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AGE CHANGES IN THE STRUCTURE OF HUMAN ATRIOVENTRICULAR ANNULI

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SUMMARY

Atrioventricular annuli are important in hemodynamic stability and support to tricuspid and mitral valves. Anatomical features of the annuli such as circumference, organization of connective tissue fibers, myocardium and cellularity may predispose to annular insufficiency and valvular incompetence. These pathologies increase with age and are more common in females, although the anatomical basis for this disparity remains unclear. This study therefore aimed to investigate age-related changes in the structure of human atrioventricular annuli. One hundred and one hearts (48males, 53 females) from subjects (15 to 60 years) were studied in three age groups (≤ 20 yrs, 21-39 yrs and 40-60 yrs). Annular circumferences were measured and corrected for heart weight. Routine histology was carried out on 21 hearts. Differences in annular circumference between the age groups were determined using one-way ANOVA while gender differences were determined using independent Students't-test. Overall, females had significantly larger annular circumference than males after correcting for heart weight ($p \leq 0.05$). The annular circumference generally increased with age however there was a significant increase in the 21-39 year age group ($p \leq 0.05$). Microscopically, myocardium was consistently present in males but absent in females except in one specimen. The collagen fiber density increased with age in both gender as the fibers became more irregular. The annular cellularity, elasticity and myocardial content also declined with increasing age. The significantly wider annular circumference in the 21-39 year age group is clinically important as wider circumference is associated with decreased heart valve co-aptation and valvular incompetence. This may suggest an earlier predisposition to this pathology in the study population. The age-related decrease in annular cellularity, elasticity and myocardial content may explain the higher incidence of valvular incompetence with increasing age.

Key words: Atrioventricular annuli; Age changes; Valve incompetence.

INTRODUCTION

Atrioventricular annuli are part of cardiac skeleton that support and prevent over-distension of tricuspid and mitral valves (Moore and Dalley, 2006). They also confer hemodynamic stability to the valves (Ormniston et al., 1981) and form a firm framework for myocardial attachment and placement of sutures during valve repair (Istvan et al., 2008). The circumference of the annulus is an important parameter in annular and valvular function. An increase in this parameter may decrease heart valve co-aptation during cardiac cycle and this may be a risk for valvular insufficiency (Farry et al., 1975; Ormniston et al., 1981). This parameter shows age and gender differences and varies between populations (Singh and Mohan, 1994; Skwarek et al., 2008) however published information for the African populations is scarce.

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Histologically, the annuli are endothelial-lined fibrous structures containing collagen, elastic fibers and fibroblasts (Williams et al., 1995). Extension of the myocardium from atria to the annuli contributes to annular myocardium (Puff et al., 1978). This structural organization is important in valvular support and annular adaption to hemodynamic forces during cardiac cycle (Yacoub et al., 2004). Alteration in this structural organization is associated with heart valve incompetence (Puff et al., 1972; Angelini et al., 1988). This incompetence increases with age (Jar, 2009) and is more common in females (Carpenter and Margarita, 2004; Glower et al., 2009) although the anatomical basis for this disparity is unclear. Age changes in the structure of the annuli may provide morphological basis for the pattern of occurrence of this disease. This study therefore aimed to determine age-related changes in the structure of the human atrioventricular annuli.

MATERIALS AND METHODS

One hundred and one hearts (48 males, 53 females) of age range 15-60 years were studied in three age groups (≤ 20 yrs, 21-39 yrs and 40-60 yrs). Eighty hearts were used for morphometric analysis (Table 1), while 21 used for histology, were obtained within 48 hours of autopsy at the Nairobi city mortuary (Table 2).

