The Efficacy of Renal Radiofrequency Ablation for the Treatment of Resistant Hypertension

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The Efficacy of Renal Radiofrequency Ablation for the Treatment of Resistant Hypertension

Abstract

Background: Hypertension is a major contributor to cerebrovascular and heart disease. Of the patients who are medically managed but not meeting blood pressure goals, there is a subset of patients who have resistant hypertension, a condition requiring more aggressive technology and treatment to assist in the reduction of their blood pressure. The sympathetic innervation of the kidneys plays an intricate role in these patients and is becoming the target for future treatment alternatives. Will the use of renal radiofrequency ablation (RFA) be an effective therapeutic option for patients with resistant hypertension?

Methods: An exhaustive search of available and applicable literature was conducted using Medline-OVID, Evidence Based Medicine Reviews Multifile, CINAHL, and Google Scholar by using the key words: resistant hypertension, kidney, renal denervation, sympathectomy and radiofrequency ablation. Relevant articles were assessed for quality using GRADE and are found in the Table section of this paper. A search on the NIH clinical trials website revealed few completed trials, but showed multiple trials that are in process or recruiting for further investigation of the efficacy of renal radiofrequency ablation for the treatment of resistant hypertension.

Results: Two studies met inclusion criteria and are discussed in this systematic review. A randomized controlled study with 106 participants demonstrated a statistically significant reduction in blood pressure following renal denervation. A proof-of-principle cohort study with 50 participants demonstrated a statistically significant and sustained reduction in blood pressure for those who received renal radiofrequency ablation therapy.

Conclusion: Renal radiofrequency ablation has been shown to reduce blood pressure in patients with resistant hypertension with no evidence of serious complications. RFA has also been shown to be a cost effective therapeutic alternative when comparing the long-term cost of treating hypertension to the upfront cost of the procedure. Due to the existing low quality of available studies, more thorough research is needed to confirm long-term efficacy of RFA as a treatment option for patients with resistant hypertension.

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resistant hypertension, kidney, renal denervation, sympathectomy and radiofrequency ablation

Subject Categories
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The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
The Efficacy of Renal Radiofrequency Ablation for the Treatment of Resistant Hypertension

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 10th, 2013

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

[Redacted for privacy]
Abstract

Background: Hypertension is a major contributor to cerebrovascular and heart disease. Of the patients who are medically managed but not meeting blood pressure goals, there is a subset of patients who have resistant hypertension, a condition requiring more aggressive technology and treatment to assist in the reduction of their blood pressure. The sympathetic innervation of the kidneys plays an intricate role in these patients and is becoming the target for future treatment alternatives. Will the use of renal radiofrequency ablation (RFA) be an effective therapeutic option for patients with resistant hypertension?

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Keywords: resistant hypertension, kidney, renal denervation, sympathectomy and radiofrequency ablation
Acknowledgements

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List of Abbreviations

BP…………………………………………………………………………..Blood Pressure
eGFR………………………………………………….Estimated glomerular filtration rate
GFR……………………………………………………………...Glomerular filtration rate
RFA………………………………………………………………Radiofrequency ablation
SBP………………………………………………………………...Systolic blood pressure
BACKGROUND

Worldwide, more than a quarter of the adult population totaling nearly one billion, had hypertension in 2000. This proportion of individuals is projected to increase to 1.56 billion by 2025. There is a subset of hypertensive patients, who despite many efforts, are considered to be uncontrolled or resistant to medical management. Resistant hypertension has been defined as the failure to achieve blood pressure (BP) goals in patients who are adhering to full doses of an appropriate three-drug regimen that must include a diuretic. It is becoming a more common medical dilemma that many clinicians are challenged with and are being forced to address. As our population continues to age and as obesity becomes more widespread, resistant hypertension is expected to become even more common.

The prevalence and prognosis of resistant hypertension have not yet been examined by proper population studies, but data from
several sources suggest that this entity is not uncommon and is associated with an elevated risk of hypertensive complications”. With this elevated risk of complications, resistant hypertension is suggested to have an unfavorable prognosis. 

