First-in-Man Study of a Pacemaker-Mediated Programmable Hypertension Control Therapy


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Hypertension remains a major global health problem:
- >25% of adults in the world
- #1 attributable risk for death worldwide according WHO

Many patients (> 40% in US) remain with blood pressures above guideline recommendations despite multi-drug regimens:
- Variable drug effectiveness
- Noncompliance

Hypertension increases risk of morbidity and mortality:
- Every 20 mmHg increase doubles risk of mortality

Non-pharmacological therapies are being investigated:
- Renal Denervation
- Arterial-venous shunts
- Neurostimulation-based therapies

26.4% of the world adult population has HYPERTENSION.

~972 M of the world adult population has HYPERTENSION.

~70% of pacemaker patients have HYPERTENSION.

~700K a year have HYPERTENSION.
The Concept: Programmable Hypertension Control (PHC) Therapy

PHC therapy is an algorithm embedded in a standard dual chamber pacemaker with regular transvenous leads and implant procedure.

The algorithm delivers a sequence of alternating shorter and longer AV intervals pacing.

The algorithm reduces blood pressure by reducing ventricular filling and modulating the baroreflex responses, preventing activation of the autonomic nervous system.

The main mechanism of BP reduction is by short AV delay pacing, which reduces LV filling and thus reduces LV pressure generation (Starling Mechanism).

LV Pressure-Volume

Atrial pacing versus AV sequential pacing with short AV interval (40ms).

Acute Porcine Model
Reduction in ventricular filling immediately reduces blood pressure.

Ordinarily, such a reduction would activate the ANS via baroreceptors, increasing TPR and returning BP towards its original levels.

However, by regularly injecting a few beats with longer AV delays, baroreflex responses can be modulated and nearly abolished.

Data from acute study in patient with hypertension.

Alternation Between Short and Long AV Delay
Study Design

Hypothesis
PHC pacing reduces Systolic Blood Pressure (SBP) in patients requiring a dual chamber pacemaker implant or exchange who have persistent hypertension despite ≥ 2 antihypertensive medications.

Measurements:
- Office blood pressure (in triplicate according to standardized procedures)
- 24 Hour ambulatory blood pressure
- Echocardiography
- Medications
- Blood tests (renal function)

Informed Consent
Screening & Baseline
BP criteria? Avg > 150
YES
NO Withdraw from Study

Moderato system Implant
One month with IPG in pacemaker only mode

Run-In Phase

Moderato HTN Efficacy Evaluation
Activate Moderato HTN Therapy
3 Months Follow Up

BP criteria? >140mmHg
YES
NO

Optional Activation of HTN Therapy
3 Months Follow up
Withdraw from Study

NO

Withdraw from Study
Study Endpoints

Co-primary efficacy endpoint

• Change in office SBP measured by sphygmomanometry from the time of pre-activation to 3 months post activation
• Change in 24 hour ambulatory systolic blood pressure from baseline to 3 months post activation

Safety endpoints (measured after 3 months of PHC therapy)

• Effect on cardiac function
  o Changes in ejection fraction
  o Changes in left ventricle volumes
• Changes in the rate of cardiac arrhythmias
• Number and severity of adverse events adjudicated by an independent committee
Inclusion Criteria

Indicated for implantation or replacement of a permanent dual-chamber pacemaker

Stable (prior 2 months) regimen of ≥2 maximally tolerated antihypertension medications anticipated to be maintained for 3 months without change

Average office systolic blood pressure ≥ 150 mmHg base on repeated measures over a one-week period prior to enrollment, each measurement > 140 mmHg
Exclusion Criteria

- Subject has known secondary cause of HTN
- Subject has a history in the past year of persistent atrial fibrillation or clinically significant paroxysmal atrial fibrillation.
- Subject has ejection fraction <50%
- Subject has symptoms of heart failure of NYHA Class II or more
- Subject has hypertrophic cardiomyopathy, restrictive cardiomyopathy or interventricular septal thickness ≥15 mm
- Subject is on dialysis
- Subject has estimated Glomerular Filtration Rate (GFR) <30 ml/min/1.73m2
- Subject has prior neurological events (stroke or TIA) or carotid artery disease
- Subject has known autonomic dysfunction
- Subject has a history of clinically significant tachyarrhythmia and is not on a stable medical regimen
- Subject has had previous active device-based treatment for hypertension
- Subject has an existing implant, other than a pacemaker that needs replacing
- Subject is pregnant or has the possibility of becoming pregnant
- Subject with average Systolic BP >190 mmHg
- Subject is currently participating in another clinical study
- Subject cannot or is unwilling to provide informed consent
57 Subjects signed Informed Consent

35 Subjects were implanted with the Moderato system

-22 Subjects failed to meet Incl/Excl criteria

-1 Subject died prior to week 4 (Unrelated)

