Journal of the American Society of Hypertension 12(5) (2018) 381–391

Research Article

Rationale and evidence for the development of a durable device-based cardiac neuromodulation therapy for hypertension

Bing Yang, MD[a], Yue Wang, MS[b], Fengxiang Zhang, MD[a], Weizhu Ju, MD[a], Hongwu Chen, MD[a], Yuval Mika, PhD[c], Ricardo Aviv, PhD[c], Steven J. Evans, MD[c], Daniel Burkhoff, MD, PhD[d,*], Jie Wang, MD, PhD[b,e], and Minglong Chen, MD[a]

[a]*Cardiology Division, the First Affiliated Hospital of Nanjing Medical University, Nanjing, P.R. China;*
[b]*Academy of Clinical and Translational Research, Jiangsu Province, The First Affiliated Hospital of Nanjing Medical University, Nanjing, P. R. China;*
[c]*Backbeat Medical, New Hope, PA;*
[d]*Cardiovascular Research Foundation, New York City, NY, USA; and*
[e]*Division of Cardiology, Columbia University, New York City, NY, USA*

Manuscript received January 5, 2018 and accepted March 14, 2018

Abstract

We assessed the feasibility of achieving acute, sustained blood pressure reductions through the use of cardiac pacing algorithms delivered via standard dual-chamber pacing based on introducing short atrio-ventricular (AV) delays (SAVD). Eighteen hypertensive subjects (57.3 ± 9.8 years old; 10 male and 8 female) with average initial systolic and diastolic blood pressures of 151.2 ± 17.6/92.2 ± 12.7 mmHg already scheduled to undergo an invasive electrophysiology procedure were included in this study. Pacing sequences were applied for ~1-minute intervals with AV delays of 80, 40, 20 and 2 ms, while making high fidelity blood pressure measurements. Average reductions of 19.6 ± 7.7 mmHg in systolic pressure and 4.3 ± 3.8 mmHg in diastolic pressure ($P < .001$ each) were demonstrated with 2 ms AV delay pacing. Initial SBP reductions were followed by rebound effects which diminished the SBP reducing effects of SAVD pacing, likely due to baroceptor activation causing increased peripheral resistance. This effect was eliminated by intermittent introduction of longer AV delay pacing which modulated the baroreflexes. These findings provide the rationale and evidence underlying recent data showing significant and long-term blood pressure reductions in response to this cardiac neuromodulation therapy in hypertensive patients despite medical therapy. J Am Soc Hypertens 2018;12(5):381–391.

Keywords: Blood pressure; pacemaker; baroreceptor; autonomic nervous system.

Introduction

Hypertension (HTN) affects 1 in 3 adults in the United States, Europe, and China[1] and is a major factor contributing to cardiovascular morbidity and mortality.[2–4] Cardiovascular risk doubles for every 10 mmHg increase in systolic blood pressure (SBP).[2] Medications are usually effective in controlling blood pressure (BP). However, more than 10% of HTN patients are refractory to medical therapy, meaning they remain with BP above accepted

Relationship with industry: BackBeat Medical sponsored this study.

Conflict of interest: None.

Grant Support: This study was supported by BackBeat Medical.

Disclosures: RA, YM, and SJE are employees of BackBeat Medical. DB is a consultant to BackBeat Medical.

*Corresponding author: Daniel Burkhoff, MD, PhD, Cardiovascular Research Foundation, 1700 Broadway, 9th Floor, New York City, NY 10022, USA.

E-mail: danielburkhoff@gmail.com

https://doi.org/10.1016/j.jash.2018.03.004

target values despite prescription of appropriate medical therapies.[2,5] Another major issue with medications is low compliance in many patients.[6] Because of these factors, investigators have turned to alternate strategies to treat HTN, in particular device-based therapies. Percutaneous renal denervation,[7–9] baroreflex stimulation,[10,11] and arterial-venous shunts[12] are such examples. Although early studies of these approaches applied to patients with medically refractory HTN achieved certain levels of success, results in controlled trials have been more ambiguous and none has yet proven efficacy in reducing BP in randomized pivotal studies.[13–15] The recent SPYRAL HTN-OFF MED study,[16] which tested renal denervation in HTN patients without taking anti-HTN medications, showed, in comparison to sham controls, a 10-mmHg reduction in office SBP and a 5.5-mmHg reduction in average 24-hour ambulatory SBP at the end of 3 months' follow-up. Although these results are encouraging, the magnitude of the effect indicates that new, more potent therapies are needed.

