Determinants of Altered Atrial Na+ - Ca2+ Exchanger Function in Patients with Chronic Atrial Fibrillation

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Purpose: Dysfunctional Na+ - Ca2+ exchanger type-1 (NCX1) is implicated in atrial fibrillation (AF) triggers/drivers, but the mechanisms of NCX abnormalities in AF patients are unknown and were addressed here.

Methods: Transient inward current (I\text{ti}) was recorded with perforated patch-clamp technique in atrial myocytes from sinus rhythm (Ctl) and chronic AF (cAF) patients. The NCX1 macromolecular complex proteins were detected in atrial lysates, membrane and cytosolic fractions, or immunoprecipitates (IPs) with Western blot.

Results: In cAF myocytes, we detected a higher frequency of I\text{ti} current (5.21 ± 2.20 vs. 0.49 ± 0.35 I\text{ti} min\(^{-1}\) in Ctl, P < 0.05). The mean integral of I\text{ti}, an indicator for SR Ca2+ content, was comparable in cAF and Ctl myocytes (7.86 ± 1.04 vs. 6.86 ± 1.18 amol/pF). Amplitude of caffeine-induced peak I\text{ti} was significantly greater in myocytes from cAF (0.79 ± 0.08 pA/pF) than in Ctl patients (0.47 ± 0.07 pA/pF), pointing to increased NCX function. In membrane fractions of cAF patients protein expression of the 160 (±42%) and 120 kDa (±145%) bands was increased (Fig). Moreover, the functional 160 kDa full-length protein was responsible for more than 90% of total membraneous NCX1 protein. Using immunoprecipitation to dissect the composition of the NCX1 complex we identified the catalytic protein kinase-C\(\alpha\) and protein phosphatase type-1 (PP1\(\alpha\)) subunits along with phospholemman (PLM) in the NCX1 complex in both Ctl and cAF patients, whereas protein phosphatase type-2A (PP2A) and calcineurin-A\(\beta\) were absent.

Conclusions: We identified for the first time PKC, PP1 and PLM as part of the human atrial NCX1 protein complex. Increased membraneous NCX1 protein and a kinase-phosphatase dysbalance in the NCX1 complex may underlie the proarrhythmic NCX dysfunction in cAF.