7 Subjects did not meet the week 4 BP criteria (SBP > 140mmHG) Followed for safety

27 Subjects met the 4 week BP criteria - included in analysis of efficacy

27 Subjects completed 4 months follow-up (+3 months PHC)

continue follow for 2 years
Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>All Implanted Patients</th>
<th>Patients Continuing to Hypertension Treatment Phase (n=27)</th>
<th>Patients not meeting BP Criteria to Continue (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>73 ± 7.2</td>
<td>72 ± 6.8</td>
<td>75.0 ± 6.9</td>
</tr>
<tr>
<td>Gender</td>
<td>17 M / 18 F</td>
<td>14 M / 13 F</td>
<td>2 M / 5 F</td>
</tr>
<tr>
<td>Physical Exam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.0±10.3</td>
<td>168.3±10.8</td>
<td>166.6±9.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.3±17.3</td>
<td>84.3±17.8</td>
<td>78.4±13.1</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>64.1±12.1</td>
<td>62.9±12.7</td>
<td>67.4±9.7</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>29.1±5.5</td>
<td>29.7±5.7</td>
<td>28.2±3.6</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>62.9±5.2</td>
<td>62.7±5.3</td>
<td>65±3.4</td>
</tr>
</tbody>
</table>

Blood Pressure (office)

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>165.6±11.6</td>
<td>165.6±11.1</td>
<td>162.1±8.7</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.8±9.4</td>
<td>80.4±9.9</td>
<td>76.6±7.4</td>
</tr>
<tr>
<td>Pre-activation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>152.3±15.9</td>
<td>156.4±14.4</td>
<td>136.4±10.9</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.9±9.5</td>
<td>81.3±10.0</td>
<td>74.3±2.9</td>
</tr>
</tbody>
</table>
## Baseline Demographics

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<thead>
<tr>
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<tbody>
<tr>
<td><strong>HTN Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Number</td>
<td>3.2</td>
<td>3.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Diuretic</td>
<td>27 (77%)</td>
<td>20 (71%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>K Sparing Diuretic</td>
<td>4 (11%)</td>
<td>3 (11%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>b-Blocker</td>
<td>11 (31%)</td>
<td>8 (29%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>ACE-I</td>
<td>20 (57%)</td>
<td>16 (57%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>ARB</td>
<td>12 (34%)</td>
<td>10 (36%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>Ca++ Channel Blocker</td>
<td>21 (60%)</td>
<td>18 (64%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>(\alpha)-adrenergic antagonist</td>
<td>9 (26%)</td>
<td>6 (21%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>Ang-II antagonist</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td><strong>Past Medical History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (29%)</td>
<td>8 (29%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>History of AF</td>
<td>2 (6%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>1 (3%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PVD</td>
<td>3 (9%)</td>
<td>2 (7%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>2 (6%)</td>
<td>1 (4%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td><strong>Pacemaker Indication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sick Sinus Syndrome</td>
<td>13 (37%)</td>
<td>10 (37%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Brady-/Tachy-Syndrome</td>
<td>7 (20%)</td>
<td>3 (11%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>II(^\circ) AV Block</td>
<td>12 (34%)</td>
<td>8 (30%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>III(^\circ) AV Block</td>
<td>4 (11%)</td>
<td>4 (15%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (20%)</td>
<td>6 (22%)</td>
<td>1 (14%)</td>
</tr>
</tbody>
</table>
Co-Primary Endpoints

Office SBP

24 Hour Ambulatory SBP

SBP (mmHg)

Time (months)

SBP (mmHg)

Time (months)

Run-In          PHC Therapy

-16.1±15.1      p<0.0001

-14.2±9.8       p<0.0001
Office Systolic Blood Pressure
Ongoing Longer Term Follow Up in Subset of Patients

Change in SBP (mmHg) vs Time (months)

PHC Therapy Phase

P<0.01 for all time points
Changes in 24 Hours Ambulatory Systolic Blood Pressure from Pre-activation

-10.1 ± 13.0
P = 0.004

N = 16

Run-In
PHC Therapy

Change in SBP (mmHg)

Time from Activation (months)

-1 0 1 2 3
One patient died during the Run-In phase (unrelated)

11 SAEs in 5 patients (adjudicated by an independent committee)

• 8 events adjudicated as being unrelated to the PHC therapy
• 3 events adjudicated as being possibly related to the PHC therapy

ambulatory MI with development of heart failure, prolonged atrial fibrillation requiring DC cardioversion, cardiac asthma

No significant change in global cardiac function or ejection function

Significant reduction in ventricular volumes

No significant change in rate of ventricular or supraventricular arrhythmias

No significant change in kidney function
Summary and Conclusions

In hypertensive patients requiring a pacemaker, PHC therapy reduces office blood pressure by an average of 23.8 mmHg and 24Hr ambulatory pressure by an average of 14.2 mmHg.

Study design having a run-in period allows estimation of the impact of study participation (Hawthorne/Placebo effects) on blood pressure.

- Office and ambulatory blood pressures decreased by 7.8 and 5.3 mmHg, respectively, during the run-in period.
- After PHC activation, office and ambulatory blood pressure decreased further by additional 16.1 and 10.1 mmHg, respectively.

This is a pilot study providing proof of concept of a novel approach to treating hypertension.

Study limitations: nonrandomized, open label, small number of patients, short duration of follow-up.

First Patients Already Enrolled in a Randomized Double-Blind Study
Summary and Conclusions

The therapy is currently investigated for patients requiring a pacemaker:

- Implant required irrespective of the therapy
- >70% of patients with pacers have HTN
- >50% of these patients have SBP > guideline recommendations

If proven safe and effective, this therapy could be applicable to a broader population of patients with medically refractory hypertension
Contributing Sites

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