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Homocysteine can induce calcific aorta valve stenosis with or without coronary artery disease in the elderly surgical and medical measures

Abstract

Calcific aortic stenosis (CAS) more frequently was found in aged patients with elevated homocysteine (Hcy) levels. Endothelial dysfunction, oxidative stress, sub-endothelial accumulation of lipids and inflammatory cells, reactive oxygen species (ROS) production, extracellular matrix (ECM) remodeling and others are the leading causes inducing aortic stenosis (AS). Subsequently, these valvular aortic areas can converge in large calcified masses, causing CAS. On the other hand, risk factors acting on aortic valvular leaflets can also cause atherosclerotic coronary artery disease (CAD). The coexistence of CAS and CAD rather occurs in aged patients, but more frequently is present in those with HHcy. Traditional therapeutic interventions, such as surgical aortic valve replacement (SAVR) + coronary artery by-pass grafting (CABG), must be performed in patients contemporarily suffering of severe CAS and symptomatic CAD. But, a mini-invasive treatment, such as percutaneous coronary intervention (PCI), can be coupled to SAVR ("hybrid" treatment), or with transcatheter aortic valve implantation (TAVI) when the aged patients have a high-risk or are inoperable. Folic acid or vitamins $B_{6\text{-}12}$ supplementation, even if decreases HHcy don't reduce the incidence of AS. On the contrary, Angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers can be used to delay AS when systemic hypertension coesists. Likely, some anti-lipemic drugs, as Niacin, can be employed in the presence of contemporary hyperlipemia. Finally, specific compounds, such as Biphosphonates, Denosumab or vitamin K must be given for reduce or delay the aortic valve calcification.

Keywords: calcific aortic stenosis, CAS, homocysteine, coronary artery disease, CAD

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Abbreviations: CAS, calcific aortic stenosis; ROS, reactive oxygen species; ECM, extracellular matrix; Hcy, homocysteine; AS, aortic stenosis; CAD, coronary artery disease; CABG, coronary artery by-pass grafting; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; LDL, low-density lipoproteins

Introduction

Calcific aorta valve sclerosis (CAVS) is a common disorder, mainly happening in aged individuals[1] that may, slowly but progressively, evolve in calcific aortic stenosis (AS) with or without valve calcification.[2] CAVS is the most common valvular hearth disease in developed countries and, in the future, its impact on public health is expected to bright increase.[3,4] Nowadays, CAVS affects over 25% of patients over 6yrs. and its prevalence in elderly is around 13%.[5] But, most of these have only mild thickening with preserved valve function, and 2-5% alone evolve in significant AS, with obstruction of left ventricular outflow tract.[6] Accumulate evidences suggest that chronic inflammation and other risk factors are responsible for AS beginning from CAVS. The frequency of AS increases with ageing because the atherosclerotic progressively rises with advancing age. In 2050, population aged >/=65years is espected to rise by two-fold and so, AS in elderly can reach the percentage of 6-8%.[7] It must also add that AS, with or without valve calcification, increases side by side with coronary atherosclerosis. But, the risk factors related to the development of AS play also a role in the development of coronary artery disease (CAD).[8] Common causes of AS are: male gender, advanced age, smoking, systemic hypertension, high low-density lipoproteins (LDL), metabolic syndrome, and diabetes mellitus.[5] But, increased homocysteine (Hcy) levels also are considered as an independent risk factor for atherosclerosis and therefore for AS.[9]

In the review, we debate about the main causes and the frequency of AS in aged patients with increased Hcy serum concentration in comparison to aged individuals without high Hcy serum levels. The main studies about the relationship between high Hcy levels and AS are reported in Table I. In addition, the possible causes of AS calcification, and the modalities of surgical treatments are described.

Table 1 The main studies connecting Hyper-homocysteinemia with Aortic Stenosis

Plasma homocysteine and calcific aortic valve disease.
The relation between homocysteine and calcific aortic valve stenosis.
Role of homocysteine in aortic calcification and osteogenic differentiation.
Association between homocysteine levels and calcific aortic valve disease: a systematic review and meta-analysis.