The specimens used for histological study were obtained from individuals who had died suddenly either from gunshot wounds, strangulation or road traffic accidents. Hearts with obvious gross pathology of the leaflets, myocardium or annuli were excluded. Ethical approval was granted by Kenyatta National Hospital-University of Nairobi/ Ethical Review Committee before commencement of the study. The mediastinum was opened by cutting bilaterally through costal cartilages. Harvesting of the heart was done by dividing great vessels 2cm from superior extent of its base. The hearts were weighed using a digital weighing balance, ABC Japan (accurate to 0.01g). Harvesting of the annuli was done by making circular incision around bases of corresponding valve leaflets, and entire annuli with attached cusps were harvested intact. Annular circumferences were measured using a flexible ruler and corrected for heart weight [circumference/heart weight]. For light microscopy, 5mm thin sections were harvested from anterior and posterior parts of both annuli. Routine histological processing was done and 7 micron thick sections were obtained using a Lenz Wezlar (Germany) sledge microtome. Masson's trichrome stain and Weigert's elastic with Van Gieson counterstaining were used to demonstrate collagen and elastic fibers respectively. Samples were viewed using a bright-field light microscope (Leica model BME, Germany). A Fujifilm A235 digital camera was used to take photomicrographs. Data obtained was analyzed using SPSS version 17.0 for Windows. The age-group differences in annular circumference were determined using one-way ANOVA while gender differences were determined using independent Student's t- test. A p- value of less than 0.05 was taken as significant.

Table 1: Specimens used for morphometric analysis

Age group	Number of males (M) and females (F)	Total
≤ 20 years	M= 10 F= 12	22
21-39 years	M= 16 F= 17	33
40-60 years	M= 12 F= 13	25

Table 2: Specimens used for histological study

Age group	Number of males (M) and females (F)	Total
≤ 20 years	M= 3 F= 4	7
21-39 years	M= 4 F= 3	7
40-60 years	M= 3 F= 4	7

RESULTS

The circumference of the annuli generally increased with age in both males and females. However, there was a significant increase in annular circumference in the 21-39 year age group (Table 3). The average heart weight was 286 ± 84g in males and 222 ± 76g in females ($p= 0.001$). The uncorrected annular circumferences were larger in males although the differences were statistically insignificant (Table 4). After correcting the circumference for heart weights females had overall significant wider circumference than males ($p\leq0.05$) and in the 21-39 year age group this difference was also significant (Table 5). The annuli in both sexes were endothelial-lined fibrous structures containing collagen and elastic fibers. In males myocardium was consistently present at the annulo-myocardial zone, Fig. 1 (part of the annulus adjacent to atrial myocardium), while this was absent in females except in one specimen (Fig 2). There were age-related changes in annular cellularity, organization and density of collagen and elastic fibers, and thickness of annular muscle fibers. Except for annular myocardium, these changes were similar for males and females. There was a general decline in the cellularity of the annuli with increasing age (Fig. 3). Collagen fibers increased with age as the fibers became more irregular (Fig. 3). Elastic fiber density decreased with age and the fibers were more disrupted and irregular (Fig. 4). In males, the number of annular muscle strips declined with increasing age (Fig. 5).

