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The Rheos System, a Baroreflex Activation Device for use in a Resistant Hypertension Population: a Systematic Review

Tasha Harrington

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The Rheos System, a Baroreflex Activation Device for use in a Resistant Hypertension Population: a Systematic Review

Abstract

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**Method:** Exhaustive search of available medical literature was conducted using Medline, CINAHL, Web of Science and Google Scholar. Exclusion criteria was applied and resulted in a total of three studies. Search terms used: baroreflex activation therapy, resistant hypertension, Rheos, carotid sinus, baroreceptor

**Results:** Three studies were evaluated on the Rheos system, two prospective cohort and one randomized control trial within the United States and Europe. Patients were prognostically similar between studies, based on age and number of hypertensive medications. Surgical implantation at the carotid sinus was evaluated for safety and efficacy both for the device itself as well as BAT use. Decreases in SBP and DBP were seen at an acute response as well as maintained during follow-up visits.

**Conclusion:** Baroreflex activation therapy is a new and exciting technology for potential treatment of resistant hypertension. However, there is still a great deal of research and evaluation that must take place before the Rheos system can be used as routine therapy. It should be used in patients who have exhausted pharmaceutical agents as well as thorough lifestyle modifications to manage their hypertension.

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**Degree Name**
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**First Advisor**
Annjanette Sommers MS, PA-C

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The Rheos System, a Baroreflex Activation Device for use in a Resistant Hypertension Population: a Systematic Review

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
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For the Masters of Science Degree, August 11, 2012

Faculty Advisor: Professor Annjanette Sommers
Clinical Graduate Project Coordinator: Annjanette Sommers MS, PA-C
Biography

[Information redacted for privacy]
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List of Abbreviations

BAT.................................................................Baroreflex Activation Therapy
DBP.............................................................Diastolic Blood Pressure
FDA............................................................. Food and Drug Administration
JNC-7.........................................................The seventh report of the Joint National Committee on
Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
RCT............................................................ Randomized control trial
SAE.............................................................Serious Adverse Event
SBP.............................................................Systolic Blood Pressure
BACKGROUND

Hypertension continues to be a vogue topic amongst the medical community, both for its increasing prevalence as well as for its long-term complications. Current statistics show that hypertension is the second most common reason for medical office visits in the United States.\(^1\) It also remains the most frequent indication for prescription medications in adult patients.\(^1\) According to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) guidelines, hypertension is defined as having a systolic blood pressure (SBP) of greater than 140 mmHg and/or a diastolic blood pressure (DBP) of greater than 90 mmHg.\(^2\)

While many patients can successfully be managed by means of pharmaceutical intervention and/or lifestyle modifications, there is a population that continues to battle high blood pressure regardless of the aforementioned therapies. A recent US government study suggests that as many as 30% of hypertensive patients are not fully controlled with medications and are therefore deemed resistant to treatment.\(^3\) These patients are classified as resistant hypertension, or failure to attain an ideal blood pressure of <140/90 (or <130/80 for diabetic patients or those with chronic kidney disease).\(^4\) The definition also requires that the patient is compliant with at least three hypertension drugs, including a diuretic.\(^4\) This population of patients is frequently linked to co-morbid conditions such as diabetes, obesity and chronic kidney disease. Without adequate control of blood pressure,
the compounding nature of these other associated conditions may dramatically reduce a patient’s quality of life.

This group of uncontrolled hypertensive patients is expected to grow in the coming years, as both life expectancy and the cardiovascular burden of obesity/metabolic syndrome increase dramatically. A new technology is making its way into the world of hypertension management by tapping into the central nervous system’s ability to assist in lowering blood pressure. By increasing the afferent signaling from baroreceptors to the brain, stimulation of the carotid sinus nerve will result in a decreased sympathetic response.5 This in turn will systemically lower blood pressure. Though this method was studied in the 1960s, technology was limited both in surgical technique and device precision. The implant was large in size and lacked the ability to adequately control electrical currents.6 Continuous research and development has led to the invention of a new device known as the Rheos Baroreflex Hypertension Therapy System. This system, which consists of a pulse generator, two leads and a programmer, operates via an external pulse generator.4-6 These electrical pulses stimulate the implanted carotid sinus device, with a goal of creating the desired effect of lowering a subject’s blood pressure.

