Editorial

OxPL

Elusive Risk Factor in Calcific Aortic Valve Disease or Another Piece of the Puzzle?

Patricia J.M. Best, Nalini M. Rajamannan

Calcific aortic valve disease (CAVD) is the most common indication for surgical or transcutaneous valve therapy in the world.[1] The mechanisms responsible for the development of calcification in the aortic valve are under intense investigation using translational databases. Randomized clinical trials testing the role of statins in the slowing of progression of disease have been negative to date, despite the overwhelming evidence that traditional risk factors such as elevated LDL are associated with disease progression.[2–5] The emerging role of cardiovascular risk factors, genetic predisposition to CAVD, and mechanistic studies in the development of osteogenic calcification in the heart have become the cornerstone in the triad hypothesis for calcification in the aortic valve.

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Published in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*,[6] the investigators from the Copenhagen General Population Study sought to identify the role of oxidized phospholipids (OxPL) in the progression of CAVD. In a case–control study performed within the Copenhagen General Population Study (n=87 980), 725 cases of CAVD were compared with 1413 controls. The investigators tested in this population database the level of lipoprotein(a) levels as a carrier of OxPL, OxPL carried by apolipoprotein B_{100} (OxPL-apoB) and apolipoprotein(a) (OxPL-apo(a)). *LPA* kringle IV type 2 repeat and rs10455872 genetic variants were measured and correlated with the lipoprotein levels. The role of genetics in CAVD is a rapidly evolving risk factor in the progression of calcification in the aortic valve.[7] The discovery of Notch1,[8] LDLR,[9] and other genetic mutations in genes which are responsible for increased risk for calcification in the heart is part of the first axis in the triad hypothesis of CAVD.[10]

OxPL-apoB and OxPL-apo(a) levels correlated with lipoprotein(a) levels among cases (r=0.75 and r=0.95, both P<0.001) and controls (r=0.65 and r=0.93, both P<0.001). OxPL-apoB levels associated with risk of CAVD with an odds ratio of 1.2 for the 34th–66th percentile levels, 1.6 for 67th–90th percentile levels, and 2.0 for 91st–95th percentile levels. For levels, >95th percentile, versus levels <34th percentile. The corresponding odds ratios for OxPL-apo(a) were 1.2, 1.2, 2.1, 2.9, and with a similar trend for lipoprotein(a). *LPA* genotypes associated with the risk of CAVD, a doubling in genetically determined OxPL-apoB, OxPL-apo(a), and lipoprotein(a) levels with an odds ratio of CAVD of 1.18, 1.09, and 1.09. The authors concluded that OxPL-apoB and OxPL-apo(a) are novel genetic and potentially causal risk factors for CAVD and mechanistically helps us to understand the association of lipoprotein(a) with CAVD. Thanassoulis[11] and Smith et al[12] have further proposed that targeted therapy of Lp(a) may be a novel target for treating CAVD, after confirming the genetics of Lp(a) in patients with CAVD. MESA also confirmed the discovery of Lp(a) as a significant risk factor for CAVD.[13] MESA was designed to test subclinical atherosclerosis markers and measure calcification burden in the aortic valve using computed tomography measurements.[13–15] The role of lipoprotein(a) and oxidized lipoproteins as part of the second axis of the triad hypothesis of CAVD as shown in the Figure is rapidly becoming the central focus for the lipid hypothesis in CAVD. Future studies in lipoprotein biology and calcification in the heart will likely lead to new clinical trials to slow progression of CAVD.

Understanding the risk factors associated with calcification in the heart has been a critical feature of cardiovascular research for the past century. Large cohort databases have been instrumental in the understanding of the initiation of atherosclerosis[16] and eventual calcification in the valve.[17] The possible link between cardiovascular disease and osteoporosis has been termed a bone–heart paradox. Studies in the field of atherosclerosis and osteoporosis have focused on the risk factor of oxidative stress as a mechanism for decreased bone formation in the bone and increased bone formation in the heart.[18–20] Vascular calcification and osteoporosis are both active biological processes, which share common mechanisms, including the BMP pathway, Wnt Pathway, and OPG.[15,21,22] Osteogenic bone formation in the heart has become the third axis in the triad hypothesis of CAVD as shown in the Figure.

