The Effect of Renal Denervation on Exercise Tolerance in Patients with Heart Failure

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Abstract
Background: Heart Failure is a growing clinical syndrome that results in major impacts on patients and the medical system. Previously, therapy has improved symptoms while leaving the patient disabled in the later stages. Renal denervation (RDN) is a procedure that is being researched for its effect on improving the condition of heart failure along with its symptoms and increasing exercise tolerance in patients.

Methods: Exhaustive search of available medical literature using MEDLINE via PubMed, CINAHL, Web of Science and Google Scholar using the keywords renal denervation, heart failure and exercise tolerance. The studies that fit the eligibility criteria were appraised with the GRADE system for quality.

Results: Three studies were considered after the exclusion criteria were applied. The first study assessing RDN for patients with heart failure was terminated early due to low recruitment. Another study by the same group showed that RDN was a promising treatment needing more research and clinical evidence. The most recent study, an RCT, found that RDN safely improved cardiac function and exercise tolerance in patients with heart failure.

Conclusion: RDN does improve exercise tolerance in patients with heart failure. More clinical evidence is needed to place this treatment in common practice but RDN should be considered when reviewing options for patients with heart failure.

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The Effect of Renal Denervation on Exercise Tolerance in Patients with Heart Failure

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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 10, 2019
Faculty Advisor: Kim Lovato, PA-C
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List of Abbreviations

BP          Blood pressure
EF          Ejection fraction
HF          Heart failure
RDN         Renal denervation
HFpEF       Heart failure with preserved ejection fraction
HFrEF       Heart failure with reduced ejection fraction
NT-proBNP   N-terminal pro B-type natriuretic peptide
SNS         Sympathetic nervous System
T1DM        Type 1 diabetes mellitus
UFH         Unfractionated heparin
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BACKGROUND

Heart Failure (HF) is a clinical syndrome that has major impacts on patients, families, practitioners, resources and the medical system. Clinical Key defines HF as a clinical syndrome characterized by structural or functional impairment of ventricular filling or ejection of blood resulting in insufficient perfusion to meet metabolic demands.¹ Cardinal manifestations include edema, dyspnea, and fatigue. Its later stages, HF severely impacts quality of life and exercise tolerance. Lack of exercise tolerance can make activities of daily living (ADL) impossible and is an important patient centered outcome that should be considered when implementing various treatments.

There are many ways to categorize HF and this paper will look at studies addressing many types. Heart failure with preserved ejection fraction (HFpEF) is a form of diastolic dysfunction which is often caused by ventricular hypertrophy due to long standing hypertension. Heart failure with reduced ejection fraction (HFrEF) is the more common subtype of HF commonly occurring in the presence of coronary artery disease. This type of HF is due to ventricular dilation resulting in an inadequate pump.¹

There are many complications including arrhythmia and risk of thromboembolism. The treatment of HF is mainly pharmacologic and palliative in its end stages.¹ With standard treatment, often the functional status declines and the only benefit is seen in symptom control. Much focus has been placed on improving outcomes due to the significant patient impacts and the burden to the health care system. The rates of re-hospitalization are also placing burden on the health system and new treatments may help curb this problem for the patient and the system. This review aims to evaluate the effect
on exercise tolerance in patients with HF by using Renal Denervation (RDN) for treatment.

RDN is a procedure that uses ablation of the renal nerve to dampen the effects of the sympathetic nervous system. This procedure has been studied for its effects in HTN but shows promise in the hormonal regulation of HF. The procedure has changed as the equipment and technique advances but access is commonly through the femoral region with a sheath inserted to pass a catheter through. As seen in the First-in-man safety evaluation of RDN, the procedure was safely performed in 7 patients with no pre or post procedural complications noted.

METHODS

An exhaustive search was performed using MEDLINE via PubMed, CINAHL, Web of Science and Google Scholar using the keywords renal denervation, heart failure and exercise tolerance. Inclusion criteria consisted of patients with heart failure receiving RDN for treatment. Exclusion criteria consisted of human studies and English language only. As a note, this author chose to use RDT for renal denervation treatment where studies use various abbreviations. In addition, this review looks at studies assessing HFpEF, HFrEF or HF unspecified. Studies were assessed for quality using GRADE criteria.

RESULTS
Of 278 studies produced by a search of the keywords, 3 fit all criteria and were included in this review. The 3 studies\(^4-6\) were evaluated with the GRADE criteria and ranked accordingly. See Table 1.

