Cardiac Neuromodulation Therapy – a novel device-based therapy for patients with hypertension and indications for pacing

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Abstract

Cardiac Neuromodulation Therapy (CNT) is a novel device-based therapeutic method for reducing systolic blood pressure (SBP). It incorporates an asymmetrical pacing algorithm with alternating shortened and prolonged atrioventricular intervals into the existing pacemaker hardware. It has been developed to meet the growing demand for non-pharmacological therapies for patients with resistant arterial hypertension (HTN) and indications for permanent pacing. In this article, we explain the mechanism of the programmable therapy and review current literature, including the most recent clinical trials.

Epidemiology of Hypertension

Hypertension (HTN) is the leading risk factor for cardiovascular disorders, doubling the risk of ischemic heart disease or stroke with every 20 mmHg increase in systolic blood pressure (SBP).[1] It affects more than 26% of adults in the world, with long-term projections suggesting the prevalence will reach 29% by 2025, accounting for 1.56 billion people globally.[2]

Patients with indications for cardiac pacing represent a substantial number of individuals with cardiovascular disorders, with more than 1 million pacemakers being implanted or replaced worldwide each year. There is evidence that 71% of those patients suffer from hypertension, with the disease not being appropriately managed in 55% of cases, reaching 1 million implanted dual-chamber pacemakers combined in patients with uncontrolled HTN.[3]

There is a need for alternative treatments in order to address the subset of hypertensive patients unable to achieve guideline-recommended blood pressure values despite multi-drug therapeutic regimens established by physicians. Lack of adequate results can be explained either by ineffectiveness of the pharmacological therapy or noncompliance.

Resistant hypertension is defined as blood pressure which remains above goal, despite treatment with 3 classes of antihypertensive drugs. These drugs should be administered at maximum or maximally tolerated dose.[4] A significant subset of patients who do not respond to ≥3 classes of prescribed antihypertensive medications are also patients who are noncompliant with therapy[5]. This forces investigators to seek out innovative, device-based strategies. To target these issues, numerous non-pharmacological treatment methods have been explored, including arterial-venous shunts[6] [7], renal denervation[8] [9] or baroreflex stimulation[10] [11]. While some of these methods seem promising, further evidence is required to support their unambiguous role in antihypertensive therapy.

Pathophysiology of Hypertension

Arterial blood pressure regulation is generally dependent on two components, cardiac performance and peripheral vascular resistance. The primary determinant, ventricular pressure generated by the heart, is highly dependent on specific variables. Left ventricular (LV) preload according to the Frank-Starling law of the heart, has a direct effect on cardiac performance. This can be measured as ventricular stroke volume or cardiac output. Reduction in blood pressure can be obtained by decreasing end-diastolic volume (preload), total peripheral resistance (TPR) or both factors simultaneously. An appreciable percentage of ventricular filling is determined by atrial contractions in patients with a normal sinus rhythm. [12] Mechanisms shortening atrioventricular (AV) delay have been proven to cause reduction in ventricular filling. In the heart, the AV delay results in an immediate decrease of blood pressure due to atria contracting against partially closed mitral and tricuspid valves. However, an abrupt decline in blood pressure stimulates responses of the autonomic nervous system via baroreceptor-mediated neural and hormonal pathways, aiming to restore the blood pressure to the original baseline value. This stimulation of sympathetic activity can lead to sudden increases in peripheral resistance, heart rate, and myocardial contractility. This subsequently results in blood pressure exceeding the initial values. With the intention of long-term reduction in blood pressure, modulation of such baroreflex responses should be addressed.

