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Programmable Hypertension Control: Another Possible Indication for Implanted Pacemakers

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Hypertension is a leading modifiable risk factor for cardiovascular morbidity and mortality[1]; effective blood pressure control significantly decreases the risk of cardiovascular events, particularly in those with other risk factors or preexisting coronary artery or cerebrovascular disease.[2] Therefore, blood pressure control has been a cornerstone of both primary and secondary prevention of cardiovascular events.[3]

However, in a subset of patients, adequate blood pressure control is difficult to attain even with 3 or more antihypertensive medications. This has generated great interest in tackling this significant clinical problem by addressing a root of the problem, sympathetic over-activity leading to increased peripheral vascular resistance.[4] Over the past decade, many investigators have enthusiastically worked at developing devices that could modulate the sympathetic nervous system in order to decrease blood pressure, attempting to replicate the success that device-based therapies have had in other areas such as cardiac resynchronization therapy in patients with heart failure with reduced ejection fraction[5] or deep brain stimulation for Parkinson's disease.[6]

Strategies to approach this problem include: renal sympathetic denervation and carotid baroreceptor stimulation. Each initially showed very promising results in pilot studies,[7,8] claiming proof of concept to the respective method of sympathetic down-regulation. However, neither met efficacy end points when compared with those with sham or device-off treatment in randomized phase III studies.[9,10] Several major lessons were learned from these trials, such as the Hawthorne effect and unreliability of using office blood pressure measurements alone without 24 hours ambulatory blood pressure monitoring.[11] Taking these into account, along with improvements in design of the catheter to deliver more complete renal sympathetic denervation, the SPYRAL HTN OFF-MED study was conducted as a randomized, sham-controlled study in patients with mild to moderate hypertension who were taken off all antihypertensive medications. The investigators showed a 5 (95% confidence interval 0.2–9.9) mm Hg drop in 24 hours ambulatory systolic blood pressure (SBP) and 4.4 (95% confidence interval 1.6–7.2) mm Hg drop in 24 hours ambulatory diastolic blood pressure (DBP).[12] This was the first time investigators were able to definitively provide proof of concept of renal sympathetic denervation as an effective therapy for a blood pressure lowering.

It is in this context that Neuzil and colleagues present the findings of the Moderato-HTN study[13] in this issue of *JAHA*. This was a non-randomized, single-arm open label proof of concept study for a novel method of device-based blood pressure control, using a pacing algorithm called programmable hypertension control (PHC) which paces continuously in the RV and alternates between 8 and 13 beats with short (20–80 ms) AV delay and 1 to 3 beats with longer (100–180 ms) AV delays. The short AV delays function to decrease blood pressure by reducing cardiac preload and output. Normally, this would be accompanied by a reflex increase in sympathetic nervous system activity and vasoconstriction, but as the authors elegantly demonstrate, this is mitigated, if not completely suppressed, by the alternation with several beats with a longer AV delay. This pacing algorithm is programmed in a dual-chamber, rate-responsive pacemaker generator which interfaces with standard IS-1 bipolar endocardial leads.

The authors enrolled 57 patients with hypertension, defined as an office SBP greater than 140 mm Hg on 2 separate days, with average ≥150 mm Hg, who had indications for new implant of a dual-chamber pacemaker, generator exchange, or upgrade from a single chamber pacemaker. Thirty-five patients fulfilled inclusion/exclusion criteria and underwent device implantation with the PHC algorithm turned off. A run-in phase was then carried out for 4 weeks, where

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office and 24-h ambulatory blood pressure monitoring (added partway through the study after the negative results of SYMPLICITY HTN-3 were released) had to continue showing SBP >140 mm Hg to continue in the trial. Seven patients no longer met criteria of hypertension in this run-in phase, all of whom were undergoing a new implant and likely had reflex hypertension related to the presenting bradycardia. Twenty-seven patients met these criteria, at which time the PHC algorithm was turned on and optimized. These patients were followed for a minimum of 6 months with office and ambulatory blood pressure monitoring to assess their response. Echocardiography was also performed at enrollment and after 6 months.

