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Adaptations Processes in Human Atrial Fibrillation

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*I*t is well known that an abrupt increase in heart frequency, like in atrial fibrillation (AF), causes an immediate (within one action potential) and then a gradual (reaching steady state over several minutes) decrease in action potential duration (APD) [1]. These alterations in APD reduce atrial effective refractory period (AERP) and shorten the wavelength for reentry, which will facilitate the occurrence and maintenance of reentrant arrhythmias like AF. The rapid nature of these changes suggests that the short-term APD adaptation to rate is due to functional changes in ion channels. With longer periods of sustained atrial tachycardia, changes develop over the course of hours to days [2–4]. The latter alterations appear to concern mainly ion channel density and are due to modified gene expression [5,6]. Studies have revealed that the rapid shortening of the AERP in animal experimental AF mainly involves functional changes in the L-type Ca^{2+} channel [5,6]. In human AF the relationship between changes in AERP and ion channel gene expression was investigated by studying the regulation of L-type Ca^{2+} channel and K^+ channels and their relation to AERP in patients with persistent and paroxysmal AF [7]. This study demonstrated a positive correlation between the ion-channel protein expression of both the L-type Ca^{2+} channel and K^+ (!) channels and the AERP in patients with persistent and paroxysmal AF. Low ion-channel protein levels (of both L-type Ca^{2+} channel and K^+ channels) were associated with short AERP and poor rate adaptation. This indicates that electrical remodeling is paralleled by *general* ion-channel protein reductions as part of the adaptation mechanisms during AF. Since shortening of AERP can be explained by decrease in L-type Ca^{2+} channel gene expression or activity, the reductions in L-type Ca^{2+} channel could represent an explanation for the electrophysiological changes during AF.

Post-Transcriptional Regulations

Furthermore, a remarkable finding during studies of mRNA and ion-channel protein remodeling [7,8] was a discrepancy between changes in mRNA and protein levels in patients with paroxysmal AF. Whereas protein levels of ion-channels were substantially decreased, mRNA contents were essentially unaffected in paroxysmal AF. This discrepancy was also observed in other studies [9, 10] and lead to the idea that an adaptative mechanism which was unknown in AF so far could play a role: activation of a proteolytic system. Different proteolytic pathways could be involved in AF. Since cytosolic calcium is increased during AF [11,12], proteolysis may be invoked by calcium dependent neutral proteases, calpain I and II. Calpains are proteases which cleave mainly cytoskeletal and membrane-associated proteins into 'limited fragments' without further degradation [13]. In cardiac cells, calpains mediate cell death and are involved in troponin proteolysis and cross-linking following cardiac stunning and calcium overload [14–16]. We found an increased calpain activity in atrial tissue of patients with paroxysmal and persistent lone AF [17]. This increase was predominantly due to elevation of calpain I activity and expression. The calpain I protein was found to be mainly localized at the nucleus and intercalated discs of atrial myocytes. At these intercalated discs calpain can interact with Ca^{2+} and thereby become an active proteinase in turn degradating important ion-channels, but also proteins directly involved in excitation-contraction coupling. At the nucleus calpain can induce degenerative features leading to apoptosis, which has been observed to occur in human AF.

Furthermore, calpain activity correlated with the expression levels of ion-channel proteins, the degree of structural changes, measured AERP and the rate adaptation coefficient of AERP. The results suggest that induction of calpain activation represents a missing link between the calcium overload observed in AF and remodeling of atrial myocytes during AF.

Structural Remodeling

In addition to electrophysiological, functional ion-current and ion-channel gene expression changes,

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AF is associated with alterations in morphology. An increase in degenerative contraction band necrosis has been observed in patients with persistent and paroxysmal AF [17]. Furthermore, the ocurrence of alterations resembling those observed in myocardial hibernation (loss of sarcomeres and pale nuclei) has been demonstrated in patients with persistent AF, and correlated positively with the duration of AF. This indicates that in human persistent AF hibernation could be the specific structural change due to AF, which is in accordance with development of hibernation in the goat model for AF [18]. Abundant degenerative features were observed in lone, paroxysmal AF. These could represent the prelude to the vulnerability to AF by inducing dispersion of conduction. Once persistent AF has been developed, hibernation (which depends on protracted periods of sustained AF) is more abundant considered that cells liable to degeneration have now disappeared. These notions are supported by the finding that in our patients with persistent AF, hibernation increased with the duration of AF, while degeneration decreased. Possibly, hibernating myocardium is protected against degeneration, as found after ischemic preconditioning.

Since AF is promoted by slow conduction studies investigated the gap-junction proteins, connexins, that play an important role in homogenous wavefront propagation and conduction velocities in the heart. Gap-junctions are clusters of channels which span the closely apposed plasma membranes, forming cell-to-cell pathways. Connexins are permeable to ions and small molecules up to 1 kDa in molecular mass, like second messengers such as inositol triphosphate, cyclic AMP and calcium. In a recent study the gap junctional changes in relation to stabilization of AF were studied [10]. In goats that were in sinus rhythm the distribution of connexin40, a connexin that gives high conductance, was homogeneous. After 2 weeks in AF, which was the time associated with markedly increased intracellular Ca^{2+} deposition [11] and just before AF became sustained, heterogeneity in the connexin40 distribution was observed. The connexin40 distribution pattern correlated with the occurrence of structural changes (myolysis) in atrial myocytes.

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