Cardiac Neuromodulation Therapy

Cardiac Neuromodulation Therapy (CNT) introduces a new approach to control resistant hypertension by delivering an asymmetrical pacing sequence of alternating shorter and longer AV intervals. While prior studies show that continuous shortening of AV delay leads to abrupt reduction in blood pressure, the decrease was only transient.[13] This is due to the subsequent baroreflex response, rapidly overshooting the baseline values. It has been hypothesized that short atrioventricular delays (SAVD), followed by alternating beats with longer AV delays, could be introduced to prevent stimulation of the autonomic reflex response and, therefore, maintain reduction in blood pressure. There is growing evidence of successfully lowered SBP in patients with resistant HTN, showing significant differences between patients managed with CNT and control groups, managed only with antihypertensive medications. [14] The most recent studies have been promising; however, further studies are necessary to ensure the efficacy and safety of this novel method of treatment.

Mechanism of CNT

CNT is a system delivering standard rhythm management therapy with additional algorithms incorporated into a dual-chamber, rate-responsive implantable pulse generator. Impulses alternate between shorter and longer AV intervals, preventing autonomic nervous system activation. Individual optimization of the pacing sequence is possible in all subjects, with a duration of the delay usually varying from 20 to 80ms for short AV delays, and from 100 to 180ms for longer AV delays. Generally, the pacing sequence would consist of 8 to 13 beats with the shorter AV delay, followed by 1 to 3 beats with the longer AV delay. Immediate effect can be observed during the brief programming procedure. Thus, it allows for customized adjustment of the settings in order to obtain an instant drop in blood pressure without sympathetic stimulation. The device implantation and exchange procedures are performed according to local standard dual-chamber pacemaker implantation protocols.

Preclinical Trial

A preliminary preclinical animal study has shown that CNT algorithms can achieve a significant, sustained reduction of SBP. An average decrease for all canine subjects was 32.5±12.7 mmHg over a 1-month duration of the study (N=4), suggesting a potential success in human patients.

Feasibility Trials

The first feasibility study performed by Neuzil et al.[15] was an open-label, non-randomized, single-arm multicenter clinical trial. Its main goal was to test CNT in adult patients with resistant hypertension, indicated for an implantation or replacement of a dual-chamber pacing device. Adults whose office systolic blood pressure (OSBP) measured on 2 separate days averaged ≥150 mmHg, despite a stable (at least 2 months prior to the visit) regimen of ≥2 antihypertensive medications, were potentially eligible for the study. Reasons for scheduled pacemaker implantations or replacements included sick sinus syndrome, as well as second- and third-degree AV block. Left ventricular ejection fraction (LVEF) <50%, OSBP >190 mmHg, and a history of persistent atrial fibrillation were amongst the exclusion criteria.

The study consisted of a 1-month run-in period with standard pacemaker programming without CNT activation. This was to assess BP stability (N=35, BP=165.6±11.6/78.8±10.3 mmHg). Patients whose OSBP >140 mmHg at 2 and 4 weeks during the run-in phase were enrolled into the 3-month therapy with active CNT (N=27). Their BP averaged 156.4±14.4/81.3±10.0 mmHg, with an average drop in SBP of 7.8±13.5 (P=0.005). The OSBP dropped further and remained lower until the 3-month follow-up, decreasing by an additional 16.1±15.1 mmHg to 141.4±14.2 (P<0.001), whereas 24-hour ambulatory systolic blood pressure (ASBP) decreased by 10±13 mmHg compared with pre-CNT activation (P<0.01). These effects on OSBP were sustained in patients who were followed-up throughout a 2-year period, however, not all values had been collected before the time of publishing.

There were no significant changes in diastolic blood pressure throughout the study. Safety was assessed by Holter monitoring 2 weeks before and 1 month after CNT implementation, along with estimation of glomerular filtration rate with creatinine, and echocardiography evaluating heart size and function. Adverse events possibly attributed to the device-based therapy included cardiac asthma, prolonged atrial fibrillation requiring cardioversion, and ambulatory myocardial infarction with subsequent symptoms of heart failure.

Yang et al.[13] designed an open-label, single-arm, treatment-only and single-center feasibility study. The study was conducted to evaluate the difference between symmetrical and asymmetrical pacing and evaluate the effectiveness of asymmetrical pacing sequence in order to obtain potential long-term reduction in blood pressure. 18 patients scheduled for an invasive electrophysiological procedure participated in the study, with values of initial BP equal to 151.2±17.6/92.2±12.7 mmHg, despite being treated with ≥1 anti-hypertensive medication. Atrial fibrillation, LVEF <45%, a history of symptomatic heart failure were amongst the exclusion criteria.