This systematic review will evaluate and discuss the findings of current research on the Rheos System and determine its effectiveness for future implications in clinical practice.
METHOD

An extensive literature search was performed using Medline, CINAHL, Web of Science and Google Scholar. Keywords used in the literature search included “baroreflex activation therapy”, “resistant hypertension”, “Rheos”, “carotid sinus” and “baroreceptor”. These terms were utilized in database searches both individually and in combination with one another. Inclusion criteria required studies performed on humans only as well as articles that discussed the Rheos system specifically.

RESULTS

Three studies returned and all were included due to the limited nature of the topic. These studies included two prospective cohort and one randomized controlled trial. All were completed within the United States or Europe and were performed in the past seven years. The GRADE System was applied to each article (see Table I: Characteristics of Studies) to evaluate for the strength of evidence given for the clinical question at hand.

Study #1: European study

This article was a prospective cohort study that took place in nine clinical centers throughout Europe. A total of forty-five nonrandomized subjects were deemed appropriate for surgery based off of the established exclusion criteria. This criteria included prior baroreflex failure, significant orthostatic hypotension, cardiac arrhythmias, chronic atrial fibrillation, clinically significant cardiac valvular disease or hypertension secondary to a treatable cause, carotid artery atherosclerosis with >50% stenosis as determined by ultrasonography, prior implant or radiation in the carotid sinus region, currently implanted electrical medical devices, dialysis and pregnancy or contemplating
pregnancy. The mean age of subjects was 54 (standard deviation +/-9). These forty-five subjects were implanted with the Rheos device between March 2004 and November 2007. Due to safety and efficacy protocols that were not discussed in the article, three subjects were excluded from analysis following implantation. There were also four subjects that dropped out of the trial and one additional subject that missed the required visits, leaving thirty-seven subjects that were evaluable.5

The device was activated in all patients after one month of implantation to allow time for surgical wound healing. Subjects were analyzed on a monthly basis for the first three months following device activation, then on a yearly basis. At these visits, blood pressure measurements were taken both sitting and after ambulation to determine efficacy of the Rheos device. In addition to these measurements, the study evaluated functional safety measures by testing the subject’s activity while exercising in a 6-minute hall walk test, combined with changes in orthostatic blood pressure at 1, 3 and 5-minute intervals of upright standing. This occurred after the subject had been in the supine position for 5 minutes. All subjects were maintained on their previously prescribed anti-hypertensive medications, which ranged from a total of 3 to 9 prescriptions per subject. The 6-minute hall walk was used in 14 subjects, they improved by an average of 48 meters at the 1 year evaluation. Much like the hall walk test, orthostatic blood pressure was a measurement only performed in a percentage of the subjects. Regardless, there was no evidence of orthostatic hypotension, nor concerns with either syncope or collapse in the 32 subjects evaluated with this test. The article briefly mentions a significant increase in serum creatinine in 22 of the 26 participants at the 1-year evaluation, but fails to provide either data or an explanation for this finding.5
This study aimed to measure both procedure safety as well as device safety by monitoring serious adverse events (SAE). These included the following events: death, life-threatening situation, inpatient hospitalization, prolongation of existing hospitalization, or persistent or significant disability. There was a total of 8 SAEs in the cohort of 42 subjects, 7 as a result of the surgical procedure and 1 in relation to the device itself. Of these SAEs, 1 was fatal and 2 were corrected by means of additional surgery.

Efficacy of the Rheos device was provided by mean change in blood pressure at each office evaluation. At the 3-month visit, SBP decreased by an average of 21 mmHg (SD +/- 4), 30 mmHg (SD +/- 6) at the 1-year visit and 33 mmHg (SD +/- 8) for subjects who continued in the study through the 2 year evaluation. An e-mail to the study correspondent was sent as a request for individual data on subject’s blood pressure readings, but failed to receive a response.