When considering this public health concern, the necessity of maximizing the effectiveness of existing therapeutic approaches as well as expanding available treatment options for both patients and clinicians are priorities. Ideally, development of additional therapeutic alternatives would not only assist in improving blood pressure control, but it would also beneficially impact comorbid conditions commonly associated with hypertension. The prospective of new therapeutic alternatives, such as renal radiofrequency ablation, has the potential to improve the management of resistant hypertension by selectively targeting organs or nerves without competing with, or opposing the systemic effects of medical management. The consideration and implementation of such therapeutic alternatives may be an increasingly important adjunct therapy for patients with resistant hypertension who fail to be controlled with medical management alone.

The role of the sympathetic nervous system in hypertension has been thoroughly studied. In general, the various effects of increased renal sympathetic nerve activity include, but are not limited to, renal vasoconstriction, decreased glomerular filtration rate (GFR) and renal blood flow, increased renal vascular resistance, increased renal sodium retention and increased release of renin and norepinephrine. In considering these effects, the renal sympathetic nerves likely serve as a critical link between the sympathetic nervous system and the kidney when looking at hypertension. With this knowledge,
clinicians can take a closer look at finding a therapy that targets the kidneys and their intricate causal relationship with hypertension.

Sympathectomy is a type of procedure that has been around for many years. Specific for the treatment of hypertension, one of the first attempts to modify the course of hypertensive disease by sympathectomy was done in 1924. In the process of preforming these early attempts, two known effects of sympathectomy were discovered and mentioned. The first was the overall modification of blood pressure levels, and the second was the modification of the reflex regulation of blood pressure, or baroreflex, resulting from the inactivation of certain components of the vasoconstrictor mechanism. It is this reason for which RFA of the renal artery is becoming a targeted therapy option for patients with resistant hypertension.

Catheter-based renal artery sympathetic denervation is considered to be a minimally invasive procedure where the procedure universally begins by gaining percutaneous access through the femoral artery and then a guide catheter is introduced, and subsequently engaged into the renal artery. At this point, a specially designed catheter is advanced, placed at the distal section of the renal artery and low-power radiofrequency energy is delivered to the endothelial layer. Delivering radiofrequency energy causes transmural lesions and consequently damages the sympathetic fibers traveling in the adventitia of the arterial wall. Overall, RFA therapy is directed at disrupting the sympathetic innervation to the kidneys. Is the use of renal radiofrequency ablation an effective therapeutic option for patients with resistant hypertension?
METHODS

An exhaustive search of available and applicable literature was conducted using Medline-OVID, Evidence Based Medicine Reviews Multifile, CINAHL, and Google Scholar by using the key words: resistant hypertension, kidney, renal denervation, sympathectomy and radiofrequency ablation. The search was narrowed to include only English language articles as well as only randomized control trials or observational studies in order to evaluate literature with the highest level of evidence. Multiple studies referencing RFA were found, but many were focused on various other endpoints or were case series type studies, all of which were subsequently excluded. The bibliographies of the articles were examined for any additional relevant information. Articles specific to renal denervation as a therapy for resistant hypertension with blood pressure reduction as the primary endpoint were included for further analysis and support documentation. Relevant articles were assessed for quality by using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). A search in the National Institute of Health (NIH) clinical trials website revealed few completed trials; however, it showed multiple trials that are in the process of recruiting patients for further investigation of the efficacy of renal RF ablation for the treatment of resistant hypertension.

