

Atrial structural remodeling in patients with atrial chronic fibrillations and in animal models

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Abstract

Arrhythmia's atrium fibrillation (AF) is the most often met in clinical setting and it is associated with an increased in mortality risk. For profound the structural changes in chronic AF, we are studied the morphological changes of atrium biopsies to be effected at 175 patients. With sustained AF malformative and valvular acquired cardiac diseases operated under extracorporeal circulation. Similar studies we are effected to 11 dogs with partial coronary obstructions to a made periodical EKG investigations. The morphological changes mainly concern accommodation (dedifferentiation) of cardiomyocytes (particularly at experimental model) and mal-accommodation (degeneration of cells with fibrosis replacement features) particularly in acquired valvular diseases. These changes were often interfered. Over study, maintain the hypothesis that the structural changes to be an accommodation more than degenerative response to AF.

Keywords: atrial myocardium, chronic atrial fibrillation, morphophysiological changes.

■ Introduction

Atrium fibrillation (AF) is the most often met in clinical sections and it is associated with an increase in mortality risk that is strongly related with old age. Risk factors include also diabetes, high blood pressure, congestive heart failure, valvular diseases, congenital cardiac diseases, myocardial ischemia, and strokes. These morphological changes often interfered, concern accommodation (differentiation of cardiomyocytes) and mal-accommodation in human and experimental models. The relationship between structural remodeling are not enough understood, only combined implementation electrophysiological, morphological and molecular biological techniques will enable scientist to reveal the nature of this arrhythmia.

■ Materials and Methods

Hundred and seventy-five patients with chronic atrium fibrillation during mitral, aortic valvular diseases, congenital cardiac diseases, and myocardial ischemia are selected for intra-surgical interventions with atrium biopsies at the beginning of surgical interventions effected under extracorporeal circulation (V. Cândeа). The slides from atrium were histological examined (HE, VG, Lie, PAS-Alcian, Gömöri); histoenzymological (SDH, LDH, acid and alkaline phosphatases, cytochrome c-reductase, non-specific esterase, ATPase), biological techniques (TUNEL, propylene oxide) and electron microscopy.

Experimental model was effected 11 community dogs by partial anterior descending coronary obstruction during three months, with repeated EKG investigations

effected by C. Carp, and further the same techniques was make as in human slides.

■ Results

In numerous slight examined with histological and ultra-structure technique we find in enlarged atrium an interferences of mal-accommodation (degeneration of cells with fibrosis) and accommodation (dedifferentiation of cardiac myofibrils) features. Histological, in patients with AF degeneration of cardiac myofibrils consisted on vacuolization, sarcoplasmatic acidification, tendency to atrophy than to hypertrophy. On observed ultra-structure changes: mitochondrial lesions towards to swelling (Figure 1), interstitial edema, cardiac myofibrils lesions (Figure 2), secondary lysosomes (Figure 3) and lipid droplets widening of the undifferentiated portion of the intercalated discs replacement of myofibrils by glycogen granules (Figure 4) loss of membrane structure and organization increase the extracellular spaces through edema and fibrosis. The histoenzymological technique confirms these features. Similar observation was made on patients by Mary-Rabine L *et al.* [2], Frustaci A *et al.* [3], Laky D *et al.* [1, 4–6].

In other areas, especially in experimental model cardiac myofibrils presented several accommodation (dedifferentiations) changes such as hibernating. Cardiac myofibrils gradually disposed of their contractile material become gradually clear starting from the perinuclear region toward the periphery of the cell. Remnant of sarcomeres, especially clumps of two-band material were observed. Glycogen especially had accumulated in sarcomeres depleted areas (Figures 4 and 5) between mitochondria network of disorganized, probably altered

profile of sarcoplasmic reticulum, were present in myolytic area. Mitochondria took enlarged shape (Figure 8) with longitudinal oriented crystal, which appeared as small. Nuclear heterochromatin showed a homogenous distribution (Figure 6) thorough the nucleus-plasma similar with in fetal stadium. These changes showed similar to finding after prolonged sustained fibrillation in goats by Ausma J et al. [7–9] were the degenerative altered expression of bcl-2, p53 or proliferating cell nuclear antigen nor increase in TUNEL reactivity could be demonstrated suggesting that apoptosis does not play from plead also the lack of increase in extracellular space (fibrosis). EKG disturbances also appear (Figure 7).

Comparatively in absence of atrium fibrillation, at human and experimental model the structural changes were much diminished (Figure 8).

