Hypertension Therapies Including Renal Denervation

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TCT-402

Renal Norepinephrine Reduction Following Radiofrequency Renal Denervation Correlates with Extent of Nerve Ablation: Roles of Ablation Areas, Anatomy, and Number of Treatments

Abraham R. Tzafriri[1], Felix Mahfoud[2], John Keating[3], Gee Wong[3], Anna-Maria Spognardi[3], James Stanley[3], Debby Highsmith[4], Patrick O'Fallon[4], Elazer Edelman[5]
[1]CBSET Inc., Lexington, MA, [2]Saarland University Hospital, Homburg/Saar, Germany, [3]CBSET, Inc., Lexington, MA, [4]Cordis/Biosense Webster, Inc. a Johnson & Johnson Company, Irwindale, CA, [5]Harvard-MIT Biomedical Engineering Center, Cambridge, Massachusetts

Background: Renal denervation is a treatment option for resistant hypertension. Preclinical models that explain the dependence of efficacy on treatment parameters can help differentiate and optimize device efficacy.
Methods: A total of 150 porcine renal arteries were treated with an irrigated multi-electrode helical catheter (Biosense Webster, CA). Between 2-5 electrodes were activated for 30-60 sec with power set points ranging from 6-20 W. Renal norepinephrine (NEPI) was measured 7 days post treatment and correlated with morphologic and morphometric assessments of treated sections. Measured nerve distributions and ablation areas informed a computational model for predicting the percentage of affected nerves (AN).
Results: NEPI levels across the range of treatment parameters exhibited a threshold-like, dependence on %AN, remaining in the range of control levels ($\geq$360 ng/g) up to AN=35% and dropping by 50% and 75% as AN increased to 52% and 70%, respectively. For 15W/30sec treatments, both NEPI and nerve effects tracked with number of activated electrodes (statistically significant for 5 vs 2 electrodes). Threshold ($\sim$50%) nerve and NEPI effects were only attained when $\geq$4 electrodes were powered. Average %AN increased with total ablation area as predicted by the computational model when accounting for the (average) measured non-uniform radial nerve distribution, but assuming that electrode-induced ablation areas achieved are mutually independent and predictable. Deviations from model-predicted %AN correlated variable nerve locations and sizes and/or deviant ablation areas. In particular, aberrantly low ablation areas were observed when electrode treatments were directed at neighboring blood vessels.
Conclusions: Variable ablation effects can be explained by the confluence of variable nerve locations and sizes and variable ablation shapes. The additive biomarker effects seen with angularly staggered treatments can be leveraged to optimize device design (e.g. electrode number and spacing) and treatment protocols (e.g. catheter rotation between two consecutive treatments) in the face of unknown variable micro-anatomy.

TCT-403

Peripheral Endothelial Function and Sympathetic Influence on Dermal Microcirculation Correlate with Long-Term Blood Pressure Response in Renal Denervation Patients

Alexander Jabs[1], Meike Fluhr[1], Katharina Beck[1], Selina Muxel[1], Zsofia Bardonicsek[1], Thomas Munzel[1], Tommaso Gori[1], Ulrich Hink[1]
[1]University of Mainz Medical Center, Mainz, Germany

Background: Renal denervation (RDN) has emerged as an interventional treatment option for treatment-resistant hypertension. Hypertensive patients are often characterized by an increased sympathetic tone as well as impaired endothelial function. However, there is a paucity of diagnostic tools to identify those hypertensive patients that will benefit from RDN (responders), and to proof successful RDN application. We therefore aimed to investigate the effects of RDN on vascular reactivity and sympathetic vascular response, with the ultimate goal to establish potential markers of therapeutic success.
Methods: In 23 patients (mean age 64 years, 13 men, mean ambulatory blood pressure monitoring (ABPM) 148/83 mmHg; $\geq$ 3 (mean 4.78) antihypertensive drugs in adequate dosage and combination) that underwent RDN (Medtronic Symplicity® (n=16), St. Jude Medical EnligHTN® (n=7)), flow-mediated dilation (FMD) and low flow-mediated constriction (L-FMC) as non-invasive measures of endothelial function were assessed. Sympathetic component to vasomotor function in dermal microcirculation was determined by laser Doppler flowmetry.
Results: 13/23 (57%) of the patients showed an ABMP reduction $\geq$ 5mmHg at 6 months and hence were considered RDN-responders. Responders had a mean ABPM reduction of -21/-6 mmHg as compared to baseline ($p \leq 0.003$). In these patients, L-FMC was found to be significantly reduced (-2.54 to -4.02, $p \leq 0.017$), and sympathetic influence on vascular tone was reduced from 54 to 50 % ($p \leq 0.037$), while non-responders did not show any significant differences.
Conclusions: Non-invasive endothelial and sympathetic functional assessment parameters correlate with successful blood pressure reduction responses to renal denervation in patients with treatment-resistant hypertension. Further and larger scale studies are necessary to analyze the potential predictive utility of these parameters in the clinical RDN setting, in particular with regard to optimized patient selection for the procedure.