Some studies about the connection between Hyperhomocysteinemia and Aortic Stenosis

Table 2 Peak velocity measured in m/s, aortic mean gradient in mmHg, and valvular aortic area (AVA) measured in cm^2

Parameters	Mild	Moderate	Severe
Peak velocity (m/s)	<2.6-2.9	3.0-4-0	>40
Mean gradient (mmHg)	<20	20-40	>40
AVA (cm^2)	>1.5	1.0-1.5	<1.0

Homocysteine

Hcy is a sulphur-containing amino acid that can be further metabolized via two pathways respectively called: remethylation and transsulfuration routes. In the first, Hcy is remethylated to Methionine by methionine synthase (MS), which uses vitamin B_{12} as cofactor and by methylentetrahydrofolate reductase (MTHFR) that uses folic acid as coenzyme. In transsulfuration pathway, Hcy reacts with serine to form cystathionine. This reaction is catalyzed by cystathionine ß-synthase (CBS), a vitamin B_6-dependent enzyme. This pathway continues, until the synthesis of cysteine.[10]

Calcification of aortic stenosis (CAS)

The aortic valve leaflets are made up of highly organized extracellular matrix (ECM) and valve interstitial cell (VIC) surrounded by endothelial cell layers. These are composed by the "ventricularis" layer that includes fibers of elastin aligned in a radial direction. The "fibrous" layer that comprises fibroblasts and collagen fibers. The "spongiosus" layer prevalently composed by connective tissue,[11] with ageing, the number of adipose cells in the spongious layer increases and extends into adjacent fibrous layer, with raised leaflet thickness. The subsequent phase is characterized by a calcium deposition in leaflets of the aorta.[12] Calcified nodules primarily are present at base of the cusps. Subsequently, their presence gradually extends toward the orifice. The pathophysiology of calcification of aortic stenosis (CAS) includes endothelial dysfunction, chronic inflammation, lipoproteins and fibrin accumulation, calcification, with limitation of blood flow through the valve.[13,14] Tran thoracic echocardiography is the method of choice to non-invasively evaluate the valve anatomy, to measure CAS severity, and to define left ventricular response to chronic pressure overload.[15] Echocardiography is also a diagnostic method to evaluate the calcification of sclerotic aortic leaflets. That is defined by bright echoes of 1 mm or more on cusps of the aortic valve (Figure1). The primary hemodynamic parameters are defined by doppler-echocardiography (Figure 2). In table II the values of peak velocity, AV mean gradient and aortic valve area, recorded in mild, moderate and severe AS, are reported.[16]

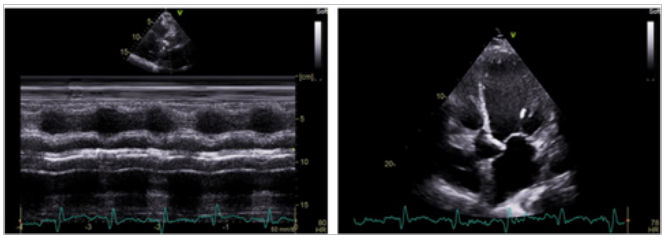

Figure 1 (sin.) Aortic leaflets calcification with reduced diastolic opening, at mono-dimensional echocardiography. (dx.) Calcification of aortic valve, seen at B-dimensional echocardiography.

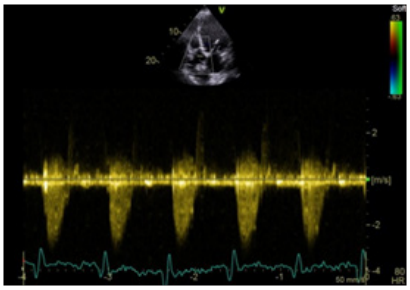

Figure 2 Doppler-echocardiography. Aortic mean gradient (23mmHg) indicative of light-mild stenosis.

Apart mild AS, symptoms of moderate/severe disease includes exertional dyspnea, heart failure, angina and/or syncope. Symptomatic disease requires no effective medical therapy, but aortic valve replacement. Traditional intervention happens via surgical aortic valve replacement (SAVR). Transcatheter aortic valve implantation (TAVI) is now available for patients with multiple and severe comorbidities. It is recommended in inoperable patients, and in those at high-risks (Figure 3).[17]

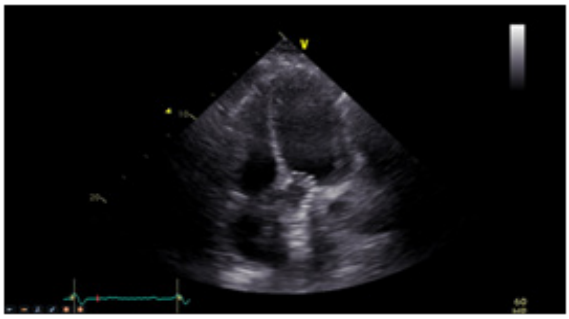

Figure 3 LV 2D-Echocardiography recorded in five chambers approach showing transcatheter aortic valve implantation (TAVI) on the aortic valve.