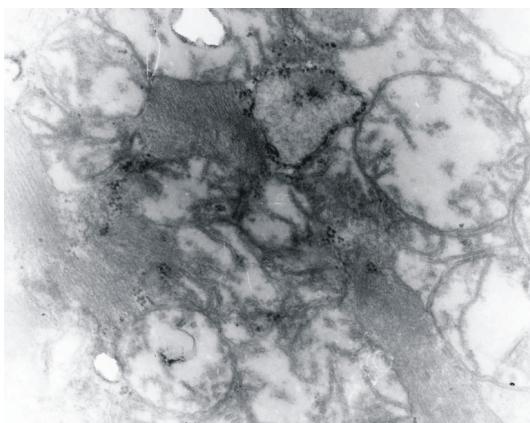


Figure 1 – Mitochondrial lesions toward to swelling, $\times 25\,000$.



Figure 2 – Myofibril lesions interstitial edema, $\times 6000$.

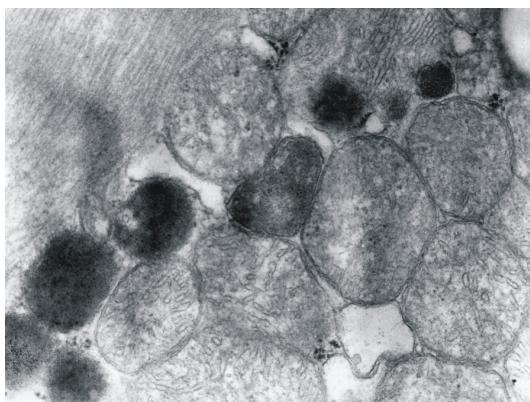


Figure 3 – Accumulation of secondary lysosomes, mitochondrial cristae lesions, $\times 9500$.

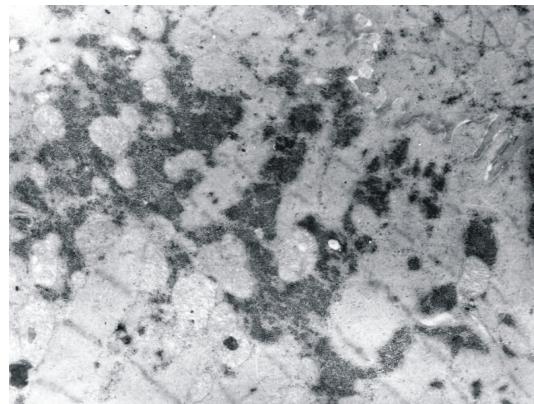


Figure 4 – Zone with replacement of myofibrils by glycogen granules, $\times 4500$.

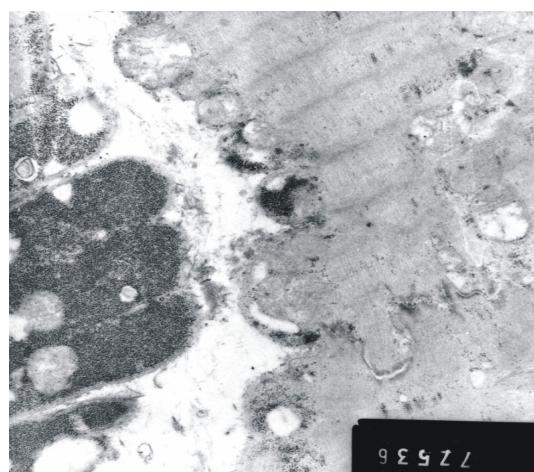


Figure 5 – Experimental model: glycogen accumulated in depleted area of sarcomeres, $\times 4500$.

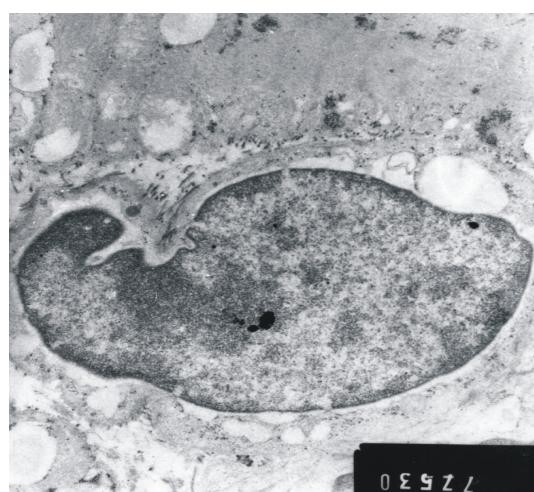


Figure 6 – Experimental model: redistribution of chromatin with nucleus after two weeks of partial occlusion of descending anterior coronary, $\times 9500$.

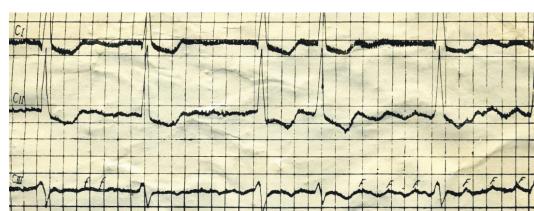


Figure 7 – EKG: dog with AF during coronary partial occlusion: fibrillation and flutter.

