Increased NaV1.8 expression in patients with sleep-disordered breathing induces pro-arrhythmic activity

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Background: Sleep-disordered breathing (SDB) is often associated with atrial fibrillation, but detailed mechanisms remain elusive. Interestingly, late Na current (late INa) has been shown to be increased in patients with SDB, while expression of cardiac Na channel NaV1.5 and peak Na current were decreased. Indeed, recent data demonstrated that enhanced NaV1.8-dependent late INa may also induce pro-arrhythmic activity.

Purpose: We tested whether Na-V1.8 expression and subsequent NaV1.8-dependent pro-arrhythmic activity are increased in patients with SDB.

Methods: We prospectively analysed 29 right atrial appendage biopsies of patients undergoing elective coronary artery bypass grafting. SDB was assessed using polygraphy in the preoperative night and an apnoea-hypopnea index (AHI) $\geq$15/h defined SDB. Micro-dissected atrial trabeculae were electrically field stimulated (at 1 Hz, 5 V for 50 ms, at 37°C) to elicit regular contractions. Trabecular arrhythmias were induced using 100 nM isoproterenol at $[Ca]_o$ of 3.5 mmol/L and pro-arrhythmic activity was scored from 0 (no arrhythmias) to 5 (salve). Sarcoplasmic reticulum Ca leak was estimated by the contractility after paused stimulation (at 2 Hz, normalized to before pause). To correlate functional and expression data for each individual patient, NaV1.8 mRNA expression was quantified in each trabeculum using qPCR.

Results: NaV1.8 mRNA expression was increased in patients with SDB, leading to a significant positive correlation with the severity of SDB (i.e. AHI, p=0.02, r^2=0.22, Fig. 1A). Multivariate regression analysis revealed that this association was independent from age, sex, atrial fibrillation, heart failure, diabetes mellitus, and renal function (p=0.03, r^2=0.35). Accordingly, selective NaV1.8 blockade with PF-01247324 (PF, 1 µM, 30 min) significantly improved post-pause contractility of isolated trabeculae from 1.69±0.31 to 2.95±0.54 in patients with SDB (p=0.001), whereas no significant improvement was observed in patients without SDB. This resulted in significant positive correlations between the PF-dependent improvement of post-pause contractility and both AHI (p=0.047, r^2=0.19) and NaV1.8 mRNA expression (p=0.03, r^2=0.17). Most importantly, we also observed a significant increase in arrhythmia severity in patients with SDB of 2.21±0.52 (vs. 1.00±0.49, p=0.03) that could be significantly reduced by selective NaV1.8 inhibition with PF to 0.25±0.18 (p=0.0008, Fig. 1B). In accordance, there was a significant positive correlation between arrhythmia severity and AHI (p=0.01, r^2=0.28) that was abolished in the presence of PF (interaction analysis: p=0.00001, r^2=0.46).

Conclusion: In patients with SDB, enhanced NaV1.8 expression contribute to atrial pro-arrhythmic activity independent from comorbidities. Selective NaV1.8 inhibition may have therapeutic implications for patients with SDB.

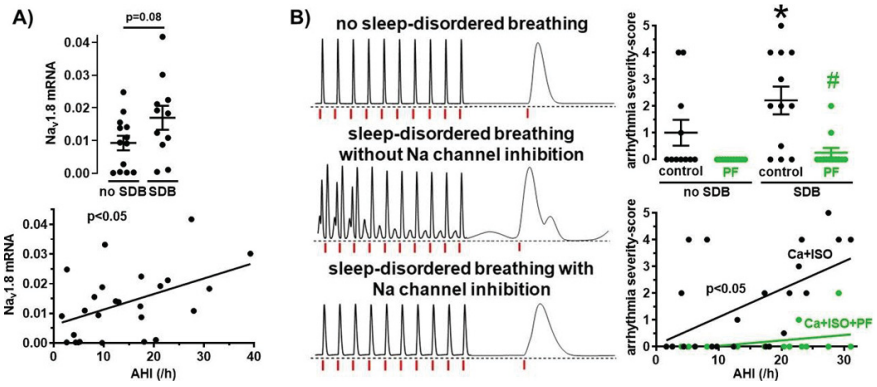

Figure 1