However, the role of statins in the field of CAVD has been elusive. All of the randomized clinical trials have been negative to date. Only the open-label trial, RAAVE,[23] treated patients with elevated LDL at baseline and compared progression to patients with normal LDL, without the need for a statin therapy. The study was positive with slowing of progression of stenosis. The epidemiological risk factor database, imaging, cellular, and molecular biology of CAVD have evolved incrementally over the past 20 years.[1] The NIH recognizes this field of science with RFAs and working group studies[1] which continue to promote the understanding and

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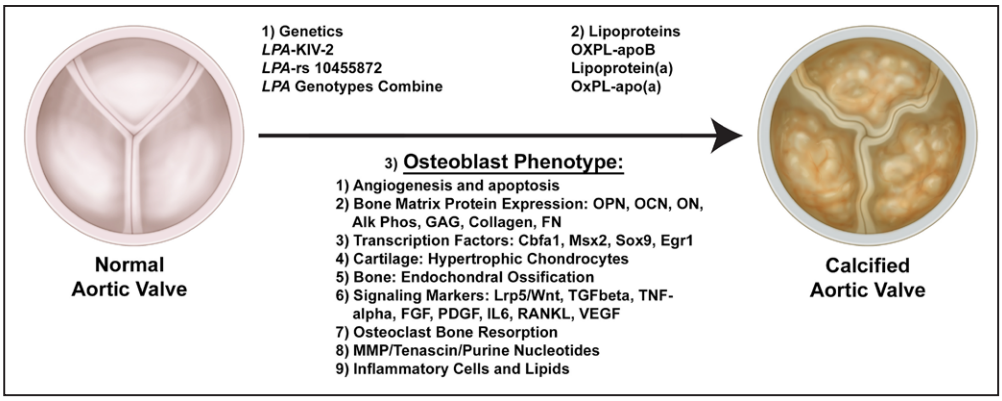

Figure. Triad hypothesis of calcific aortic valve disease (CAVD), including the role of genetics, lipoproteins in the initiation of the osteogenic phenotype which is the final common pathway to CAVD. Adapted from Rajamannan[10] with permission of the publisher. Copyright © 2009, the American Heart Association, Inc. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. KIV-2 indicates kringle IV type 2; and OxPL, oxidized phospholipids.

development of novel therapies to slow progression of aortic valve calcification. In Canadian studies,[24–26] investigators have studied the role of statins in the progression of aorta calcification in familial hypercholesterolemia and found that age was the only predictor of progression and that statins did not slow progression of calcification.

Will modifying the level of LDLR, versus lipoprotein(a) using antibody therapy, or lowering PCSK9 levels help to slow progression of this elusive disease process? A recent study indicates that PCSK9 increases by an unknown mechanism the secretion of apolipoprotein(a) by hepatocytes.[27] The potential role of PCSK9 inhibition and or antisense Apo(a) inhibition in the slowing of the progression of CAVD may be a novel arena for clinical trials and will test this hypothesis.

The understanding in this study for the genetic association of oxidized lipoproteins with Lp(a) advances the recent genetic discoveries for the role of Lp(a) in the mechanism of CAVD.[9,11,28] The only limitation of the study is defining the degree of stenosis with the amount of OxPL and other traditional risk factors important in the progression of CAVD.[1] The patient population with CAVD in this study did have aortic valve jet velocity >2.5 m/s and aortic valve area of <2.0 cm^2. However, the role of lipoproteins in the early development of aortic valve sclerosis versus severe aortic valve stenosis secondary to severe calcification is still an open biological question. The critical question in the future understanding of CAVD is how do various lipoproteins affect the process of atherosclerotic initiation to osteogenic differentiation during the progression from sclerosis to stenosis.[29] The cellular biology of CAVD is complex with the underlying differentiation of valve interstitial cells[30] into an osteogenic phenotype.[31,32] For now, the Figure demonstrates the importance of these novel discoveries of the General Copenhagen study which will provide new direction toward the development of medical therapies for CAVD.

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