After placement of the device, numerous combinations of alternating shorter (8-25 beats of 2-80ms) and longer (1-4 beats of 60-300ms) AV delays were programmed, aimed to appropriately adjust the intervals. Duration of each test was approximately 45 minutes, and every combination was followed by a subsequent baseline period consisting of atrial pacing at a rate 10% greater than the intrinsic heart rate. Safety was measured by recording the number and severity of adverse events occurring during and after the study, including changes in cardiac output, mixed venous oxygen saturation, pulmonary artery pressure, and incidence of discomfort.

The results of symmetrical shortening of AV delay (SAVD=2ms) were consistent with the expected baroreceptor-mediated response of the sympathetic nervous system, with initial sudden drop in blood pressure followed by an exponential increase to the baseline. There was an overshoot of the original value after withdrawal of SAVD, eventually returning to the baseline. By changing the number and magnitude of shorter and longer AV delays, various combinations were tested until there was no evidence of baroreflex activation and sudden response to lowered blood pressure. In all 14 patients participating at this stage of the study, it was possible to obtain an optimized combination, acquiring the most efficient results with SAVD=2ms and the longer AV delay ~150ms.

There were no serious adverse events throughout the study duration. Short periods with premature ventricular beats were observed in 8 subjects during positioning of catheters, immediately resolved with repositioning.

Moderato II – Randomized Clinical Trial

The most recent data from a large, multi-center clinical trial demonstrated promising results, having met its primary efficacy and safety endpoints. Moderato II[14] was a prospective, double-blind, randomized study, comparing changes in SBP in patients managed with CNT versus patients on a stable pharmacological therapy, consisting of ≥1 antihypertensive medication. The trial targeted patients with uncontrolled HTN, who are already indicated for a dual-chamber pacemaker due to existing co-morbidities. In patients treated with CNT, the study showed a decrease of 11.1 mmHg (p<0.001) in mean 24-hour ASBP at 6-months follow-up. When contrasted with the control group, the reduction in SBP was equal to 8.1 mmHg (p=0.01). The study documented no statistical difference in occurrence of major cardiac adverse events (MACE).

The study enrolled 47 patients with persistent HTN (ASBP ≥130 mmHg and office SBP ≥140 mmHg), despite being managed with one or more antihypertensive medication, and an indication for a dual-chamber pacemaker. The run-in period lasted 30 days and involved standard pacing, addressing subjects' rhythm disturbances only, along with their multi-drug antihypertensive therapy. Patients who met the follow-up screening criteria were then randomized to CNT or control group. In both groups, mean ASBP was 136.3 mmHg, despite being treated with, on average, >3 antihypertensive medications.

An overall response rate was high (85%) in the experimental group, even though 88.5% of patients had isolated systolic HTN. 6 months post-randomization, mean ASBP was lowered by 11.1 mmHg (p<0.001) in the treatment group, while ASBP in the control group decreased by 3.1 mmHg (p=0.17). Moreover, the treatment group experienced a substantial reduction in OSBP, equal to 12.4 mmHg (p=0.02). There were no MACE

in the CNT group, while there were 3 reported events in 2 patients in the control group, yielding no statistical difference. There were no changes in diastolic BP and heart rate between the two arms, and there were no significant differences found on echocardiogram.

All in all, the study met its primary safety and efficacy endpoints, obtaining a statistically significant reduction in SBP in patients with resistant HTN and indications for permanent pacing.

Discussion

The recent search of alternative non-pharmacological antihypertensive therapies has been triggered by large populations of patients exhibiting persistently elevated BP, with SBP significantly above the guideline-recommended levels. This long-standing HTN was maintained despite various combinations of multi-drug regimens, attributable to ineffectiveness of the medication or noncompliance with medical treatment. A large number of patients also need treatment for various co-morbidities. Taking into account a group of hypertensive patients requiring a permanent pacemaker, methods for combining the treatment for both conditions have been explored and developed.

