Calcification of the Aortic Valve: the Arrival Point of a Complex Degenerative Process

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Abstract — The histology of the calcified aortic valve has been sequentially revisited in the light of modern concepts of cardiovascular pathology. Fifteen cases of calcified aortic valves, surgically removed for an acquired steno-insufficiency, have been investigated by histochemistry (Weigert’s stain, Van Gieson’s stain, Verhoeff’s stain, Alcian blue / PAS stain). Following the lipidic infiltration of the endothelium, a diffuse proteolytic phenomenon, mainly related to aging, gives rise to tissue degeneration. The subsequent remodelling attempt is ineffective to maintain the valve function, as demonstrated by the limited presence of newly formed muscle-like cells. The arrival point of this degenerative process is represented by a marked calcification, involving the aortic leaflets and the annulus. Proteolysis, absence of an effective remodelling mechanism and calcification are the fundamental sequential steps of the acquired aortic steno-insufficiency. At the basis of this complex pathological cascade of events, genetic and metabolic disorders play an important role. The conventional histological techniques permit to easily distinguish calcification of the aortic valve from endocarditis and rheumatic lesions and they allow to demonstrate pathogenetic mechanisms in common with thoracic aortic aneurysms.

Keywords — Aortic valve, calcification, histochemistry, proteolysis, remodelling, steno-insufficiency, Weigert’s stain.

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INTRODUCTION

Nowadays, the calcific pathology of the aortic valve is absolutely common, often originating the clinical syndrome of the aortic valve steno-insufficiency. Many aspects of this disease were largely investigated.¹ Our aim has been to revisit its morphological features in order to demonstrate that it can be considered the arrival point of a complex degenerative process. This process is different from that observed in other diseases of the aortic valve, where calcification, if present, is secondary to endocarditis or rheumatism.

METHODS

Our histological analyses have been focused on fifteen aortic valves, surgically removed from adult patients, aged between 65 and 80 years. We have excluded from our series unicostipid and bicuspid aortic valves or other congenital malformations, infective endocarditis, rheumatism, retrograde aortic dissection and autoimmune diseases.

The surgical specimens were fixed in 10 % neutral buffered formalin and then paraffin embedded. In addition to haematoxylin and eosin, histochemistry for elastic fibers (Weigert’s stain, Van Gieson’s stain, Verheff’s stain) and mucins (Alcian blue / PAS stain) was performed, following the standard protocols.

RESULTS

In all our cases, we have observed the partial disappearance of the valvular endothelial lining and a sub-endothelial lipidic deposition, confirmed by the presence of foamy cells. This primordial lesion can be considered the starting event of a complex degenerative process. A weak activation of monocytes and macrophages with dilatation of blood capillaries can be also observed, but with a limited extension.

The subsequent step is represented by proteolysis, involving the elastic and collagen components of the fibrosa layer, bundles and fibres. In the spongiosa too, the extracellular matrix, especially its prominent glycosaminoglycan counterpart, appears widely involved by proteolysis. In the ventricular layer the collagen and elastic fibres are submitted to fragmentation.

The scanty amount of newly formed muscle-like cells denotes a poor attempt of remodelling. The abundant presence of fibroblasts (Fig. 1 and Fig. 2) and mucoid substance (Fig. 3) in the degraded extracellular spaces represent an unspecific finding. The evolution of these cells towards an osteoblastic line well predisposes to the final diffuse calcification (Fig. 4), involving both the leaflets and the aortic annulus. In the final stage of the disease, as usually it arrives to our clinical observation, common atherosclerotic lesions can be still noticeable.

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DISCUSSION

Our morphological revisiting of the main pathological features of the calcified aortic valve well correlates with the underlying physio-pathological mechanisms. We have considered, as promoting pathological event, the endothelial discontinuity with concomitant lipid deposition. The following activation of inflammatory cells, as usually observed in atherosclerosis, can be considered responsible for the induction of a proteolytic enzyme cascade, able to degrade elastic and collagen fibres of all layers of the aortic valve.

These above-mentioned aspects of the disease are common with those of the aortic degenerative incompetence. The subsequent remodelling process does not evolve towards a vigorous generation of newly formed muscle-like cells or of other specialized vasculo-connective elements. On the contrary, a proliferation of new fibroblasts, which will evolve in osteoblast-like cells, can be ascertained.

At this point, a final process of calcification is evoked, favoured by local conditions, as mechanical strain, or by particular biochemical states, as hypercalcemia.

The ancient atherosclerotic lesions appear less evident than those of other vascular districts. Nevertheless, their persistence, even if limited in extension, confirms their importance as a promoting event.

CONCLUSION

Our observations permit to find logical consequences between the different morphological aspects of the typical aortic valve calcification. In this disease, the interstitial cells play an important role, together with different molecular mechanisms.

Comparing calcific aortic valve disease and vascular atherosclerosis, many pathogenic common factors can be denoted, while many others remain specific, as mechanical stretching. A careful histological examination permits to clearly distinguish this disease from other conditions, which can involve the aortic valve, such as endocarditis or rheumatism.

Calcification of the aortic valve usually starts from a common primitive atherosclerotic lesion. Subsequently, a diffuse proteolytic process is established, not followed by an equivalent remodelling, as described for internal thoracic artery.

Proteolysis can be correlated primarily with aging, but also with hypertension and atherosclerosis. At this stage, a phenomenon of diffuse mineralization is promoted by multiple pathogenetic factors. Nevertheless, the genetic bases of this phenomenon need to be deeply investigated.

In case of bicuspid aortic valve, some histopathological aspects of the calcified aortic valve have been considered analogous to those found in thoracic aortic aneurysms or dissections and common pathogenic mechanisms have been demonstrated.

Fig. 1. Aortic valve (Haematoxylin-Eosin, ×40). A sub-endothelial proliferation of fibroblasts is noticeable.

Fig. 2. Aortic valve (Weigert's stain, ×20). The same sub-endothelial proliferation of fibroblasts is also appreciable by histochemistry.
However, we underline that pathogenic factors are common between calcification of the aortic valve and thoracic aortic aneurysm: the two diseases can appear simultaneously or, in other cases, successively one to other. This possibility advices a careful pre-operative study and a vigilant follow-up.

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Fig. 3. Aortic valve (Weigert's stain, x4). Fibroblasts and mucoid substance (arrows) occupy the spaces left empty by the proteolytic degradation.

Fig. 4. Aortic valve (Haematoxylin-Eosin, x4). A cellular osteoblastic evolution promotes the final valve calcification (insert).