We developed and tested a new therapeutic concept that employs novel cardiac pacing algorithms to reduce BP.[17] These algorithms use standard dual-chamber pacing impulses that employ short atrioventricular delay (SAVD) pacing with periodically introduced beats with longer AV delays. Prior studies showed that continuous SAVD pacing provides only short-term BP reduction, likely due to autonomic nervous system activation and compensation.[18,19] However, our recent study showed that use this novel programmable hypertension control (PHC) pacing algorithm based on repeated sequences of SAVD and longer AV delay pacing could achieve sustained reductions of BP over follow-up periods extending through 2 years.[17]

The purpose of the present study was to describe the acute kinetics of BP changes following introduction and withdrawal of SAVD pacing and how periodic introduction of beats with longer AV delays provides a means of quenching autonomic nervous system activation. Studies were performed in patients with HTN (SBP $>$ 140 mmHg) scheduled to undergo an electrophysiologic diagnostic or therapeutic procedure. The results clarify the theory and provide the initial experimental verification thereof, for this novel device-based approach to HTN therapy.

Material and Methods

Study Subjects

This was an exploratory single-arm, unblinded, treatment-only feasibility study conducted in 18 patients already scheduled to undergo an invasive electrophysiology procedure at a single center (The First Affiliated Hospital of Nanjing Medical University, Nanjing, China). This study was approved by the hospital ethics committee, and informed consent was obtained before any study-related procedures. The study was registered on www.clinicaltrials.gov (NCT02382484).

To be included in the study, patients were required to have systolic pressures greater than 140 mmHg despite at least one antihypertensive medication, as well as have a clinical indication and electrophysiology study involving the introduction of transvenous electrophysiology catheters into the right atrium and right ventricle. Eligible patients also needed to be at least 18 years of age, willing, and able to provide informed consent. Patients were excluded from the study for any of the following reasons: (1) atrial fibrillation at the time of the study; (2) ejection fraction (EF) less than 45%; (3) history of symptomatic heart failure, regardless of EF; (4) undergoing an ablation procedure for a bypass tract; or (5) history of resuscitation from ventricular fibrillation or sustained ventricular tachycardia. Although 19 patients were initially consented, one patient developed atrial fibrillation before the start of the study and was excluded.

Study Procedures

On the day of the study, the patient was brought to the electrophysiology laboratory, prepared and draped in sterile fashion according to standard hospital procedure. Catheter-based bipolar electrode leads were generally used and introduced via a femoral vein. In each case, one lead was positioned in the right atrium and a second lead positioned in the right ventricular (RV) apex. Femoral arterial access was used for the insertion of a solid-state pressure sensor (Millar Instruments, Houston, Texas) to continuously monitor aortic BP; this signal was digitized simultaneously with the ECG for offline analysis. In a subgroup comprising the first four patients, an extra femoral venous access sheath was used to introduce an OptiQ catheter for measuring cardiac output (Hospira; Q2 and Q2 Plus CCO/SO2 System), pulmonary artery (PA) pressure, and mixed venous oxygen saturation (SvO_2).

After placement, the leads were connected to a modified pacing system (MPS) capable of delivering pacing signals with a wide range and patterns of AV delays. The MPS allowed measurement of lead impedances, sensing (mV), and pacing thresholds (V). First, the heart was paced in DDD mode (i.e., dual chamber pacing, dual chamber sensing and dual chamber pacing inhibition), with the atrial rate set $\sim$10% greater than the intrinsic heart rate with a long AV delay that permitted native ventricular activation (baseline). The MPS was then programmed to deliver pacing signals in two phases. In phase 1, AV pacing was performed using SAVDs of 80, 40, 20, and 2 ms, for periods of $\sim$1 minute followed by a period of several minutes of pacing with a longer AV delay to characterize the kinetics of BP responses to initiation and withdrawal of SAVD pacing.