One of the methods, implemented into well-established pacing devices, used SAVD in order to reduce BP. The acute effects of SAVD were studied in two clinical trials conducted on patients with prior indications for invasive electrophysiological procedures. In both instances, findings were consistent with expectations of baroreceptor-mediated sympathetic response, occurring shortly after a sudden decline in BP due to SAVD. However, asymmetrical stimulation with longer AV delay sequences appeared to prevent baroreflex activation, lowering SBP without the instantaneous rebound effect.

There are numerous potential advantages of CNT, including incorporation of the algorithm into existing devices and procedural protocols related to pacemaker hardware, leads and lead positioning. Brief optimization with adjustment of parameters allows the operator to instantly tailor variables to subject's individual needs based on the immediate observation of acute responses to changes in blood pressure. Noncompliance issues could be eliminated with the use of CNT technology, decreasing the burden of uncontrolled long-lasting hypertension, lowering morbidity and mortality of this particular subset of patients. Reduction of SBP greater than 10 mmHg is associated with lower risk of incidence of myocardial infarction and stroke [16] [17], pointing towards a beneficial risk-benefit ratio in this population.

A limitation of two of the studies was non-randomization and treatment-only unblinded designs, small numbers of patients, and a relatively short duration of the follow-up period. In Neuzil at al.'s study, the follow-up was at 24 months, creating a possibility of occurrence of other long-term adverse effects, therefore all participants should be closely monitored before any long-term safety assumptions can be made. It is hypothesized that long-term right ventricular pacing may contribute to development of new-onset heart failure. In one study, 26% of patients were found to develop heart failure after a median follow-up of 7.8 years, following a pacemaker implantation.[18] However, this new-onset heart failure could be attributed to progression or development of concomitant diseases, associated with increasing age as one of the contributing factors. In Neuzil at al.'s clinical trial, there were no significant changes in LVEF at 3-month follow-up, in spite of reduction in LV end-diastolic volumes. However, no definitive conclusions can be drawn due to short duration of the study. Another potential consequence is increased atrial stress due to shortened AV delay possibly contributing to atrial enlargement and occurrence of subsequent atrial arrhythmias. In Yang et al.'s trial, no determination of intermediate or long-term adverse effects was possible due to the nature of the study.

The Moderato II study overcame the design issue by implementing a double-blind, randomized design, presenting quality evidence of statistical difference between the two groups. However, the number of participants was low, and the results were noted after only 6 months of treatment. More data is needed in order to observe long-term effects of the therapy, note potential MACE or changes in heart muscle structure and function. Future investigations will provide more insight on the device-based treatment, involving larger groups of patients and evaluating long-term efficacy of this method.

Conclusions

Cardiac neuromodulation therapy has been tested in three separate clinical trials. These involve numerous centers around the world, recruiting patients indicated for invasive electrophysiological procedures, suffering from persistent hypertension (SBP >140 mmHg), in spite of diverse pharmacological regimens. Up-to-date studies provide initial evidence for effectiveness of the novel antihypertensive treatment using variably-timed, alternating shorter and longer AV delays, implemented into standard pacing devices. The use of this mechanism significantly lowered SBP and prevented activation of sympathetic baroreflex response. Optimal parameters can be instantaneously modulated in a short optimization procedure. The predefined safety and efficacy endpoints have been met in the existing literature, including the most recent double-blind, randomized clinical trial, showing potential for a revolutionary approach to patients with resistant HTN and co-existing rhythm disturances. The results are promising, as the obtained difference is clinically relevant to patients' prognosis. However, a longer follow-up period is required to exclude association with hemodynamic, morphological and functional effects of long-term shortening of AV delay and ventricular stimulation. With further consistent proof of successful outcomes, CNT could considerably lower morbidity and mortality associated with resistant hypertension, and potentially extend its target population to include patients without indications for a pacemaker.

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