TCT-404

First Clinical Experience with Neurotropic Agents for Treatment of Sympathetic Hypertension

Horst Sievert[1], Nicholas N. Kipshidze[2], Konstantin Kipiani[3], Vato Kipiani[3], Tea Mukhuradze[3], Michael Wholey[4]
[1]CardioVascular Center Frankfurt, Frankfurt, Germany, [2]Lenox Hill Hospital, New York, United States, [3]Center for Vascular and Heart Disease, Tbilisi, Georgia, [4]Univ Texas San Antonio, San Antonio, TX

Background: New device-based solutions to treat hypertension are focused on the overactive sympathetic nervous system as the therapeutic target. Early results from electrical stimulation of carotid baroreceptors and energy-based (radiofrequency, ultrasound) ablation of renal nerves have shown the ability to reduce blood pressure.
Methods: We investigated a simple, catheter-based approach of delivering neurotropic agents near renal nerves, specifically targeting nerve axons, to interfere with sympathetic nerve function. A small volume of NW2013 (proprietary formulation developed by Northwind Medical, San Jose, CA), was injected into renal artery walls using an endovascular catheter with microneedles.
Results: Seven (7) patients were technically successfully treated through local administration of NW2013 near renal nerves. There were no serious procedure-related, device-related or agent-related complications. Injury to the renal artery wall was minimal with no spasm, dissections or vessel perforations. Mild to moderate pain was reported during agent injection, which was managed by 5mg of morphine, and was significantly less compared to energy-based therapies. Five (5) patients completed their 1-month and 3-month follow ups and were included in the analysis. Mean systolic/diastolic office blood pressure (OBP) and 24-hour ambulatory blood pressure (ABP) at baseline were 181/92 and 164/105 mm of Hg, respectively. At 1 and 3 months after treatment, the average OBP reduction was 33/8 and 45/8 mm of Hg, respectively; equivalent ABP decrease was 12/13 and 22/16 mm of Hg. These results are very promising and demonstrate that treatment of sympathetic hypertension patients using local delivery of neurotropic agents is safe and feasible. In addition, the therapy offers advantages over energy-based methods in terms of nerve specificity, less pain and cost effectiveness.
Conclusions: Local administration of selective neurotropic agents surrounding renal arteries seems to be a safe and feasible procedure to treat sympathetic hypertension. Long-term data from randomized clinical studies are needed to further evaluate efficacy and durability of this procedure.

TCT-405

SYMPLICITY HTN-3: Outcomes in the African-American and non-African American Populations

John Flack[1], George L. Bakris[2], David Kandzari[3], Barry T. Katzen[4], Martin Leon[5], Laura Mauri[6], William W. O'Neill[7], Suzanne Oparil[8], Krishna Rocha-Singh[9], Raymond R. Townsend[10], Deepak L. Bhatt[11]
[1]Wayne State University, Detroit, United States, [2]The University of Chicago Medicine, Chicago, Illinois, [3]Piedmont Heart Institute, Atlanta, United States, [4]Baptist Cardiac and Vascular Institute, Miami, FL, [5]Cardiovascular Research Foundation, New York, United States, [6]Harvard Clinical Research Institute, Boston, Massachusetts, [7]Henry Ford Hospital, Detroit, United States, [8]University of Alabama, Birmingham, AL, [9]Prairie Heart Institute, Springfield, USA, [10]University of Pennsylvania, Philadelphia, PA, [11]Harvard Medical School, Boston, MA

Background: SYMPLICITY HTN-3 was a randomized, blinded, sham-controlled trial of renal denervation (RDN) in patients with resistant hypertension that demonstrated safety but not efficacy of RDN. Results for the prespecified African-American (AA) and non-African American (non-AA) subgroups are presented.
Methods: All patients were required to have an office systolic blood pressure (SBP) $\geq$160 mm Hg and an ambulatory 24-hour SBP $\geq$135 mm Hg while taking $\geq$3 antihypertensive drugs at maximally-tolerated dose, including a diuretic. Baseline clinical and procedural characteristics, baseline and 6-month antihypertensive medication use and changes in office and ambulatory blood pressure were compared between groups.
Results: AA patients comprised (26.2%) of the cohort in this trial. AA were younger, included more females, had a lower incidence of coronary artery disease and had a greater incidence of asthma, stroke and heart failure than non-AA patients. Change in office and ambulatory BP measurements are shown in the table. Differences in Office SBP reduction at 6 months were not apparent at earlier time points. The use of vasodilators (majority hydralazine) was greater in the AA than the non-AA subgroup (47% vs 34%, p=0.03 for RDN patients and 56% vs 41%, p=0.09 for sham patients). The SBP decrease in the AA sham group on vasodilators was -21.9 mm Hg and -12.7 mm Hg in the AA cohort not on vasodilators (p=0.276; p for interaction =0.185).