RESULTS

The initial search yielded 109 articles for review. After screening these articles for the primary endpoint of blood pressure reduction, two articles met specific inclusion criteria. This includes one randomized control trial (RCT) and one observational cohort study (Table I).
Symplicity HTN-2 Trial

This multi-center, prospective, randomized trial examined the effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension. The trial screened 190 patients, of which 84 were excluded by not meeting blood pressure inclusion criteria, by having an anatomical renal abnormality, or by declining to participate. In total, 106 patients were designated to either the treatment or control group. The primary endpoint measured in this study was the average, office-based change in systolic blood pressure from baseline to 6 months. Secondary endpoints included acute procedural safety and chronic procedural safety, looking specifically at reduction in estimated glomerular filtration rate (eGFR) or intimal damage to the renal artery causing a new area of stenosis. There was also a composite cardiovascular endpoint (myocardial infarction, sudden cardiac death, new-onset heart failure, death from progressive heart failure, stroke, aortic or lower limb revascularization procedure, lower limb amputation, death from aortic or peripheral arterial disease, dialysis, death because of renal failure, hospital admission for hypertensive emergency unrelated to non-adherence or non-persistence with drugs, and hospital admission for atrial fibrillation).

Eligibility criteria included patients 18-85 years of age, systolic blood pressure (SBP) of 160 mmHg or more, SBP of 150 mmHg or more in patients with type 2 diabetes, persistent hypertension even when compliant on three or more antihypertensive medications. Screening was done at 24 centers in Europe, Australia, and New Zealand where patients underwent renal artery anatomy evaluation, baseline lab evaluation, as well as baseline blood pressure monitoring before being assigned to their prospective
groups. Patients were then randomly assigned in a 1:1 ratio to either the renal
denervation group or control by sealed envelopes. There were 52 patients allocated to the
renal denervation group and 54 allocated to the control group. The participants assigned
to both the intervention and control group were balanced in regards to baseline clinical
characteristics. For patients randomly assigned to undergo renal denervation, the femoral
artery was accessed and the Symplicity Catheter System (Ardian, USA) was advanced
into the renal artery whereby multiple, low-power radiofrequency treatments were
applied along the length of both renal arteries.\textsuperscript{12}

RFA therapy significantly reduced the primary endpoint of office-based systolic
blood pressure (Table II). More specifically, results after 6 months illustrated that with a
blood pressure average of 178/96 mmHg, measurements in the renal denervation group
were reduced by 32/12 mm (p<0.0001 for systolic and diastolic blood pressure). For the
control group, with a blood pressure average of 178/97 mmHg, measurements changed
by 1/0 mm Hg, p=0.77 for systolic blood pressure, p=0.83 for diastolic blood pressure.
Three patients from each group were lost to follow-up.\textsuperscript{12}

All other endpoint results are based on 6-month follow-up and are listed below.
Results in regards to the secondary endpoint of acute procedural safety revealed no
serious complications related to the device or procedure. There were several minor
periprocedural incidents noted including one femoral artery pseudoaneurysm requiring
manual pressure only, one post-procedure drop in blood pressure requiring change in
medication, one urinary tract infection, one extended hospital stay due to paraesthesia, and
one evaluation of back pain with resolution. Chronic procedural safety illustrated that
eGFR remained unchanged and no new lesions of the renal artery were attributed to the
procedure itself. The composite cardiovascular endpoints identified five hospital admissions for hypertensive emergency that were unrelated to non-adherence to drug therapy (three of these patients had renal denervation and two were controls); no other composite cardiovascular events occurred.\textsuperscript{12}

**The Cohort Study**

This proof-of-principle cohort study\textsuperscript{13} examined the safety and blood pressure reduction effectiveness when using renal sympathetic denervation in patients with resistant hypertension. The trial enrolled a total of 50 participants, of which 5 were excluded for anatomical renal artery abnormalities. In total, 45 patients were treated with renal denervation and the remaining 5 patients were followed for comparison. The primary endpoints in this study were safety and blood-pressure lowering effectiveness of the procedure. Secondary endpoints of this study included the effects of the procedure on renal noradrenaline spillover and renal function.\textsuperscript{13}