The authors found that, as previously shown in other studies, the office blood pressure in those 27 patients who remained hypertensive throughout the run-in period indeed dropped (mean 7.8±13.5 mm Hg, from an average of 165±10.2 to 157.4±14.2 mm Hg). Following 3 months of PHC therapy, the average blood pressure further dropped to an SBP of 141.5±14.2 mm Hg. No significant change in DBP was noted at any time point, as would be expected.

An analysis of individual patients showed that 24/27 (85%) patients experienced a greater than 5 mm Hg drop in ambulatory SBP. For the 16/27 patients who had 24 hours ambulatory monitoring performed immediately before PHC activation, 14/16 (87.5%) had a greater than 5 mm Hg drop in ambulatory SBP. Similar rates were found in office blood pressure response. It is notable, however, that actual blood pressure reduction varied widely between patients, even amongst these responders. Some patients experienced a drop of 20 to 30 mm Hg in ambulatory SBP, though most experienced between 10 and 20 mm Hg drop. As an open-label study, medication changes were left to the discretion of treating clinicians: more instances of decreases in medication dose were reported than increases.

Echocardiographic analysis showed a slight decrease in LV end diastolic volume (median decrease 6 mL, IQR 23) with no significant change LV end systolic volume, LV ejection fraction, or left atrial dimension. No significant rhythm changes were noted, though the authors did find an initial small increase in average heart rate from 68.9±9.4 to 73.5±10.1 bpm, which returned to pre-PHC activation levels by 3 month follow-up, potentially signifying that transient reflex sympathetic activation does still occur. Safety outcomes were deemed acceptable by the data safety monitoring board, with adverse outcomes as expected for pacemaker implantations and patients with similar comorbidities.

These results are compelling and indeed encouraging, but in the context of prior attempts at device-based therapies for hypertension, the results of this non-randomized pilot study should be considered with cautious optimism while we await the findings of their double-blinded randomized controlled trial (NCT02837445). The authors should be congratulated for incorporating the lessons learned from the prior studies and addressing them appropriately, such as using a run-in period with ambulatory monitoring before PHC initiation. Medication changes, though left to the discretion of managing clinicians, were also decreased more frequently than they were increased. However, the biases inherent in a single-arm, non-randomized study persist.

Many potential concerns about the safety and quality of life effects of the PHC algorithm also remain unanswered, some of which cannot be answered by a small pilot study, and some not addressed by the study protocol. Though the authors did not find any significant change in LV systolic function, much larger studies have demonstrated that chronic RV pacing, which the PHC algorithm utilizes, can increase the risk of heart failure, particularly in patients with preexisting cardiomyopathies.[14,15] The use of short AV delays can also potentially cause a pacemaker syndrome and increased risk of atrial fibrillation and result in sympathoexcitation.[16] Indeed pacing the heart results in a neural signature of sympathoexcitation as recorded directly from cardiac neurons.[17] Exercise capacity was also not addressed in this study: the putative antihypertensive mechanism of the PHC algorithm, via decreasing cardiac preload and output, could increase fatigue or dyspnea with exertion in physically active patients. This algorithm would also not be effective during atrial fibrillation when mode switching is necessary, so remote or frequent office monitoring of AT/AF burden would be necessary to confirm ongoing effectiveness. It is also not clear what predicts response to the PHC algorithm: while some patients did not have any decrease in blood pressure, others responded remarkably raising the question of how we might be able to better identify the subgroup of patients who have the best chance of response.

If proven effective and safe, however, the potential benefit of the PHC algorithm would be significant. Many patients with indications for dual chamber pacemakers have comorbid hypertension[18] and this algorithm could serve to replace one or more antihypertensive medications, which could lead to cost savings and improvement in quality of life, particularly in this more elderly population where polypharmacy is a major concern.

For now, though, we must await the results of the investigators' randomized controlled study and continued basic and translational work on cardiac neurobiology to better guide and interpret these studies.

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Disclosures

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