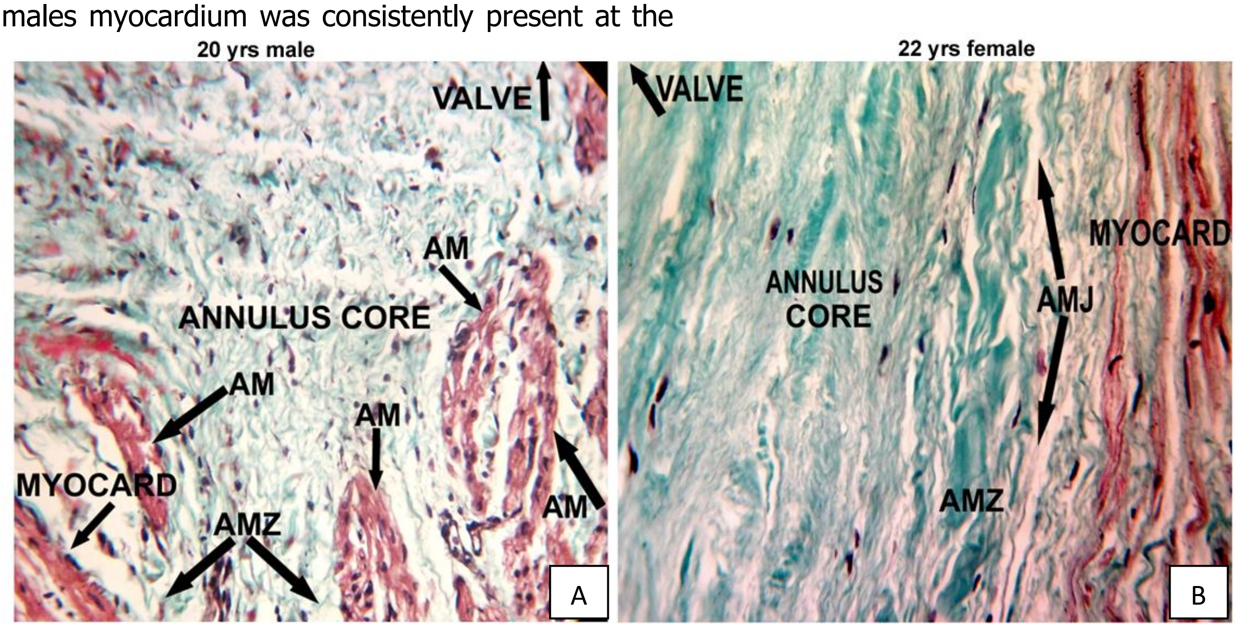

Fig 1: Sex difference in the occurrence of annular myocardium. Note the prominent cardiac muscle bundles at the annulo-myocardial zone (AMZ) in the male annulus (Fig 1A), and the absence of this in the female specimen (Fig 1B). **AM**: Annular myocardium; **AMZ**: Annulo- myocardial zone; **AMJ**: Annulo- myocardial junction (Masson's Trichrome stain; Magnification x400).

Table 3: Age-group differences in annular circumference

PARAMETER	AGE GROUPS			One-way ANOVA (p values)
	≤ 20 years	21-39 years	40-60 years	
Tricuspid circumference (cm)	7.6 ± 2.0	8.9 ± 1.5	9.5 ± 1.6	< 0.01*, 0.21**
Mitral circumference (cm)	6.0 ± 1.6	7.1 ± 1.1	7.6 ± 1.1	< 0.01*, 0.14**

*significance between ≤ 20 and 21-39 age groups **significance between 21-39 and 40-60 group

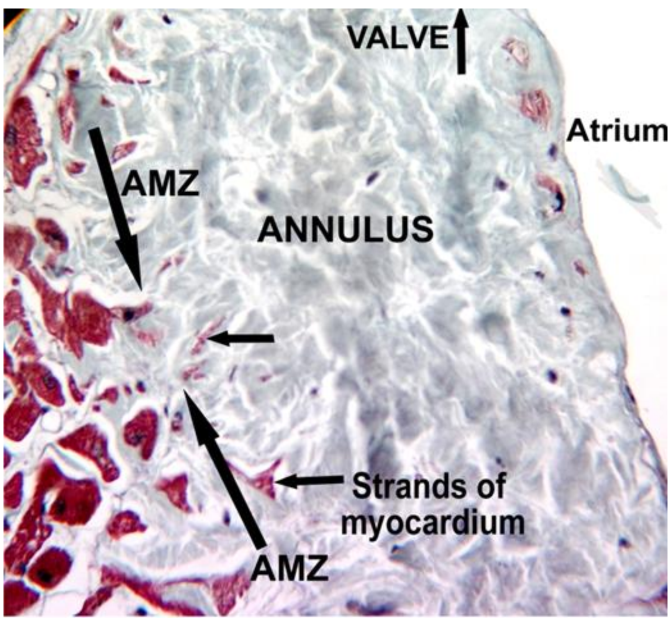

Fig 2: Strands of myocardium in an isolated female specimen (35 yrs). Photomicrograph of an annulus from a 35 year old female. Note the strands of myocardium at the annulo-myocardial zone (AMZ). This was demonstrated only in this specimen.