Eligibility criteria included patients at least 18 years old, non-pregnant, no known secondary cause of hypertension, GFR of 45 mL/min/1.73m\textsuperscript{2}, an office-based SBP of 160 mm Hg or more despite being treated with at least three antihypertensive drugs (including one diuretic), or confirmed intolerance to current medication regimens. Patients were recruited from 5 centers in Australia and Europe. Initial screening included anatomical evaluation as mentioned above, physical exam, baseline vital signs, basic lab work, and a pregnancy test where applicable. In 12 patients, 24-hour ambulatory blood pressures were monitored pre- and post-procedure. Patients in the treatment group were initially staged to evaluate safety where the first ten patients underwent procedures with single renal artery treatment, followed by angiogram and treatment of the contralateral artery 1
month later. Eight patients had simultaneous bilateral treatments with renal angiogram 1 month after treatment, and the remaining 27 patients had simultaneous bilateral renal artery treatment without follow-up angiogram. Treatment included femoral access, guide catheter engagement into the renal artery with the Symplicity catheter, and then a series of discrete radiofrequency ablations were applied within each renal artery.  

The participants of this study were all balanced in regards to baseline clinical characteristics. Of the 45 patients that were treated with renal denervation, 26 were available for follow-up at 6 months and only 9 patients were available at 12 months. Of the 5 patients who were not treated, all were available for follow-up at 6 months and only 2 were available at 12 months.  

This study revealed that RF ablation therapy resulted in a significant and continued blood-pressure reduction (Table II). More specifically, results for office-based blood pressure revealed that with an average baseline blood pressure of 177/101 mm Hg, the patients who received renal denervation seen at 1 month, 3 months, 6 months, 9 months, and 12 months had mean reductions of -14/-10, -21/-10, -22/-11, -24/-11, and -27/-17, respectively (p<0.001 with exception at 12 months, p=0.05). The results also demonstrated that 6 of the 45 patients (13%) had systolic blood-pressure reductions of less than 10 mm Hg (no response). The 5 patients who were only followed for data purposes showed an increase in mean blood pressure overall. In regards to the other primary endpoint of safety, in 45 patients, one patient had a renal artery dissection due to catheter placement before therapy was initiated and another patient developed a pseudoaneurysm at the femoral artery access site without further complication.
Secondary endpoints included the evaluation of renal noradrenaline spillover and renal function, which are as follows. Ten patients were evaluated and assessed for the effectiveness of the procedure in achieving efferent renal denervation after procedure changes specific to renal noradrenaline spillover. The mean reduction in these patients was 47% (95% CI 28–65%). These same patients had a mean 6-month office blood-pressure reduction of 22/12 mm Hg, which was similar to the overall treatment group. In follow-up, the renal function of 25 patients was assessed by comparing baseline GFR values to post-procedure values. Patients with low baseline GFR seemed to have a greater but not significant (p=0.30) increase in GFR, in other words, there was no significant decrease in renal function.

DISCUSSION

Catheter-based renal radiofrequency ablation is proven to be an effective treatment option for resistant hypertension as evident by the Symplicity HTN-2 trial and the cohort study. In addition, RFA reduced cardiovascular mortality by 30% and all-cause mortality by 15% over a 10 year period. The One-Year Results of the Symplicity HTN-2 RCT, posted December 2012, reports that follow-up of the initial renal denervation cohort of patients who showed a mean reduction of 32 mmHg at 6 months after RFA is sustained with a reduction of 28 mmHg at 12-month follow-up. Currently, there is additional work being done to further support this existing data. The Symplicity HTN-3 trial is an ongoing prospective, single-blind, randomized, controlled study investigating the safety and effectiveness of renal denervation in subjects with uncontrolled hypertension. This trial is investigating 530 patients with a primary endpoint of change in office-based systolic blood pressure from baseline to 6 months. In
addition to the previously mentioned benefits of RFA as a therapeutic option, patient important outcomes have also been considered. The overall quality of life for patients after RFA has shown a noticeable reduction in subjective health-related quality of life issues predominantly related to mental health.  