**Study #2: phase II Rheos feasibility trial**

This study was a phase II feasibility study with a prospective cohort format. It was performed in the United States and managed by the Food and Drug Administration. Ten non-randomized subjects were approved for device implantation, ranging in ages from 33 to 71. There were four females and six males, all having an established diagnosis of resistant hypertension per JNC-7 definition. The entrance criteria for this study included exhaustion of anti-hypertension treatment, removal of any secondary causes of hypertension, lack of baroreflex dysfunction and lack of carotid artery disease.

Since this article discussed the initial evaluation of the Rheos device within American borders, it discussed at length both the surgical details of carotid lead placement as well as anesthetic induction and procedure completion. It was the only
study to discuss and evaluate the effects of the device’s capability for voltage administration between 1 and 7.5 V. This dose-response testing was performed both in the surgical suite prior to wound closure for acute response analysis and once again prior to hospital discharge (either day 1 or 2 post-operatively). During these testing intervals, voltage was initiated at 1 V and then increased by 1-V intervals every 60 seconds until the selected maximum dose of 6 V was reached. The exception to reaching 6 V was if the subject reached one of three hemodynamic end points, including a mean arterial blood pressure of <60 mmHg, a heart rate of <50 per minute or a SBP of <90 mmHg. In these cases, the maximum tolerated voltage was recorded. Results from the intra-operative voltage testing resulted in a mean SBP decrease of 37 mmHg at 6 V. The DBP also decreased significantly by a mean of 24 mmHg and the heart rate decreased on average from 71 to 63 beats per minute.\(^6\)

During the first post-operative dose testing, the mean SBP dropped by 41 mmHg, with DBP and heart rate displaying a significant mean drop of 19 mmHg and 9 beats per minute, respectively. In these post-operative readings, it is noted that only 5 of the 10 patients were able to reach a 6 V dose, as hemodynamic end points were reached at either 4 or 5 V for these patients.\(^6\)

In this study, there were no unanticipated serious adverse events (SAEs) from either the procedure or the device. The article does not disclose their interpretation of an unanticipated event, but also notes that there were no perioperative deaths as a result of the Rheos device placement. The only unwanted post-surgical effect noted by an undisclosed number of subjects was muscle twitching, which was most likely a result of peripheral nerve stimulation from the implant itself.\(^6\)
The mean follow-up as of publication of the article (May 2006) was 10 months. All patients had completed a minimum of 4 months follow-up. During this follow-up time frame, 2 of the subjects required device battery replacements and 1 subject suffered a non-fatal infection. This infection occurred after 4 months of follow-up and resulted in excision of the device. As of publication, the article states that the subject was not re-implanted.

**Study #3: phase III Rheos feasibility trial**

This study was a phase III feasibility study and is the only randomized control study to date on this topic. Both subjects and investigators were blinded to the treatment groups until each participant’s 12-month clinical visit. This study was performed in the United States and approved by the FDA. Forty-nine clinical centers evaluated potential subjects between March 2007 and November 2009. A total of 326 subjects were eligible for implantation, with each of the forty-nine centers given up to two non-randomized subjects to initially place the device. This was seen as a means of establishing the learning curve of the new Rheos procedure and a total of 55 subjects were categorized under this stage of the study, with all but 4 displaying an acute response. If an immediate baroreflex activation therapy (BAT) response was not detected before surgical closure, the device was deemed ineffective in that patient and explanted. Two of the non-randomized subjects had the device explanted following surgery due to infection, leaving a total of 265 subjects for randomization. A 2:1 ratio between the study groups was created, placing 181 individuals in Group A (immediate BAT) and 84 into Group B (delayed BAT until after month 6).
The study aimed to determine both the safety and efficacy of the Rheos system by implementing five coprimary endpoints. These included analysis of both acute and sustained efficacy, as well as procedural safety, BAT safety and device safety. Of these endpoints, neither the acute efficacy nor the procedural safety criteria was met. The acute efficacy endpoint was established to determine whether immediate BAT following implantation indicated an advantage over a delayed response to 6 months post-operatively. This was analyzed by measuring the number of subjects in each group that attained a drop in SBP by at least 10 mmHg between Month 0 and Month 6. Results indicated that 54% of subjects in Group A met this criteria and 46% of subjects in Group B. Due to the 20% superiority margin that was put in place for this endpoint, the goal was not reached. The second endpoint that was not met related to procedural safety. This was intended to analyze the event-free rate of subjects who had neither a procedure nor system-related SAE within 30 days of implantation. The investigators established an 82% objective performance criterion based off of prior literature on event rates for other implantable devices such as defibrillators and pacemakers. This endpoint reached a 74.8% event-free rate, with a large portion of subjects (9.2%) suffering the result of improper carotid sinus lead placement, leading to temporary or permanent nerve damage. Other indications for failure included 4.8% of subjects with a generalized surgery complication and 2.6% with wound complications or respiratory concerns. The article does not disclose the reasons behind the final 2% of events, but does indicated that 76% of all previously-mentioned occurrences resolved completely.