Hcy as cause of CAS

The mechanisms by Hcy can induce CAS aren't completely understood, and the relation between increased Hcy levels and CAS still remain unclair.[18] For a long time, the pathophysiological mechanism for the aetiology of CAS was believed to be a simple degenerative process, with a progressive reduction of diastolic separation among three aortic leaflets, characterized by passive accumulation of calcium in the aortic cusps. But, recent data suggest that CAS is an active process progressively involving the cusps of the aortic valve.[19]

Concerning the relationship between AS and Hcy, it is known that an increased Hcy plasma levels is as an independent risk factor for atherosclerosis.[20,21] Several causes can induce this degenerative process. The factors favouring the plaques' formation (such as platelets' activation, prevalence of pro-coagulant factors, inhibition of anticoagulant mechanisms, impairment of fibrinolysis) and others are included.[20–23] But, the most important cause verifying in early-stage of atherosclerosis must be reported to endothelial dysfunction (ED). That is caused by increased synthesis of Asymmetric-D-Methyl Arginine (ADMA), an endogenous inhibitor of endothelial NO synthase.[24,25] The cause of increased synthesis of ADMA is still unknown . This elevation can be is caused by an increased ADMA production, or its decreased metabolism, or another mechanism such

as altered renal clearance that reduces its excretion.[26] On other hand, the dysfunctional endothelium caused by ADMA is characterized by platelets' hyperaggregability, monocyte adhesion via activation of chemokine receptors, adhesion molecule expression, abnormal fibrinolytic activity, and immune cells' migration in the subendothelial layer leading to early and subclinical phases of atherosclerosis.[27–29] In addition, the inhibition of NO syntheses, in association with DNA hypomethylation (due to hyperhomocysteinemia), induces vascular smooth muscle cells proliferation and may contribute to the thickening of media layer of the endothelium.[30] Furthermore, elevated Hcy levels favour the synthesis of reactive oxygen species (ROS) that play an important role in the pathogenesis of AS.[31] Concordantly, hyperhomocysteinemia promotes oxidation of low lipoproteins, likewise involved in AS formation.[32,33] In Figure4 the leading causes Hcy-dependent of AS are reported. But, the mechanisms of leaflets' calcification is not completely known. Probably, upon endothelium cells damage, oxidized LDLs trigger a pro-inflammatory cytokines, disrupting cross-talk between valve endothelial and interstitial cells. Subsequently, these cells transform in osteoblasts, mineralizing the aortic leaflets (Figure 4).[14–34,35] Mechanical and metabolic stresses contribute to calcification too.[36]

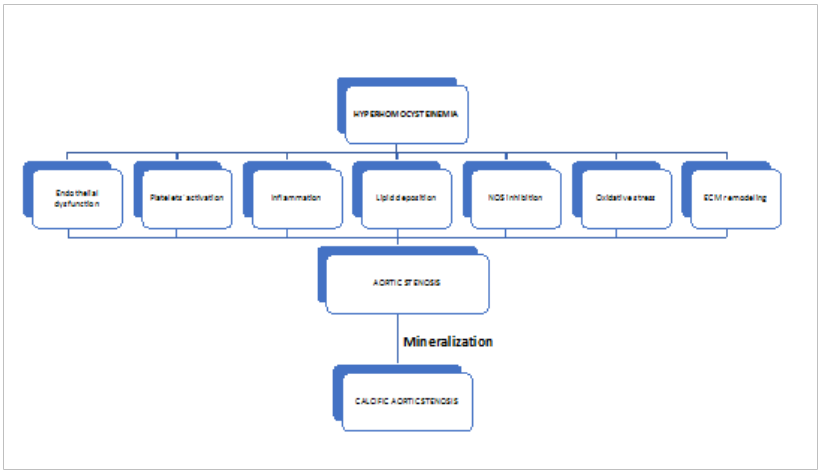

Figure 4 Pathogenesis of calcific aortic stenosis caused by hyperhomocysteinemia.