RFA is currently being used as therapy option for resistant hypertension in Europe, Australia, and New Zealand as illustrated in the previous studies. In the United States, RFA is not yet approved, however, the results from the Symplicity HTN-3 trial will be submitted to the US Food and Drug Administration for evaluation and approval of catheter-based renal denervation as a treatment option for resistant hypertension. In addition to official studies that are being conducted, recent news reports are focusing on RFA as a future therapy. The latest from Medical News Today on February 15, 2013 reported that a “novel drug-free treatment consisting of blasting nerves in the kidneys with radio waves is helping to decrease high blood pressure in patients”. With the existing demonstrated efficacy and current efforts for more solid evidence, RFA should be considered as a potential forefront for future treatment of resistant hypertension.

There has been some cost analysis in regards to RFA since its inception. The statistical model estimated the renal radiofrequency ablation procedure cost to be $12 500 and that hypertension management costs an average of $868 annually. This directly reflects the fact that the cost of the procedure is incurred up front while the subsequent savings is acquired over a lifetime. This information further supports the potential use of RFA as a therapeutic option.

However, there are several limitations that exist in both the RCT and cohort study discussed previously. In regards to the RCT, the methodology here is slightly
limited in regards to blinding. Performance bias automatically exists in this scenario due to the fact that even though data-analyzers were masked, it is impossible to mask the participant. With this, there is potential concern for the Hawthorne effect whereby patients are influenced by their situation, ie, treatment or control. The study addresses this issue and states that controls showed no Hawthorne effect.\textsuperscript{12} In addition to performance bias, there is also risk of publication bias as the study mentions funding from the catheter company.

In regards to the cohort study,\textsuperscript{13} limitations include first and foremost, the fact that this is a small proof-of-concept study\textsuperscript{13} with no official control group. With this, the Hawthorne effect is a concern again, whereby patients have the potential to be influenced by their particular therapy as previously mentioned. There is a risk of publication bias as the study addresses that fact that the sponsor of the study participated in the design of the study, analysis of data, and review of the final manuscript. The different types of monitoring and follow-up mentioned in this particular study were proven to not be very consistent. The study mentions several issues below where only a few patients were monitored and followed for each: ambulatory blood pressure monitoring, assessment for renal noradrenaline spillover, follow-up renal angiograms, and follow-up renal magnetic resolution angiography.\textsuperscript{13}

CONCLUSION

Both the RCT and cohort study included in this systematic review have provided evidence to support the use of renal radiofrequency ablation as an effective therapy option for blood pressure reduction in patients with resistant hypertension. The overall combined quality of these studies is low based on the GRADE criteria. However,
research is moving forward with a larger, blinded, randomized control trial to further validate RFA as a good, safe and long-term alternative when treating resistant hypertension. Renal denervation has also been demonstrated to be a cost effective option for the reduction of blood pressure in patients with resistant hypertension. In terms of clinical practice, the use of renal RFA is an interesting and potentially valuable option in the future once higher quality studies and long-term results have been addressed.
References


Table I. Characteristics of Reviewed Studies

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<tr>
<td>Participants Design Limitations Indirectness Imprecision Inconsistency Publication bias likely Large effective Magnitude Confounding Factors reducing effect Dose response gradient</td>
<td>Renal Sympathetic Denervation in Patients with Treatment-resistant Hypertension (The Symplicity HTN-2 Trial): A Randomized Controlled Trial</td>
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<td>106 RCT Serious limitations* No serious indirectness No serious imprecision No serious inconsistencies Yes</td>
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<td>Catheter-based Renal Sympathetic Denervation for Resistant Hypertension: A Multi-center Safety and Proof-of-principle Cohort Study</td>
<td>45 Obs Serious limitations* No serious indirectness Serious imprecision* No serious inconsistencies Yes</td>
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*aNo blinding in either study 12,13  
bSmall sample size

Table II. Summary of Findings

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<tr>
<td>Symplicity HTN-Trial 12</td>
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<td>Control (n=54)</td>
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<td>The Cohort Study 13</td>
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<tr>
<td>1 month</td>
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<tr>
<td>RFA (n=45)</td>
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<tr>
<td>No treatment (n=5)</td>
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