Table 4: Uncorrected age-group specific sex differences in annular circumference

Age group	Tricuspid circumference (cm)	p-value	Mitral circumference (cm)	p-value
≤ 20 years	M= 7.6 ± 1.7 F= 7.5 ± 1.6	0.81	M= 6.1 ± 1.6 F= 5.9 ± 1.7	0.77
21-39 years	M= 8.9 ± 1.5 F= 8.7 ± 1.4	0.69	M= 7.1 ± 0.9 F= 7.1 ± 1.3	0.96
40-60 years	M= 9.7 ± 1.5 F= 9.4 ± 1.3	0.59	M= 7.6 ± 1.1 F= 7.5 ± 1.0	0.89

M: Male F: Female

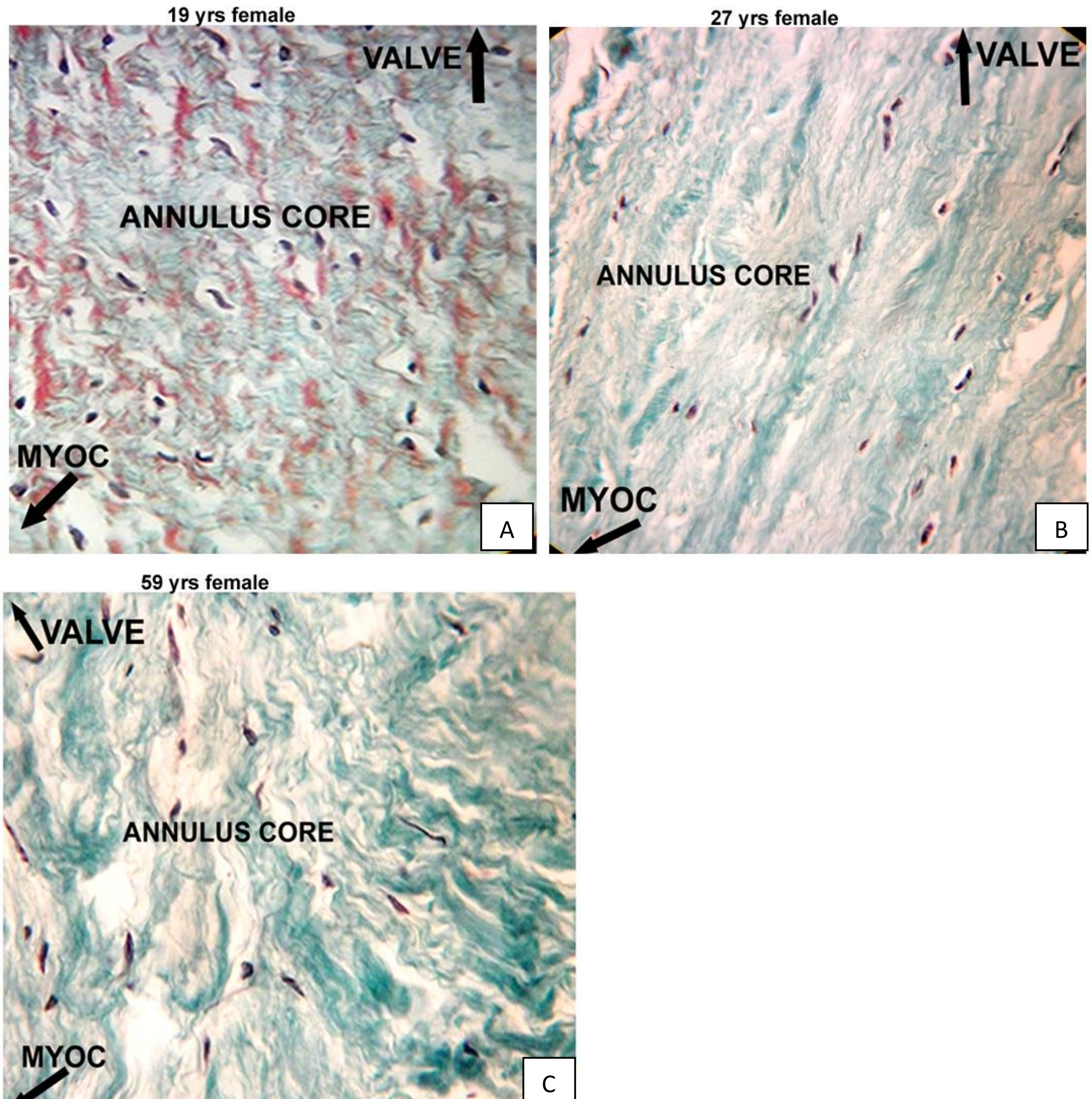

Fig 3: Age changes in annular cellularity and collagen fibre density. Photomicrographs of tricuspid annulus showing an increase in collagen fiber density and irregularity with age. Note the decreasing cellularity (Figure 3C). **MYOC:** Atrial myocardium (Masson's Trichrome stain; Magnification x400)

Table 5: Corrected age-group specific sex differences in annular circumference

Age group	Tricuspid circumference	p-value	Mitral circumference	p-value
≤ 20 years	M= 0.48 F= 0.64	0.17	M= 0.38 F= 0.49	0.19
21-39 years	M= 0.30 F= 0.37	0.01	M= 0.25 F= 0.29	0.02
40-60 years	M= 0.33 F= 0.31	0.40	M= 0.24 F= 0.28	0.07

