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Circulating Neuropeptide Y as a Biomarker for Neuromodulation in Atrial Fibrillation

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The autonomic nervous system influences atrial fibrillation (AF) burden. Recent clinical trials investigating neuromodulation (e.g. Low-Level Tragus Stimulation (LLTS)) in AF treatment have shown promising results[1]. However, the variable response to LLTS suggests that mechanisms underlying its efficacy are poorly understood. Specifically, whether sympathetic signaling, a driver of AF, is mitigated by LLTS, or whether biomarkers of sympathetic activity can guide patient selection for LLTS remain undetermined.

The sympathetic co-transmitter Neuropeptide Y (NPY) is a promising biomarker of sympathetic hyperactivity following myocardial infarction[2] and heart failure[3]. Here, we investigate the role of NPY as a biomarker of AF progression and LLTS response in the prospective randomized clinical TREAT-AF (Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation, NCT02548754)[1]. All patients provided written informed consent prior to participation and the study was approved by the University of Oklahoma institutional review board.

We randomized patients with paroxysmal AF to LLTS (20Hz, 1mA below pain threshold) using a tragus clip (n=26) or ear lobe (n=27) for one hour daily over a 6-month period[1]. At baseline, and at 3- and 6-months following randomization, AF burden was assessed by

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2-week non-invasive cardiac monitors, while NPY levels were measured by immunosorbent assay (ELISA).

The study included 29 females (55%) with paroxysmal AF (median duration 24 months) and structurally normal hearts [mean left ventricular ejection fraction 60±5.4%][1]. Mean NPY levels were 41.64±4.4 pg/ml (mean±SEM), expectedly lower than levels in chronic heart failure patients[3]. On univariate analysis, baseline NPY levels positively correlated with age (r = 0.32, p=0.029); BMI (r=0.38, p=0.01); and heart rate (r=0.38, p=0.026). During follow up, heart rate during AF was 14.4 bpm lower in the LLTS group vs. ear lobe (95% CI 2.9 – 25.9 bpm, p=0.014), while episodes of rapid ventricular response during AF were less frequent in LLTS vs. ear lobe groups (OR=0.36, 95% CI 0.18 – 0.72, p=0.004, logistic regression analysis) demonstrating the efficacy of LLTS in this cohort.

There was a significant group by time interaction for NPY levels (p=0.018), indicating that NPY levels changed differently over time in the two groups (Figure 1A). Specifically, the ear lobe group NPY levels significantly increased at 6 months vs. baseline (63.2±5.9 vs. 42.7±4.7 pg/mL, p=0.01); however, in the LLTS group, 6-month NPY levels were comparable to baseline (37.1±4.8 vs. 39.3±4.6 pg/mL, respectively, p=0.64) (Figure 1A). At 6 months, NPY levels in the LLTS group were significantly lower than ear lobe (37.1±4.8 vs. 63.2±5.9, respectively, p=0.008). Notably, LLTS group NPY levels negatively correlated with change in AF burden during follow up (r=−0.48, p=0.036), indicating that higher baseline NPY levels were associated with greater responses to LLTS.

To determine whether NPY receptor (NPYR) expression was associated with AF progression, we examined NPYR RNA abundance using RNA sequencing of left atrial tissue samples obtained from patients during open heart surgery. Study approval, consent, clinical details and methodology for RNA isolation and sequencing in this cohort were previously published[4]. We studied NPY1R-NPY5R mRNA abundance in patients with known AF (paroxysmal, n=59; persistent, n=103; and longstanding persistent, n=60). NPY3R transcripts were absent in all patient samples. Except for NPY2R, atrial RNA counts ($\log_2$ scale, Figure 1B) were significantly greater in patients with persistent or long-standing persistent AF compared to those with paroxysmal AF, suggesting an association between AF progression and left atrial NPYR expression.

We present the first evidence of a significant association between AF progression, left atrial NPYR expression, and circulating NPY levels in response to neuromodulation. Circulating NPY levels increased over time in patients treated with ear lobe stimulation while no change was observed with tragus stimulation These findings are supported by increased left atrial expression of NPY1R, NPY4R, and NPY5R. Our findings implicate NPY-NPYR signaling in AF progression and response to neuromodulation. Further studies to validate and extend these findings are warranted.

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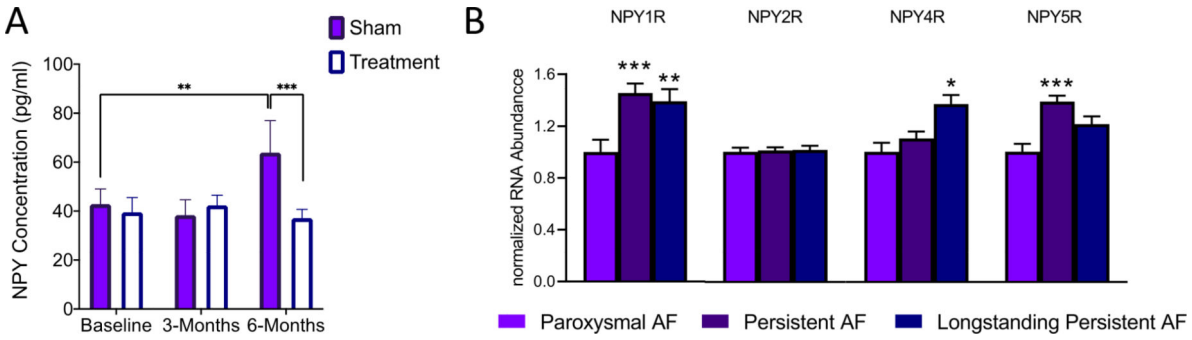

Figure.

Circulating Neuropeptide Y (NPY) concentration is associated with atrial fibrillation (AF) progression and response to Tragus Stimulation.

A, Circulating NPY levels by randomization and time. N= 26 and 27 subjects for Treatment groups respectively. Data were analyzed using a mixed linear model (SAS™, SAS Institute, Cary, NC). Time by group interaction p value = 0.018. B, Normalized RNA abundance in left atrial tissue (log_2 RNA count) for NPY1R, NPY2R, NPY4R, and NPY5R. N=59 (paroxysmal), N=103 (persistent), N=60 (longstanding persistent). *p<0.05, **p<0.01, ***p<0.00. Brown-Forsythe ANOVA with pair-wise comparisons performed with Games-Howell's test.