain an association with AVS, which is thought to be an ongoing process of injury and tissue repair responses sharing risk factors with atherosclerotic disease. In humans, apolipoprotein (a), B, and E have been found in early to late-stage aortic valve lesions (but not in unaffected valves). [66, 67].

AVS with or without underlying congenital abnormalities and subsequent post-stenotic turbulent flow leading to Lp(a) increases, potentially also depending on isoform size, could be an additional explanation for the relationship of Lp(a) levels with risk of AVS. However, because AVS cannot change a person's LPA genotype, reverse causality cannot explain the relationship of genotype with AVS. Furthermore, for the relationship of LPA genotypes with AVS risk to be confounded by, say, a concurrent bicuspid valve, the LPA genotypes must be in linkage disequilibrium with genes implicated in congenital bicuspid valve development, which has never been reported to the best of our knowledge. Furthermore, given the stepwise relationship of the LPA rs10455872 SNP and the amount

of KIV-2 repeats with the incidence of AVS, confounding by linkage disequilibrium is extremely improbable. In smaller case-control studies, higher Lp(a) levels were linked to an increased risk of AVS or aortic valve sclerosis, which is thought to be a precursor to AVS. [68-70]and in an older population, those with levels above the 75th percentile had a 23% higher incidence of mainly aortic valve sclerosis compared to those with levels below the 25th percentile in cross-sectional analysis. [71, 72].

A genome-wide association analysis has found the LPA rs10455872 minor allele to be linked with the presence of aortic valve calcium, a putative early phenotype for valvular heart disease. An instrumental variable analysis employing just this variation in a subgroup of individuals showed a link between increased Lp(a) levels and aortic valve calcium. They contributed confirmatory data (i.e., rs10455872 genotypes in the CCHS) to the study, demonstrating an association of rs10455872 with clinical AVS in the CCHS (73) and demonstrated a clear stepwise increase in risk of AVS with increasing levels of Lp(a) in the general population in this combined study of the CCHS and the CGPS. Furthermore, it provides genetic data based on three LPA gene variants, accounting for 41% of the total variation in plasma Lp(a) levels and demonstrating a 1.6-fold increased risk of AVS with a 10-fold increase in genetically elevated Lp(a) levels; importantly, Lp(a) levels can vary 1,000-fold between individuals. It is worth noting that the rarity of rs3798220 carrier status significantly restricted our ability to forecast any higher risk of AVS based only on this genotype.

In contrast to the findings for aortic valve disease, increased Lp(a) levels do not appear to have a significant role in coronary artery calcification linked with low-density lipoprotein cholesterol and apolipoprotein B levels, according to a recent study. [74] and this may reflect differences in pathobiology of valvular vs. vascular calcification. Also, we found no association of apolipoprotein B levels with risk of AVS.

Significant relationship of Lp(a) with CHD is reported in South Indian studies [75,76]. Lp(a) levels are associated with both early and advanced atherosclerosis, as well as the severity, extent, and development of atherosclerosis, as well as all CHD problems, such as re-stenosis following percutaneous transluminal angioplasty, stent, and bypass surgery. [77]. Lp(a) excess increases the risk of premature CHD 3 to 100 fold depending on the absence or presence of concomitant risk factors [78]. As a result of prosperity, urbanization, and automation, the Indian population is undergoing pandemic change. The study of Lp(a) will aid in the identification of risk variables linked with the malignant character of CHD in the Indian population. Furthermore, measuring Lp(a) levels in various groups can aid in identifying the high-risk group that requires strong pharmaceutical therapy. [79, 80].

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