The three endpoints that were successfully reached in this study included sustained efficacy, BAT safety and device safety. The sustained efficacy was determined
by comparing the response of Group A subjects between their Month 6 and Month 12 SBP readings. If the decrease in SBP at Month 12 from baseline was at least half the decrease measured between baseline and Month 6, then the criteria for a sustained response was met. An example of this finding would be to have a Month 12 reading of at least 15 mmHg lower than baseline, if the Month 6 reading was 30 mmHg lower than baseline. Other results included the objective performance criterion, which was 65% and was surpassed with 88% of subjects fulfilling this criterion. BAT safety was met by comparing Group A and Group B post-operatively between the 30-day mark and the Month 6 visit. Any therapy-related SAEs were noted as a concern for BAT safety and included hypotension, bradycardia and other events related to treating hypertension. A non-inferiority margin was established at 15%, suggesting that less than a 15% difference between groups would be grounds for BAT safety. Results indicated that there was a 2.4% increase of event-free subjects in Group A versus Group B. The most significant even that occurred in both groups was for hypertensive emergency. However, the number of these events was reduced by 40% in Group A due to immediate activation of BAT, signifying a relative risk reduction of 40% by not delaying activation of the Rheos device. Finally, the endpoint of device safety was successfully attained by requiring a Rheos device event-free rate of 72%. To reach this endpoint, investigators analyzed all SAEs and hypertension-related events between the 30-day post-operative mark and the Month 12 visit. This percentage was established based off of similar implants such as defibrillators and pacemakers. The study indicated an event-free rate of 87.2%.^4^ The study did not provide data on individual values of successful SBP decreases below 140 mmHg, but did provide a graph to display the proportion of subjects in each
group that achieved this level. An estimate from the article’s figure suggests that 42% of Group A achieved a SBP of less than or equal to 140 mmHg at the 6 month evaluation, while only 22% of Group B achieved this level. The difference between the two groups become almost insignificant at the Month 12 evaluation though, as roughly 52% of Group A and 51% of Group B attain a SBP of less than or equal to 140 mmHg. This results in a NNT (number needed to treat) of 6 based off of the Month 6 evaluation.4

In total, results of the study show that 63% of all subjects reached a SBP of less than or equal to 140 mmHg, with 81% of subjects dropping a minimum of 10 mmHg since implantation. However, it is noted that a significant number of subjects in Group B achieved a SBP of <140 mmHg before BAT was activated. While this positive finding is well-received, there are concerns with the fact that subjects and their clinicians had permission to alter hypertension medications as needed, leading to questions of pre-study medication compliance as well as necessary standardization in future studies.4
DISCUSSION

Evaluation of these three trials suggests that the groundwork has been laid accordingly for the current level of device knowledge (see Table II). It is evident that the Rheos device works well in the resistant hypertension population, but comes with the assumed risks of surgical procedures such as infection, anesthesia use and improper device placement. As a whole, the studies addressed multiple variables involved in the Rheos system, including voltage-response testing, blinded randomization, acute and sustained response, as well as safety of barereflex activation therapy (BAT), surgery and the device itself.

It is important to note that the phase II feasibility study performed in the United States presented with publication bias. Though the trial was monitored by the FDA, five of the doctors associated with the study receive clinical trial reimbursement to cover the study’s expenses. Also, 4 of the doctors are either paid consultants of the Rheos manufacturer or employees of the company itself.

