SIMVASTATIN PREVENTS CANINE AF SUBSTRATE IN CHF: ROLE OF FIBROBLASTS?
Akiko Shoyabara-Takehara, MD, PhD; Brett Burstein, BSc; Bianca JMJ Brandel, PhD, and Stanley Nattel, MD. From the Department of Medicine and Research Center (A.S.-T., B.B., RJMB, S.N.), Montreal Heart Institute and University of Montreal, Department of Pharmacology, McGill University (B.B., S.N.), Montreal, Quebec, Canada, and the Department of Radiation and Stress Cell Biology (RJMB.), University of Groningen, The Netherlands.

Congestive heart failure (CHF) is a common cause of atrial fibrillation (AF). Oxidative stress and inflammation (proinflammatory) and peroxisome proliferator activated receptor-α (PPAR-α, antifibrotic) may be involved in CHF-related atrial remodeling. We evaluated effects of simvastatin (antioxidant, antiinflammatory) and fenofibrate (PPAR-α agonist) on CHF-induced atrial structural remodeling in dogs. Methods and Results: In vivo: Dogs subjected to ventricular tachycardia (VT) for 2 weeks to induce CHF in the absence (VT, N=9) and presence of simvastatin (SIM, N=6) or fenofibrate (FEN, N=6) were compared to non-paced (NP, N=8) controls. Electrophysiological, hemodynamic, biochemical and histological analyses were performed. Induced AF duration (DAF) increased after 2-wk VT from 36:14±1005:257 s* (P<0.05). DAF increases were prevented by SIM (48:37± s*) but not by FEN (108:18±352 s). SIM attenuated VTP-induced AF substrate components (e.g. conduction heterogeneity index reduced from 1.5±0.1 to 1.0±0.1*, atrial fibrosis decreased from 19.4±1.3 to 9.9±0.8 %*) and hemodynamic changes (LVEDP from 15±1 to 5±1 mmHg*), while FEN did not. Left ventricular inducible nitric oxide synthase and nitrite/nitrate increases after 2-wk VT were also prevented by SIM but not by FEN. In vitro: Atrial fibroblasts were isolated from NP dogs and cultured. Fibroblast proliferation was evaluated by [1H]thymidine incorporation in cells pretreated with SIM (100μM), FEN (10 μM), or vehicle (V). F-5 (5μg/ml) for 24-hr FBS stimulation. The effects of SIM, FEN, and V (N=6 in each) on OSM expression (myofibroblast differentiation) were assessed in TGF-1-stimulated cells. FBS stimulation increased atrial fibroblast proliferation (from 75±135 to 738±1998%*). SIM markedly suppressed fibroblast proliferation (1108±12%*), but FEN did not (756±1479%). Similarly, SIM, but not FEN, attenuated dSMA expression in TGF-1-stimulated cells (from 1.5±0.1 to 1.0±0.1*). Conclusion: CHF-related atrial structural remodeling and AF promotion are attenuated by simvastatin but not by fenofibrate. Statin-induced direct inhibition of profibrotic atrial fibroblast responses may constitute a novel mechanism for preventing the CHF-induced fibrotic AF substrate.

LOW VOLTAGE AREAS IN PATIENTS WITH RIGHT VENTRICLE OUTFLOW TRACT ARRHYTHMIAS

Background: Despite of normal ECG, echocardiogram and angiography in patients (pts), with right ventricular outflow tract arrhythmias (RVOT), magnetic electroanatomical voltage mapping provides insight into the size and location of endocardial abnormalities. Therefore, the purpose of our study was to analyze voltage maps of RV recorded in pts with RVOT and correlate presence of endocardial voltage abnormalities with clinically malignant arrhythmia’s outcome. Methods and results: Between 2000 and 2005 65 consecutive pts (41 females, mean age: 38—19) with severely symptomatic RVOT arrhythmia (sustained ventricular tachycardia– VT, non–sustained VT and/or frequent premature beats) underwent catheter ablation with the use of electroanatomical CARTO system. All pts had arrhythmia with left bundle branch block morphology and an inferior axis. Three out of 65 pts had sustained polymorphic VT (pVT), cardiac arrest and ICD implantation. pVT was triggered by RVOT premature beats which could be abolished by catheter ablation. No structural heart disease was detected by physical examination, ECG or echocardiogram. In 16 pts cardiac MRI also showed no signs pointing ARVD/C. A three–dimensional voltage map of the RV was obtained. Abnormal low voltage area was defined as a region of bipolar electrograms <1.8nV, and areas >0.5nV were assumed as a scar. Five low voltage areas and 6 areas defined as a scar were found in 7 of 65 pts (10,8%) – in 3 pts with fast monomorphic VT and 4 pts with pVT. In all cases arrhythmia triggers identified by mapping the earliest electrical activity, confirmed by pace–mapping, were localized in scar area, or in transition zone between scar and low voltage area. Conclusions. In pts with RVOT regions characterized by abnormal low amplitude electrograms are seldom but correspond to VT site of origin, especially in pts with malignant outcome. Further follow–up will show if presence of such regions may predict future development of ARVD/C in pts with other structural abnormalities found in physical examination, ECG and echocardiogram or cardiac–MRI.