M: Male F: Female

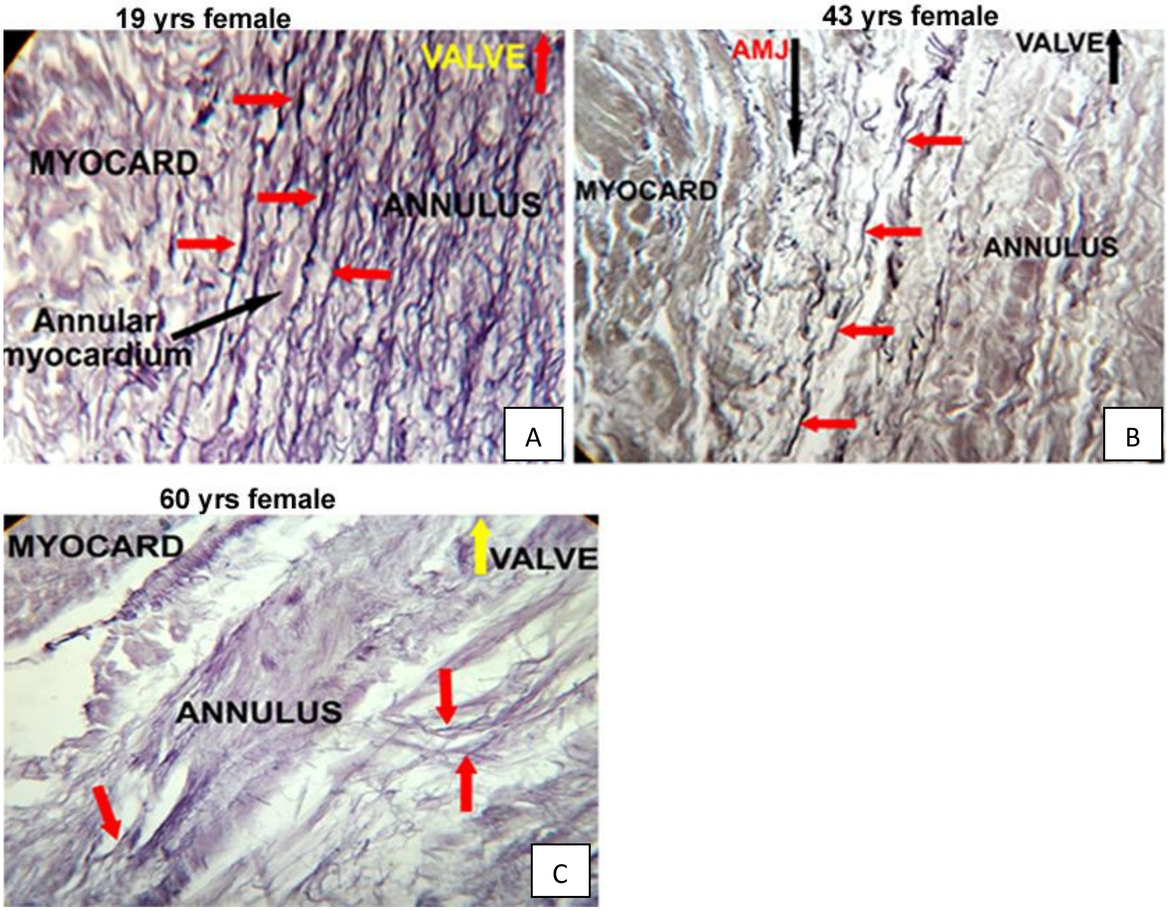

Fig 4: Age-related changes in elastic fibre organization (arrows) in the mitral annulus. Note a general decline in elastic fibre density and regularity with increasing interruption of the fibres with age (Weigert's elastic with Van Gieson counterstaining; Magnification x400).