CAS is the most common form of valvular heart valve disease. It frequently occurs in older individuals without high Hcy serum levels. But, it more frequently happens in patients with increased Hcy levels. The valvular derangement often verifies in conjunction with coronary artery disease (CAD),[37] for increased tendency to atherosclerosis.[38] In persons without high Hcy levels, CAD is present in more 50% of patients with CAS having 70 years of age and in 65% of patients with CAS over 80years.[39] Hyper-Hcy increases the risk of AS + CAD for increased thrombosis, adverse effect on endothelial function, promoting thickening of the intima and oxidative damage.[40] Treatment for symptomatic patients contemporary suffering from CAS and CAD can be respectively surgical aortic valve replacement (SAVR) for CAS and concomitant coronary artery by-pass grafting (CABG) for CAD. However, more frequently, CAD is treated with percutaneous coronary intervention (PCI). Conversely, in last year's, CAS underwent to a less-invasive intervention, via transcatheter aortic valve implantation (TAVI), that may be performed in inoperable and in high-risk patients. Nevertheless, the results of coupling PCI and TAVI remains still unclair because barely performed.[41,42] It has also been proposed that some patients may also benefit from a "hybrid" procedure, in which PCI is combined with SAVR. In these cases, usually PCI is performed prior to TAVI (when required). On the contrary, TAVI followed by PCI less frequently can be carried out.[43]

Some medical therapies can be also performed in hyperhomocysteinemic patients with CAS. Particularly, folic acid and vitamins $B_{6\text{-}12}$ supplementation seems to delay atherosclerosis, that favours AS formation.[44] In addition, in hypertensive patients (with or without high Hcy) angiotensin converting enzyme inhibitors or angiotensin receptor blockers, reducing systemic hypertension, can contribute to delay AS.[45] Likely, in presence of hyperlipemia, statins are widely used for lipid lowering. This reduction delays and reduces both atherosclerosis and inflammation, responsible for AS progression.[46] But, statins are ineffective in reducing plasma concentration of Lipoprotein (a) [Lip(a)], a major responsible of AS. However, other therapeutic agents have demonstrated their ability in to reduce Lip(a). Among these, Niacin is included.[47] Concerning valve calcification, the drugs more frequently used to antagonize bone disease, such as Biphosphonates or Denosumab, seem to have beneficial effect on vascular and valvular calcification.[48,49] Finally, calcification of aortic leaflets is delayed by vitamin K supplementation, that seems to be able to increase the bioactivity of Matrix-Gla-Protein (MGP), a potent inhibitor of cardiovascular calcification.[50]

Conclusive remarks

CAS is a most com\mon valvular disease found in ageing. In subjects with elevated Hcy levels it is more frequent than in normal controls. A recent meta-analysis demonstrated that it is due to atherosclerosis. In the same study, Wu et al. confirmed that Hcy levels are also significantly associated with other vascular artery calcifications, such as coronary artery calcification and/or carotid calcification.[18] Concerning CAS, a study by Van Campenhout et al. also confirm an independent association of aortic calcification and circulating plasma Hcy and provides a number of cellular mechanisms which may underlie this phenomenon. In particular, the results obtained support a cooperative role for aortic smooth muscle cells (AoSMC) and monocytic cells in the calcification process, modulated

by the presence of Hcy In the atherosclerotic plaque.[51] However, the detailed relationship between high Hcy levels and valvular calcification remains still unclear.

It must be also added that in patients with advanced age and high Hcy values, CAS frequently coexists with CAD, for massive atherosclerosis and other added to age-dependent atherosclerotic stigmata. The condition may be corrected (at the same time or in following stages) by different surgical techniques, ranging from chest-open treatment (SAVR + CABG),[52] to mini-invasive procedures (PCI + TAVI). Referring PCI, the ACTIVATION study demonstrated non-inferiority of this procedure compared to CABG performed before TAVI.[53] Referring to medical therapy, although the use of folate and $B_{6\text{-}12}$ vitamins is an effective treatment for reduce the increased Hcy levels, its impact on the beginning and evolution of vascular/valvular disease remains inconclusive. Contrarily, some drugs employed to antagonize common diseases prone to atherosclerosis, appear to be useful for delay and/or minimize AS. In addition, Biphosphonates, Denosumab and vitamin K treatments seem to effectively reduce CAS. But, further studies are requested to clarify the dilemma about the substantial ineffectiveness of folic acid and vitamins $B_{6\text{-}12}$ supplementation to lower the incidence of calcific aortic valve disease in aged patients, even if reduce elevated Hcy levels. The efficacy of Biphosphonates, Denosumab and vitamin K should be also tested on a more wide range CAS-individuals.

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Conflicts of interest

Author declares that there aren't conflicts of interest.

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