Inhibition of Atrial Fibrillation Inducibility by Low Level Vagus Nerve Stimulation: the Role of Nitric Oxide Signaling Pathway

Background: Low level vagus nerve stimulation (LLVNS, 50% below that which slows the sinus rate) inhibits atrial fibrillation (AF) inducibility but the exact mechanism is unclear. We examined the role of the phosphatidylinositol-3 kinase (PI3K)/nitric oxide (NO) signaling pathway in LLVNS-mediated inhibition of AF inducibility.

Methods: In 17 pentobarbital anesthetized dogs bilateral thoracotomies allowed the attachment of electrode catheters to superior and inferior pulmonary veins (PVs) and atrial appendages (AA). Programmed stimulation, at 10x diastolic threshold, was used to determine effective refractory period (ERP) at all tested sites and the width of the window of vulnerability (WOV), a measure of AF inducibility. AF was induced by rapid atrial pacing (RAP) for 6 hours. During the last 3 hours, RAP was overlapped with right LLVNS. Each hour, RAP was temporarily stopped and ERP and WOV were measured during sinus rhythm. In group 1 (n=7), no intervention other than LLVNS was done, whereas in groups 2 (n=6) and 3 (n=4), at the end of the 3rd hour, the NO synthase inhibitor L-NAME and the PI3K inhibitor wortmannin, respectively, were injected in the anterior right (AR) GP and inferior right GP. Acetylcholine, 100mM, was applied on the right AA at baseline and at 6 hours to induce AF and the AF duration was determined. Voltage-sinus rate response curves (a surrogate for GP function) were constructed by applying high frequency stimulation to the ARGP with increasing voltage until AF was induced. The maximal change in sinus rate was also determined.

Results: LLVNS significantly decreased the acetylcholine-induced AF duration (9.1±2.7 vs. 1.3±0.7 min; $p<0.001$). Both L-NAME (8.1±6.3 vs. 7.2±4.9 min; $p=0.79$) and wortmannin (12.4±3.3 vs. 9.6±2.9 min; $p=0.25$) abrogated this suppressive effect of LLVNS on AF inducibility ($p=0.0004$ and $p=0.004$ for the comparison of group 1 with groups 2 and 3, respectively). The cumulative WOV (the sum of the individual WOVs) increased significantly during the first 3 hours of RAP ($p<0.001$) and decreased towards baseline with LLVNS ($p<0.001$). L-NAME and wortmannin failed to inhibit this effect during the 4th hour ($p>0.05$), but blunted this effect during the 5th (L-NAME only; $p<0.05$) and 6th hour (L-NAME and wortmannin; $p<0.05$). LLVNS suppressed the ability of ARGP stimulation to slow the sinus rate (38±9 vs. 13±6%; $p=0.001$), whereas L-NAME (48±19 vs. 40±20%; $p=0.75$) and wortmannin (63±14 vs. 57±8%; $p=0.89$) abolished this effect.

Conclusion: The anti-arrhythmic effects of LLVNS may be mediated via the PI3K/NO signaling pathway. These data may provide new insights into the role of neuromodulators in the pathophysiology of AF and may form the basis for the development of new therapeutic targets for AF.