ABLACTION OF RIGHT VENTRICULAR OUTFLOW TRACT TACHYCARDIA BASED ON ELECTROANATOMICAL MAPPING OF ISOLATE TACHYCARDIA BEATS

Introduction: Non inducibility of right ventricular outflow tract (RVOT) ventricular tachycardia (VT) at the electrophysiologic evaluation may limit mapping and, hence, ablation. Aim: to evaluate the efficacy of ablation based on electroanatomical mapping of isolate premature ventricular beats (PBVs) with the same tachycardia morphology. Methods: 9 patients (mean age 53±14 years, 6 men) with sustained (2 patients) or recurrent (7 patients) RVOT VT and normal left ventricular function have been included. A sustained or nonsustained (≥3 beats) form of the clinical VT was not inducible at the electrophysiological study, even during isoproterenol infusion. Therefore, they underwent electroanatomical mapping of the right ventricle during sinus rhythm by CARTO XP system; subsequently, a limited re–map was performed during PBVs VTs of the clinical VT morphology, captured in the beat memory buffer of the system. The site showing the earliest activation with completely negative unipolar deflection was targeted for ablation. Bipolar voltage of the right ventricle in sinus rhythm was also evaluated, considering as low voltage a signal amplitude <1.5 nV. Results: A mean of 20±4 captured ectopic ventricular beats per patient was enough to identify the site of earliest activation in 10 RVOT VT morphologies. Earliest site was located at the posterior and inferior submural infundibulum in 3 and 7 morphologies, respectively. A mean of 4±3 radiofrequency energy pulses suppressed permanently the PBVs in all patients. No procedural complications were observed. No patients had abnormal low–voltage endocardial areas. During 10±8 months follow–up, 1 pt had recurrence of the same RVOT VT after 1 month and was successfully reablated with the same method; all the other pts remained arrhythmia–free without antiarrhythmic drugs and repeated Holter monitoring showed absence of recurrence. Conclusions: ablation of RVOT VT based on electroanatomical mapping of single PBVs is safe and permanently effective. The preliminary reconstruction of the right ventricle in sinus rhythm guides the acquisition of a very limited number of PBVs to clearly identify the site of the arrhythmogenic focus; moreover, it rules out structural right cardiopathy in these cases.

PURKINJE ACTIVATION PRECEDING MUSCLE ACTIVATION AFTER DEFIBRILLATION SHOCKS
Derek J Dowdall, PhD, Koning in Chang, MD, PhD, Jamin Gao, MD, PhD, Raymond E. Eckler, MD, PhD. University of Alabama at Birmingham Departments of Biomedical Engineering, Medicine, and Physiology, USA.

Purpose: The origin of the first activation following shocks near the defibrillation threshold (DFT) is strength is not known. One hypothesis is that postshock activation arises from the Purkinje system. Therefore, as a prerequisite for testing this hypothesis, we determined if Purkinje activations are present during the first postshock cycle. Methods: In 5 pigs, a multi-electrode basket (Constellation catheter, Boston Scientific) was inserted into the left ventricle. Endocardial activation was recorded from 32 bipolar electrodes on the basket at an 8kHz sampling rate to allow detection of Purkinje spikes. Ten times in each animal, a DFT strength biphasic shock was given 10 sec after inducing ventricular fibrillation. Purkinje activations in normal sinus rhythm (NSR) and during the first post–shock cycle were identified from the recordings and the temporal derivative of the recordings. Results: Purkinje activations were identified preceding endocardial myocardial activation in 25% (8/42 of the 32 recording sites) during NSR (Figure A). After the shocks, Purkinje activations were identified prior to myocardial activation in 9% (2/21 of the 32 sites, Figure B). Purkinje activations were identified preceding myocardial activation in at least one recording site following 92% (46/50) of shocks. Conclusion: The Purkinje system is active during the first postshock cycle following DFT strength shocks in pigs. Mapping with a greater density of electrodes is needed to determine if Purkinje fibers initiate this cycle or are excited retrogradely from working myocardial activation.