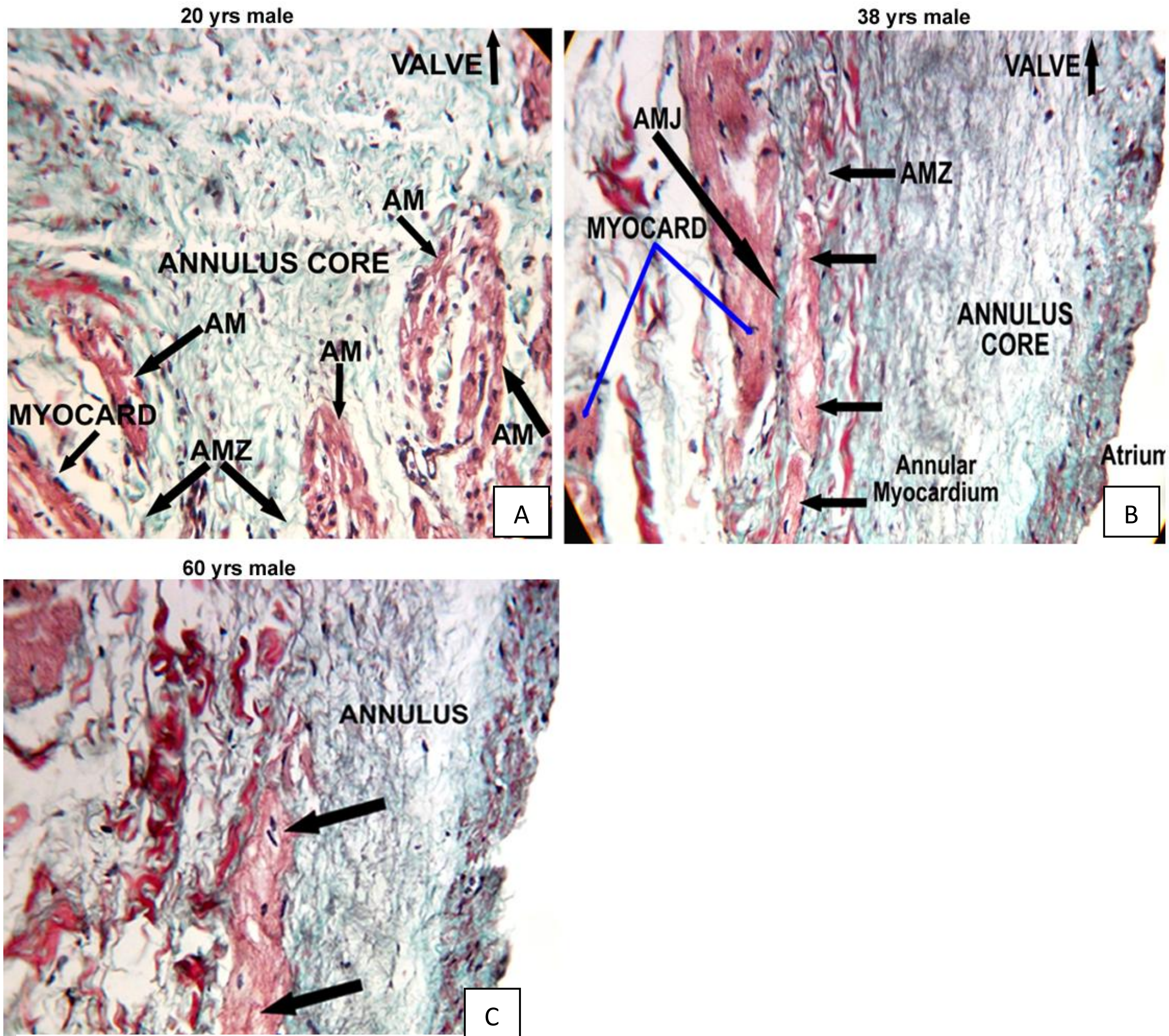

Fig 5: Age changes in the number and thickness of annular muscle strips (arrows). Note the general decrease in the thickness and number of annular muscle strips **(arrows)** with increasing age. **AM:** Annular myocardium**; AMZ:** Annulo-myocardial zone**; AMJ:** Annulo-myocardial junction (Masson's Trichrome stain; Magnification x400).

DISCUSSION

Results of the present study provide adaptations of atrioventricular annuli to hemodynamic stress in different gender and age groups, and a probable morphological basis for the pattern of diseases affecting them. The larger annular circumference in males before correction may be due to heavier hearts and probably body mass index, as previous reports have shown association between these (Sairanen and Louhimo, 1992). Thus when corrected, females had significantly larger circumference. The significant increase in annular circumference in the 21-39 year age group could be physiological, and may underscore important changes in hemodynamic loads in this age group (Puff et al., 1978). Clinically, wider circumference may decrease heart valve co-aptation during cardiac cycle (Ormniston et al., 1981), and this may be a risk for valvular insufficiency and annular incompetence (Roberts, 1983; Mutlak et al., 2007). The current results therefore suggest an earlier predisposition to these pathologies in the study population. Similarly, the corrected larger female circumferences may partly explain the higher prevalence of valvular incompetence in this gender.

The presence of cardiac muscle in male annuli is a unique finding. Dudziak et al., (2009) found no myocardium in male or female tricuspid annulus while Racker et al., (1991) demonstrated myofibres in the tricuspid annulus of a canine model. Further, comparative animal (De Biasi et al., 1984) and human studies (Gatonga et al., 2009) have also demonstrated presence of myocardium in other valvular apparatus. This therefore raises the question as to the function of myocardium in the annulus.

