Calpain in Atrial Fibrillation: Friend or Foe?

Editorial to: “Anti-apoptotic effects of a calpain inhibitor on cardiomyocytes in a canine rapid atrial fibrillation model” by Yue Li et al.

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Atrial fibrillation (AF) is associated with the occurrence of substantial structural changes in atrial tissue. AF is known to induce a cellular calcium-overload due to an increased influx of calcium through L-type calcium channels. Therefore, alterations of intracellular calcium homeostasis with activation of calcium-dependent signalling pathways like calcineurin and calpain appear of particular importance. Whereas calcineurin-dependent signalling contributes to the development of atrial hypertrophy [1–3], activation of the calcium-dependent protease calpain I may lead to destruction of cellular proteins. The histopathology of fibrillating atria is thought to be similar to chronically ischemic ventricular myocardium. A study by Goette et al. [4] showed that patients with AF have increased expression and activity of calpain I in atrial tissue. The changes in

calpain activity were accompanied by reduced amounts of TnT and morphological degradation of myofilaments in fibrillating atria. Aime-Sempe et al. [5] provided evidence of an increased rate of apoptosis in fibrillating human atria. Importantly, inflammatory infiltrates were not observed in that study either. This suggests that non-inflammatory pathways contribute for the described apoptotic cell death in atrial tissue.

The present study by Yue Li et al. [6] shows that an inhibitor of calpain I (N-Acetyl-Leu-Leu-Met; ALLM) diminishes the extent of apoptotic cell death in an in vivo canine model of AF. They show that inhibition of calpain I is able to reduce the rate of apoptosis (apoptosis index) and caspase expression as otherwise found highly increased after the 3 week period of atrial pacing. Anti-apoptotic proteins like bcl2 recovered by ALLM therapy are indicative of calpain activity being upstream of mitochondrial apoptotic pathways. Thus, the present paper provides first evidence using an in vivo model that inhibition of calpain I prevents pacing- induced apoptosis. This finding may have important implications since increased rate of apoptosis might affect the electrical and mechanical properties of fibrillating atrial tissue. Nevertheless, it still has to be proven that the demonstrated molecular effects of ALLM influence directly the occurrence/persistence of AF or the mechanical atrial function. Thus, it appears too early to state that ALLM is useful as upstream therapy in AF.

Calpain I cleaves a variety of proteins to promote apoptosis with caspase-7 being just one recent example [7]. However, there is apparent crosstalk between apoptotic and necrotic pathways and activation of calpain promotes apoptosis even during caspase inhibition. In the heart, caspase-independent induction of apoptosis has been recently shown to occur via release of apoptosis-inducing

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factor (AIF) from mitochondria [8], which in other tissues was shown to be mediated by elevated intracellular Ca^{2+} -levels [9] or calpain I [10].

Interestingly, the results of the present study are supported by data from previous studies obtained ex vivo. Rapid ex vivo stimulation of HL-1 atrial myocytes showed reduced expression of L-type Ca^{2+} -channel $\alpha 1\text{C}$ subunits by -72%. The pacing-induced reduction of L-type Ca^{2+} -channel protein was fully prevented by treatment with verapamil, the active stereoisomer of methoxy-verapamil D600, the calpain inhibitors PD150606 and E64d, and $\text{LaCl}(3)$. Interestingly, PD150606, E64d and $\text{LaCl}(3)$, but not verapamil, prevented structural changes. Swelling and disruption of mitochondria are typical morphologic findings in fibrillating atrial tissue [11]. Mitochondrial dysfunction and concomitant opening of the permeability transition pore is strongly correlated with cell death [12], and interventions to prevent pore opening have been shown to protect the myocardium [13]. AF has been shown to cause severe damage of mitochondrial structure and to provoke mitochondrial dysfunction, which is in part due to the frequency-dependent intracellular Ca^{2+} -overload [14, 15]. Accordingly, verapamil was shown to preserve mitochondrial structure and function [14, 15]. The critical requirement for mitochondrial participation in the death process is underscored by the protective effect of the mitochondrial ATP-sensitive potassium channel in preconditioning. This channel has been suggested to preserve calcium homeostasis and would therefore limit calpain activation [16]. Indeed, calpain inhibition was protective in models of ischemia/reperfusion which suggests that pore opening, if it occurs, is downstream of calpain activation [17]. The study of Yue Li et al. implies that similar mechanisms apply during AF. However, the role of apoptosis in cardiac disease and especially in AF remains unclear. Apoptosis is a consistent finding in many cardiovascular diseases. According to Lockshin et al. [18], myocyte apoptosis may reflect extensive damage to cardiac tissue rather than causing it. If so, preventing apoptosis would lead cells into necrotic death, which may be even more harmful. Preventing apoptosis appears to be beneficial in acute situations such as myocardial infarction. In more chronic situations like persistent AF apoptosis may facilitate “sterile and silent” removal of irreversibly damaged cells. Therefore, a true possible benefit of calpain-inhibitor administration in AF remains to be elucidated in future studies.

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