Currently, the ideal management of resistant hypertensive patients is through alterations in lifestyle combined with pharmaceutical intervention. These methods are established in the literature and in clinical practice, deeming them safer than any new surgical device.

Limitations of Study

Although these studies overall were well done, they are limited simply by the quantity of data and by the fact that only one randomized control trial (RCT) has been performed. Future research with additional RCT studies is necessary, as well implementing a required level of proficiency for surgeons involved in the placement of
the Rheos device. The technique of device placement at the carotid sinus is still in its infancy; until the medical community has established an efficient and standardized approach to surgical implantation of Rheos, this device will most likely remain in clinical trials alone.

**CONCLUSION**

Baroreflex activation therapy is a new and exciting technology for potential treatment of resistant hypertension. Though three in-human studies have been completed to date, there is still a great deal of research and evaluation that must take place before the Rheos system can be used as routine therapy. The device requires continued evaluation for both procedural safety as well as long-term efficacy.

Should BAT become a standard treatment for resistant hypertension, it would be limited to those patients who have pursued all other means of blood pressure management, both by exhaustng all potential pharmaceutical agents as well as thorough lifestyle modifications. While the device may have a strong future in treating those patients who have failed at other therapy modalities, there remains an additional surgical risk that undeniably must be considered before pursuing such an option.
REFERENCES


### Table I: Characteristics of Studies

<table>
<thead>
<tr>
<th>Study Design</th>
<th># of Subjects</th>
<th>Age of Subjects</th>
<th>Average # of BP medications</th>
<th>Starting grade</th>
<th>Quality Assessment</th>
<th>GRADE</th>
<th>Overall GRADE of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>European prospective cohort</td>
<td>45</td>
<td>54 (50-60, 60-70)</td>
<td>5</td>
<td>Low</td>
<td>0 0 0 0 0 0</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Phase II prospective cohort</td>
<td>150</td>
<td>50 (48-50, 50-60)</td>
<td>6.2 (5.8, 6.6)</td>
<td>Low</td>
<td>0 0 0 0 0 0</td>
<td>Very Low</td>
<td></td>
</tr>
<tr>
<td>Phase III randomized controlled trial</td>
<td>325</td>
<td>Group A: 53.7 (52.5, 55.0)</td>
<td>5.2</td>
<td>High</td>
<td>0 0 0 0 0 0</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

a: Publication bias displayed by involvement of doctors who are either accepting clinical trial reimbursements, are paid consultants, or are employees of CVF, the manufacturer of the Hoos system.

### Table II: Summary of Findings

<table>
<thead>
<tr>
<th></th>
<th>Mean SBP reduction</th>
<th>SAEs (%) of subjects</th>
<th>SBP reduction to ideal range (%) of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>European prospective cohort</td>
<td>21 mmHg</td>
<td>19</td>
<td>-NA</td>
</tr>
<tr>
<td>Phase II prospective cohort</td>
<td>41 mmHg</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Phase III randomized controlled trial</td>
<td>44 mmHg</td>
<td>9.7</td>
<td>63%</td>
</tr>
</tbody>
</table>

a: Serious Adverse Events. This includes the following events: death, lifethreatening situation, hospitalization, prolongation of existing hospitalization, or persistent or significant disability.

b: SAEs not discussed in this article. Percentage calculated based on summary of adverse events that would fall under SAE categories. Study states that 7 deaths occurred during trial, but all were due to sequelae of chronic hypertension rather than device or procedure.

c: Ideal SBP as <140 mmHg.

d: expressed as a mean of 139 mmHg, individual BP readings not given.

e: Data not available. Attempt to contact trial correspondent failed to receive reply.
How The Rheos™ System Works

1. The device delivers activation energy through the carotid leads.
2. The leads conduct activation energy to the carotid baroreceptors.
3. The baroreceptors send signals to the brain. The signals are interpreted as a rise in blood pressure.
4. The brain sends signals to other parts of the body to reduce blood pressure:
   a. Vessels
   b. Heart
   c. Kidneys

Figure I: Reproduced with permission from CVRx, manufacturer of the Rheos System