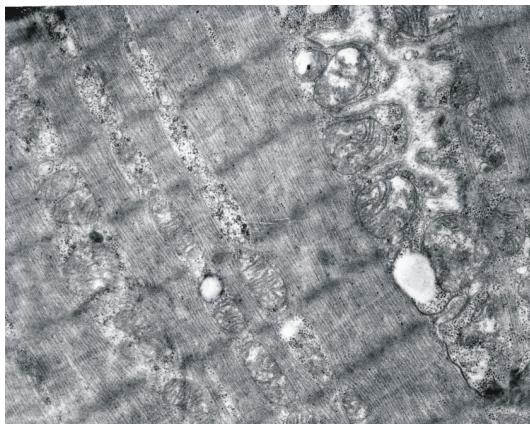


Figure 8 – Cardiac valve disease without AF: myocardial structural changes were much diminished, $\times 9500$.

Discussion

The mal-accommodative and accommodative changes are discussed about the mechanism of structural remodeling and chronic feature of the arrhythmia are not enough understood. Ausma J *et al.* [7–9] hypothesized that the perceived structural alterations appeared to be an accommodative response of dedifferentiation rather than the result of cardio-myofibrils degeneration, because many of the features seen in the atrium myofibrils during sustained AF were also present during cardiac myofibrils development. To determine whether chronic atrium fibrillation inverted atrium myofibrils to adopt an embryo-fetal dedifferentiated state, the expression of proteins that are characteristic for cardiac myofibrils development are examined. Thus α -smooth muscle actin which expression in normal cardiac myofibril is gradually lost during cardiac development, become re-expressed during AF; titin gradually disappeared in a pattern reverse to the pattern seen during cardiac development resulting in molecular organization similar to that in fetal stage. Cardiotonin, a sarcoplasmatic reticulum protein of which the expression has not been seen related during fetal development, disappeared during chronic AF, desmin, which play a role in the myofibril attachment to junction membrane was lost. This detachment of desmin from the interrelated disc resembled it organization in certain stages of cardiac myofibrils development.

Several factors may be involved in the mechanism of dedifferentiation of cardiac myofibrils such: myocardial ischemia, stretch, calcium homeostasis, molecular mechanism, altered expression of genes that are involved in several cardiac diseases [10] that are some time contest discussed. One of the possibility important changes in calcium homeostasis, which occur at the onset of AF, is Ca^{2+} overload. In goats with AF were also clear evidence of Ca^{2+} overload but it appeared that after two weeks of AF; cardiac myofibrils were able to adapt to new Ca^{2+} homeostasis and after 16 weeks of AF no more signs of Ca^{2+} overload was found. Ca^{2+} overload was suggested to cause a reduced Na^+ current density in atrium myofibrils of dogs after seven days of rapid atrium peacemaker, possible by down regulation of Na^+ channel expression level [12].

The molecular mechanisms might be involved in cardiac myofibrils accommodation of chronic AF in goats using dedifferentiated display techniques described by Liang P and Pardee AP [13] that has been used to identify or confirm altered expression of genes in several cardiac disease [14–16].

Experimental models are essential tool for investigating AF and it is important that such models mimic *in vivo* situation in human as much as possible [1, 10]. In models of lone AF, the influence of a heart, therefore, in humans, AF often occurs at a later age and lasts for many years, a situation which is difficult to simulate in animal models. Electrical remodeling (Figure 7) has been found to occur at the onset of AF and appears to completed after two weeks. The first obvious signs of structural remodeling become apparent after two to four weeks of AF and reach a steady state between eight to 16 weeks.

One the first changes seen in cardiac myofibrils after AF is the redistribution of heterochromatin within the nucleus (Figure 8) which indicates that the cell is actually reorganizing its genetic material to cope with the new situation. The development of new molecular techniques [12] to screen differences in gene [13] expression e.g. differential display, serial analysis of gene expression and DNA-array, together with the advancement of knowledge in functional genomic null help to answer questions to the nature of molecular remodeling and its role in electrical and structural during AF. Thijssen VL *et al.* [11] using mRNA technique recognize genes with transiently expressed during AF and were able to confirm the reappearance of the α -SMC-actin protein on the level of mRNA.

Conclusions

We studied to detect on atrium biopsies the structural changes before open heart surgery at 175 patients with acquired and congenital heart disease suffering chronic atrium fibrillation and at 11 dogs with partial coronary occlusions during three months, investigated periodical EKG. We find combined accommodative (dedifferentiation of cardiac myofibrils especially to experimental material) and mal-accommodative (degenerations of cells with fibrosis replacement) changes.

In condition when mechanism of changes remained uncertain after our results, we maintain the hypothesis that structural changes to be accommodative (adaptive) remodeling more when degenerative response to AF. A combined implementation morphological, electrophysiological and molecular technique will enable to reveal the nature of this arrhythmia for better treatment of patients suffering from chronic atrium fibrillation.

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