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Canadian Cardiovascular Society (CCS) Abstracts — Basic Science

P001
B-MODE ULTRASOUND-GUIDED LOW-LEVEL FOCUSED-ULTRASOUND SONODYNAMIC THERAPY OF NEOINTIMAL HYPERPLASIA USING PHOTOFRIN-LOADED MICROBUBBLES

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BACKGROUND: In vascular surgery, neointimal hyperplasia is a significant clinical phenomenon because it reduces the long-term effectiveness of surgical and endovascular procedures. We devised an experimental sonodynamic therapy protocol and tested its efficacy on neointimal hyperplasia reduction in this study, in which diagnostic B-mode ultrasound is paired with focused-ultrasound with the goal of greater safety.

METHODS AND RESULTS: Golden Syrian hamsters were subjected to endothelial denaturation damage by abdominal aorta ballooning (approximately 0.5 cm superior to the iliac bifurcation). Histopathology results after eight weeks revealed increased smooth muscle cell proliferation in the intimal layer, culminating in vessel wall thickening. The treatment group, then received sonodynamic therapy with pulsed-low-level focused-ultrasound (F= 1.1 MHz, P= 15 W, PD= 250 ms) and sonosensitizer photofrin-loaded PESDA (Perflurocarbon Exposed Sonicated Dextrose Albumin) microbubbles (100ml/kg, 2-5 105 bubbles/ml). The development of inertial cavitation in the abdominal aorta was revealed by B-mode ultrasound imaging combined with ultrasound sonodynamic therapy. In addition, when comparing the treatment group to the other groups, histopathological results revealed a substantial reduction in the mean value for smooth muscle cell density, lumen wall mean thickness, and percentage of luminal cross-sectional area of stenosis ($p < 0.05$).

CONCLUSION: Enhanced cytoxic effect of photofrin, induced by low-level focused-ultrasound sonodynamic therapy combined with enhanced sonoporation effect of focused ultrasound, induced by collapsed bubbles, can cause intimal layer thickness to be reduced and the luminal cross-sectional area of stenosis to be significantly dilated.

Trainee Research Award Finalist — Basic Science

P002
CHARACTERIZING AN ARRHYTHMIA-RELATED TITIN MUTATION USING PATIENT STEM CELL-DERIVED ATRIAL CARDIOMYOCYTES

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BACKGROUND: Atrial fibrillation (AF) is a common arrhythmia that is linked to a greater risk of ischemic stroke and heart failure. Multiple genetic studies have established an association between protein truncating variants in the titin gene and increased risk of AF in the presence or absence of cardiomyopathy. Titin truncating variants are a known cause of dilated cardiomyopathy, thus existing studies have focused on the effects of these variants in ventricular cardiomyocytes. The structural and functional consequences of titin truncating variants in atrial cardiomyocytes and how such variants lead to arrhythmias such as AF are unclear. Our objective was to investigate the cellular effects of titin truncating variants identified in patients with unexplained AF.

METHODS AND RESULTS: We identified a heterozygous titin truncating variant in a patient with early-onset atrial fibrillation and generated induced pluripotent stem cell lines (iPSCs) of the patient. We used CRISPR/Cas9 homology-directed repair to perform genome-editing of the patient iPSCs and corrected the titin truncating variant to wildtype. We differentiated patient iPSCs with the titin truncating variant and wildtype iPSCs into ventricular-like and atrial-like cardiomyocytes. We characterized cellular electrophysiology by optically mapping voltage and calcium transients and assessed the organization of sarcomere structures within cardiomyocytes through immunofluorescent staining of sarcomere proteins and confocal microscopy. iPSC-derived atrial cardiomyocytes displayed cell type-specific characteristics including faster beat rates (mean $\pm$ sem, beats/minute: 150.9 ± 21.8 vs. 21.9 ± 3.6; $p = 0.01$) and shorter rate-corrected action potentials (cAPD80: 195.9 ± 23.8 vs. 394.7 ± 42.8 ms; $p = 0.048$) compared to ventricular cardiomyocytes. Analysis of sarcomere organization showed poorer structural alignment in iPSC-derived atrial cardiomyocytes with the titin truncating variant compared to wildtype (% organization: 66.3 ± 6.8 vs. 88.0 ± 2.9; $p = 0.03$; Figure 1A and 1B). Similarly, iPSC-derived ventricular