A Not-So-Little Role for Lipoprotein(a) in the Development of Calcific Aortic Valve Disease

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Calcification of soft tissues results from the deposition of calcium, largely in the form of hydroxyapatite, in the vascular wall or valve leaflets. Previously thought to be a passive degenerative process, it has become increasingly apparent that cardiovascular calcification is an active process initiated by many triggers. Recent studies have demonstrated variation in the LPA gene, which determines the plasma concentration of lipoprotein(a) [Lp(a); pronounced “L P little a”] to be associated with calcific aortic valve disease (CAVD).2,3 Lp(a) consists of a low-density lipoprotein (LDL)–like particle in which apolipoprotein(a) is covalently bound to apolipoprotein B. Additionally, Lp(a) is a genetic risk factor for atherosclerotic events.4 As in atherosclerosis, calcifications in CAVD localize to areas with lipoprotein accumulation and inflammatory cell infiltration, suggesting a shared disease process.5 However, some noticeable differences exist, including increased mechanical stresses and calcification-involved valve obstruction in CAVD as opposed to microcalcifications leading atherosclerosis plaque rupture.6

In this issue of Circulation, Bouchareb et al7 propose a highly plausible mechanistic pathway through which Lp(a) and valve interstitial cell (VIC)–derived autotaxin may induce valve calcification by regulating inflammation-induced bone morphogenetic protein (BMP). This study connects lipid metabolism to inflammation and valve calcification and, in doing so, identifies a pathway that may help lead to the development of CAVD therapeutics, an area with high unmet clinical need. Mahmut and colleagues8 had recently reported that lipoprotein-associated phospholipase A2, an enzyme that uses oxidized phospholipids carried by Lp(a) to generate lysophosphatidylcholine, both is highly expressed in CAVD and plays a role in the mineralization of VICS. The CAVD functional role of autotaxin, a key enzyme involved in the conversion of lysophosphatidylcholine to the signaling phospholipid lysophosphatidic acid9 (LPA), has yet to be reported. Autotaxin is a member of the ectophosphodiesterase/nucleotide phosphohydrolase (ENPP) family. It is notable that ENPPs can hydrolyze ATP to varying extents to generate pyrophosphate,10,11 a known inhibitor of bone and vascular smooth muscle calcification. However, in vitro analysis of ENPP substrate hydrolysis suggests that autotaxin is a poor nucleotide pyrophosphatase/phosphodiesterase and unique among the ENPPs in acting as a phospholipase.12 Thus, autotaxin phospholipase activity converting lysophosphatidylcholine to LPA, particularly in the context of elevated Lp(a), may play a greater role in CAVD development.

LPA is a potent extracellular signaling molecule with a diverse array of physiological and pathological actions, including the induction of the mitogen renin-angiotensin system–extracellular signal-regulated kinase pathway, the phosphoinositide 3-kinase–AKT cell survival pathway, the Rho- and Rac-mediated cytoskeletal remodeling and cell migration, cell proliferation, vascular and neural development, phospholipase C activation leading to calcium mobilization, fibrosis, lymphocyte homing, and cytokine production.13 Autotaxin acts locally and signals through LPA generation and 6 LPA guanine-nucleotide–binding protein-coupled receptors (LPA1-6) located on the surface of a wide variety of cells. Lp(a) can bind to a number of receptors, including LDL receptor, lipoprotein receptor-related proteins, very-low-density lipoprotein receptor, and scavenger receptor class B type I, although the extent to which it acts as a ligand can vary widely.14 Given the role of these and other cell surface receptors in cellular metabolism and trafficking, examination of the involvement of intracellular sorting processes, including those affecting membrane composition and events such as endocytosis and exocytosis, may provide novel CAVD insight, and intracellular sorting processes should be examined in future studies.

