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Invited commentary

Inflammation and calcification: The chicken or the hen?

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In the current issue of the journal, Abdelbaky et al. [1] present a very interesting study addressing the association of aortic valve inflammation and calcification. To ascertain whether aortic valve inflammation precedes subsequent valvular calcification they utilized sequential PET/CT scans performed for cancer surveillance in patients with stable oncological disorders. Computed tomography provided information regarding the presence and extent of calcification (structural information), while PET provided functional/activity information. ^{18}Fluoro -deoxyglucose (FDG) is used extensively in oncological PET imaging and has been shown to be selectively taken up by inflammatory cells, accumulating in nascent atherosclerotic plaques and the aortic valve [2,3]. In the current study Abdelbaky et al. [1] showed that FDG uptake in the aortic valve was higher among patients who showed subsequent progression of calcification, especially in patients with no detectable calcification at baseline. Several traditional risk factors for atherosclerosis were associated with inflammation and calcification of the aortic valve at the time of the first scan including age, diabetes mellitus, dyslipidemia and hypertension. However, on multivariable analyses only age and a quantitative measure of FDG uptake (maximum standardized uptake value (SUVmax)) were associated with inception or progression of valve calcification [1]. In a prior publication the same authors made a very similar observation in aortas, where inflammation preceded subsequent calcification [4].

Is inflammation therefore a condition *sine-qua-non* for future calcification of the aortic valve? Certainly there were patients who demonstrated tracer uptake at baseline who did not calcify during a median follow up of 2 years, hence it does not appear that inflammation is a necessary and sufficient condition for future calcification. Nonetheless, numerous pieces of evidence point to the importance of inflammation in the process of progressive sclerosis of the aortic valve.

Atherosclerosis and aortic valve calcification share the same risk factors [5] and these may induce inflammation. However, in the current study inflammation was associated with future calcification independent of all risk factors except for age [1]; hence one wonders if risk factors and inflammation are at all correlated in aortic valve disease. Of interest, inflammation showed a close association with future valvular calcification but not pre-existing calcification [1]. This could suggest that long standing calcification becomes inert and/or that new stimuli may ignite a strong inflammatory response. Is it possible that calcification itself may promote inflammation, so is inflammation the chicken or the hen? Although limited, there is some experimental and human evidence that this might be the case. Calcification of the aortic valve is associated with disruption of the basal membrane, infiltration of inflammatory cells and lipids deposition [6,7]. Nadra et al. [8] showed that human macrophages exposed in culture to calcium-phosphate crystals internalize the crystals in vacuoles and release inflammatory cytokines (TNF-α, IL-1β and IL-8) via a protein-kinase-C dependent pathway. TNF-α is capable of inducing osteoblastic differentiation of vascular smooth muscle cells therefore initiating calcification of the interstitium [9]. Furthermore, recent evidence suggests that macrophages are capable of releasing matrix vesicles that are rich in annexin V and alkaline phosphatase, with high calcifying potential [10]. These results suggest that calcium may *promote* inflammation which in turn will enhance further calcification. In a randomized trial of patients affected by end-stage renal disease the compound Sevelamer arrested the progression of valvular calcification, while calcium-based phosphate binders allowed further progression [11]. Sevelamer is a non-absorbable polymer used as a gut phosphate binder and has lipid-lowering as well as mild anti-inflammatory activities [12]. This trial provided partial support to the hypothesis that calcium and inflammation may be part of a "vicious cycle".

What other risk factors could potentially ignite inflammation and calcification of the aortic valve? As oxidized lipids are found in calcifying aortic valves, it has been suggested that they could promote osteoblastic differentiation of valvular fibroblasts and macrophages via activation of the LDL receptor protein-5 (LRP5)/Wnt and Runx2/Cbfa-1 pathways, eventually inducing calcification [13]. Unfortunately, several trials of statin therapy to reduce serum LDL

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and inflammation failed to slow progression of aortic valve calcification [14,15]. These trials may have been initiated too late in the process of calcification to slow it or reverse it, however there is also laboratory evidence that statins may promote valvular calcification rather than inhibit it [16]. Interestingly, in patients with the genetic disorder familial hypercholesterolemia LDL apheresis slows atherosclerosis progression but aortic valve calcification continues to advance [17–19]. This suggests that other factors, likely related to LDL-receptor deficiency or abnormal function, play a role which is unlikely to be mediated by inflammation [20]. It remains to be seen whether the new PCSK-9 inhibitors that have little to no effect on inflammation while reducing LDL levels dramatically and the level of Lp(a) by 20–25% [21], will impact aortic valve calcification in familial hypercholesterolemia.

Evidently much remains to be done to attain a better understanding of the mechanisms and potential therapeutic approaches to aortic valve calcification. In the meantime the study by Abdelbaky et al. [1] adds another thread to the thickly woven mystery of the most common human valvular disease.

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