Current findings suggest the annuli are capable of independent contractions which may influence timing and effectiveness of atrio-ventricular valve closure (Yacoub et al., 2004). Myocardium in the annuli may therefore serve to regulate annular contraction and relaxation. The myocardium may also enhance hemodynamic pliability of the valves and contraction of this muscle may aid in closure of corresponding valve orifices during ventricular systole (Yacoub et al., 2004). Thus, the myocardial composition in males may serve to provide better hemodynamic pliability to the valves making them less predisposed to insufficiency.

The age-related decrease in annular cellularity and elasticity in the present study has been previously reported (Pomerance et al., 1967)]. The increased collagen fiber density with age may be due to decrease in the rate of fiber turnover with subsequent accumulation and cross-linking (Drury et al., 1967). This may be associated with fibrosis, a common cause of valve insufficiency (Dalane et al., 1990). Further, increased collagen fiber density may also exert forces on elastic fibers and distorting them (Fukuda et al., 1989), as shown in the present study. Elastic fibers have also been shown to undergo age-related degenerative changes such as loss of fibrillar structure and increase in foreign deposits (De Cavalho et al., 1996) which also alters their overall functional capacity. This may explain the reduced annular elasticity and flexibility with increasing age. The present study also depicted a reduction in the number of annular muscle strips with increasing age. This is not surprising considering a general decline in heart function in the aged (Dalane et al., 1990). This may imply reduced annular contractility and hemodynamic pliability with age.

In conclusion, the significantly wider annular circumference in the 21-39 year age group may contribute to decreased heart valve co-aptation and valvular incompetence, suggesting an earlier predisposition to this pathology in the study population. The age-related decrease in annular cellularity, elasticity and myocardial content may explain the higher incidence of valvular incompetence with increasing age.

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