In the study by Bouchareb et al,7 increased LPA, autotaxin lysophospholipase activity, and protein abundance were found in mineralized human aortic valves. Increased autotaxin...
levels in valves were associated with oxidized lipids, increased remodeling score, and measurements of inflammation. As pointed out by the authors, one limitation of this study was that autotaxin was examined in human aortic valves with advanced end-stage pathology. Thus, a causative role of Lp(a) and VIC-derived autotaxin in the valve calcification process could not be clearly assigned from the human tissue studies alone. The authors hypothesized that lysophosphatidylcholine may induce valve calcification through nuclear factor-κB activation, leading to interleukin-6 production and BMP2 signaling in VICs. To test whether nuclear factor-κB activation, interleukin-6, and BMP2 were involved in lysophosphatidylcholine-mediated mineralization, Bouchareb et al7 treated VICs with lysophosphatidylcholine, mineralizing medium (a combination of inorganic phosphate, insulin, and ascorbic acid), and inhibitors of BMP, nuclear factor-κB, LPARs, or silencing RNAs directed against autotaxin or interleukin-6. Disrupting any of these components strongly reduced or inhibited lysophosphatidylcholine-enhanced mineralization. The human tissue and cell culture data were partially confirmed in this study with the use of an animal model of CAVD, LDLR−/−/ApoB100/100/IGFII transgenic mice, in which autotaxin was found to be increased in the aortic leaflets. Additionally, LPA-treated mice showed a 1.7-fold increase in aortic valve leaflet calcification, along with an increase in BMP2. These results indicate that VIC- and Lp(a)-derived autotaxin and oxidized lipids lead to increased LPA that acts to induce inflammation via LPARs, nuclear factor-κB activation, and ultimately results in interleukin-6 regulation of BMP mediated valve calcification.

Approximately 50,000 valve replacements are performed annually in the United States for patients with severe aortic stenosis. Aside from valve replacement, there are currently no treatments that prevent or slow the progression of valve disease, which is responsible for >22,000 deaths each year in the United States. Bouchareb et al7 correctly concluded that inhibition of autotaxin or blocking of LPARs as potential novel CAVD therapies warrant future investigation.

Some caution should be taken in this approach because bone defects have been reported in LPA receptor–modified mice. Similarly, assessment of targeting Lp(a) itself also seems warranted, although whether lowering Lp(a) levels can reduce the rate of incidence or progression of aortic valve disease remains to be determined. However, given that a common variant in Lp(a) was reported to increase the risk of developing aortic stenosis by >50%, Lp(a) targeting therapies should be explored further in a CAVD context. Of potential interest in this area is the recent development of PCSK9-based therapeutics, which significantly reduce major adverse cardiovascular events (death resulting from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization), in addition to reducing Lp(a) levels. Further analysis of whether reducing Lp(a) levels via PCSK9 inhibition plays a role in reduced cardiovascular events, particularly in relation to CAVD, may prove to be of importance (Figure). Outside of PCSK9 inhibition, niacin and the cholesteryl ester transfer protein inhibitor anacetrapib have been shown to reduce Lp(a) levels, although whether these or similar compounds would act therapeutically in CAVD or, more specifically, in a CAVD at-risk population with elevated Lp(a) is unknown. Statins are known to act on both lipid metabolism and inflammation but have largely shown a lack of therapeutic benefit in CAVD. However, it is worth pointing out that statins have been reported to lower LDL cholesterol without reducing Lp(a), and although there are some conflicting reports showing both elevated and decreased Lp(a), several statin studies show no major changes. This result may not be too unexpected given that Lp(a) is reportedly a relatively poor ligand for LDL receptor, which serves as one of the major means of action on lipid metabolism after statin administration. Although the possibility exist that elevation of LDLR levels above that induced by statins through PCSK9 inhibition may be involved in Lp(a) catabolism.

**Figure.** Potential role of lipoprotein(a) [Lp(a)] and PCSK9 in calcific aortic valve disease (CAVD). Lp(a) may be taken up and metabolized by cells via Lp(a) receptors [receptors for which Lp(a) is a ligand]. However, in the presence of PCSK9, some of these receptors may be internalized and degraded instead of recycled back to the cell surface (A). Thus, more Lp(a)-derived oxidized lipids may be converted to lysophosphatidic acid (LPA) and be taken up by valve interstitial cells via LPA receptors. This may lead to the production of inflammation-related cytokines (eg, interleukin-6) through nuclear factor-κB (NF-κB) nuclear localization, which in turn increases bone morphogenetic protein (BMP) or other calcification-inducing processes, leading to valve calcification. PCSK9 inhibitors may act to block PCSK9 interaction with Lp(a) receptors, resulting in Lp(a) receptors being recycled back to the cell surface where they can take up more Lp(a) (B). Dashed arrows indicate multiple steps in the pathway.
In summary, the work by Bouchareb et al7 builds on previous studies to identify a mechanistic pathway through which Lp(a) and autotaxin may be driving aortic valve calcification and, in doing so, presents an important area of research worthy of additional investigation.

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None.

References

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