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Differentiating the aging of the mitral valve from human and canine myxomatous degeneration

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Abstract During the course of both canine and human aging, the mitral valve remodels in generally predictable ways. The connection between these aging changes and the morbidity and mortality that accompany pathologic conditions has not been made clear. By exploring work that has investigated the specific valvular changes in both age and disease, with respect to the cells and the extracellular matrix found within the mitral valve, heretofore unexplored connections between age and myxomatous valve disease can be found. This review addresses several studies that have been conducted to explore such age and disease related changes in extracellular matrix, valvular endothelial and interstitial cells, and valve innervation, and also reviews attempts to correlate aging and myxomatous disease. Such connections can highlight avenues for future research and help provide insight as to when an individual diverts from an aging pattern into a diseased pathway. Recognizing these patterns and opportunities could result in earlier intervention and the hope of reduced morbidity and mortality for patients.

Introduction

Myxomatous mitral valve degeneration (MMVD) causes severe valvular regurgitation and ultimately death for millions of dogs around the world.[1,2] In humans, this disease is the primary cause of mitral valvular regurgitation leading to the need for surgical valve repair.[3] For humans afflicted with MMVD, it has been observed that the mean patient age is 60 years old. As opposed to calcific aortic valve disease, which has a clearly demonstrated association with aging,[4] MMVD in humans appears distinct from age-related changes.[5—7] This review will describe the age-related changes in mitral valve composition and material behavior and

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Abbreviations

α-SMA	α-smooth muscle actin
CKCS	Cavalier King Charles spaniels
ECM	extracellular matrix
EMT	endothelial—mesenchymal transformation
GAG	glycosaminoglycan
HA	hyaluronan
MMP	matrix metalloproteinase
MMVD	myxomatous mitral valve degeneration
MVAC	mitral valve center of the anterior leaflet
MVF	mitral valve free edge
MVP	mitral valve prolapse
PG	proteoglycan
SLRP	small leucine-rich proteoglycan
TIMP	tissue inhibitors of metalloproteinase
VEC	valvular endothelial cell
VIC	valvular interstitial cell

contrast these changes with those found in MMVD, with a particular emphasis on comparisons of human, porcine, and canine mitral valves.

Gross and micro-anatomy of the mitral valve

The canine mitral valve complex, similar to human and other mammalian species, consists of the annulus, two leaflets (anterior and posterior) of different shape and size, numerous chordae tendineae, and the papillary muscles (Fig. 1A).[8,9] The function of the mitral valve is to direct the blood flow from the left atrium to the left ventricle during diastole and to prevent the backflow of blood into the left atrium during systole. In order to do so, the mitral valve complex requires all of its components, together with the adjacent atrial and ventricular muscle, to work in a synchronized fashion.[10,11]

The mitral valve leaflets each consist of four layers that differ from each other in extracellular matrix (ECM) makeup and functionality. From top to bottom, the layers are the atrialis, spongiosa, fibrosa, and ventricularis. The fibrosa, the thickest layer of the valve, is comprised of dense, circumferentially aligned collagen, in contrast to the loose collagen found within the atrialis, spongiosa, and ventricularis.[12] The dense collagen of the fibrosa provides the mitral valve leaflets with tensile strength, whereas the looser collagen and high glycosaminoglycan (GAG) content in the other

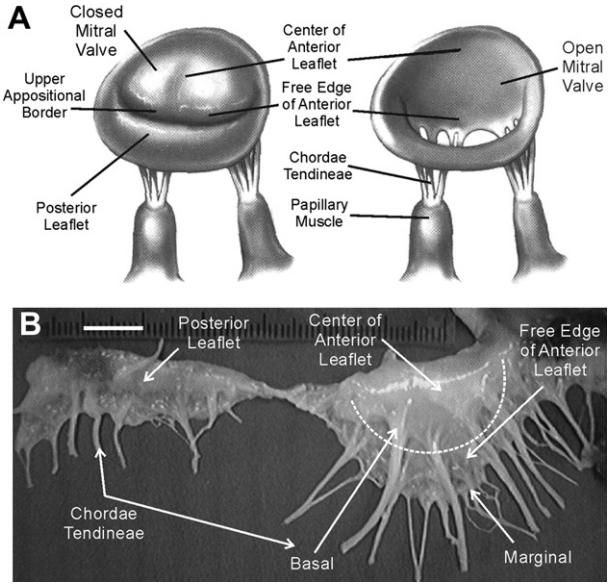

Figure 1 (A) Top (atrial) view of the mitral valve in the closed (left) and open (right) position. (B) Bottom (ventricular) view of the mitral valve, cut open at the commissures to display the posterior (left) and anterior (right) leaflets. Dotted white line demarcates leaflet center from free edge. Chordae may have basal or marginal insertion into leaflet. Scale bar = 1 cm. Reprinted from Grande-Allen KJ, Calabro A, Gupta V, Wight TN, Hascall VC, Vesely I. Glycosaminoglycans and proteoglycans in normal mitral valve leaflets and chordae: association with regions of tensile and compressive loading. *Glycobiology*. 2004; 14(7):621—33 with permission from Oxford Journals.

layers provides the leaflets with compressive strength. The atrialis, the layer located on the inflow side of the mitral valve, has an abundance of the protein elastin, which allows the valve to undergo considerable stretch and then recoil back to its original undeformed shape during the cardiac cycle.[13] The spongiosa contains a high concentration of the GAG hyaluronan (HA) and hydrated chondroitin/dermatan sulfate proteoglycans (PGs), which also provide compressive strength for the valve.[14] The ventricularis layer of the mitral valve leaflets is very thin compared with other layers and consists of elastic fibers and regularly spaced, circumferentially oriented collagen fibers. The regions containing the highly aligned collagen are also rich in small leucine-rich proteoglycans (SLRPs) that connect to and provide mechanical support for the collagen fibrils.[13]

In addition to the mitral valve leaflets, the chordae tendineae are a critical component to the functioning of the mitral valve apparatus. These chordae connect the underside of the valve