**Patel et al**

This study\(^4\) was a prospective phase II RCT which aimed to provide the first human data concerning RDN as a treatment for HFpEF by dampening the effects of the SNS. After screening 10,228 patients, 25 were randomized with 17 being allocated to receive bilateral RDT via the Symplicity™ catheter with 8 patients as a control. At 12 months, 14 in the treatment group had complete data as well as 7 in the control group. Four months after the trial start date, the protocol was adjusted to ensure proper recruitment. This adjustment allowed for patients who had not been previously hospitalized for HF to participate and decreased the EF from >50% to >40%. Computer randomization was utilized with no patient or clinician blinding due to the study being focused on safety and mechanism.\(^4\)

There were 6 efficacy endpoints consisting of: “the Minnesota Living with Heart Failure Questionnaire (MLWHFQ); peak treadmill exercise oxygen uptake (VO2 peak); B-type natriuretic peptide (BNP); E/\(e’\) (ratio of early mitral out ow velocity to average of medial and lateral mitral annular tissue velocity); left atrial volume index [LAVi from cardiac magnetic resonance (CMR)] and LV mass index (LVMi from CMR).”\(^4\) Twenty-five patients were enrolled in the study which ended after 16 months due to low recruitment. Some initial improvements in various endpoints in the RDT group was noted at the 3 month mark with no significant improvement at 12 months.\(^4\)
This study\textsuperscript{4} did not show benefit to the patient nor did it show harm and was ended early secondary to recruitment issues. As for the improvements noted at 3 months, the authors have discussed a few potential reasons with one being the Hawthorne effect which is when the patient knows they have received the treatment and therefore might try harder upon testing for effect. The author notes this effect is likely to wane over time. In addition, the possibility of a type 1 error is possible or the potential re-growth of the sympathetic nerve function. At the 12 month mark, the lack of improved endpoints were thought to be caused by under recruitment and exposing the study to a type II error. While the inclusion criteria were changed 4 months into the study, enough patients were not involved and the next effort should draw on heart failure patients around the world to ensure proper recruitment. The authors mention the catheter used, Symplicity\textsuperscript{TM}, could be an ineffective tool for ablation or that focusing on the distal portion of the renal artery may have more of an effect suppressing SNS activity.\textsuperscript{4}

**Gao et al (2016)**

This non-blinded study\textsuperscript{5} published in 2016 was attempted after the study group showed improvement in cardiac function and reduction in LV volume using a Medtronic Inc. 5F ablation catheter in pigs. The study group decided to move to a human trial including 14 patients. This prospective study was open and without a control group. “The inclusion criteria were a diagnosis of CHF; EF \(< 45\%\) on echocardiography; \(> 2\) HF episodes in the previous six months; medication with HF drugs including beta- blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blocker (ARBs) and spironolactone; and no acute HF decompensation in at least one month of drug therapy.” Patients with evidence of renal artery stenosis, GFR \(< 30\text{ml/min/1.73m}^2\),
T1DM, pregnancy or possibility of, MI or CVA (acute) or hypotension as indicated by systolic BP <100 mmHg were excluded from this study.5

All patients in the study were given chewable enteric coated aspirin or clopidogrel (300Mg both) and IV unfractionated heparin (6000-8000 U) prior to the procedure. All patients were evaluated for BP and 6-min walk distance before the intervention, at 7 days post intervention and every month thereafter to the study’s conclusion. In addition, patients were assessed for renal artery stenosis via ultra sound pre procedure and with echo and blood work at the six-month follow up. All patients were continued on their maximum tolerated doses of HF medications and adjusted as needed.5

The procedure itself was performed using a 5F radiofrequency catheter with a 39D72X Stockert EP Shuttle RF Generator (Johnson & Johnson Medical) with temperature control (8-10 W, 50°C) for rotational ablation. Immediately after bilateral ablation of 4-6 sites was performed, renal angiography was used.5

At the 6-month follow up there were noted decreases in BP (Systolic average 138.6 at baseline and 123.2 at follow up). Four patients started with NYHA functional class of IV with none in this class at six months. Ten patients started in class III and at the six-month evaluation only 1 remained in class III, 9 in class II, and 4 in class I. BNP levels dropped, on average, 361 points from baseline at 6 months. The patients in this study showed an average increase of 169m in the 6-minute walk test.5

This study5 showed improvement in exercise tolerance and 6-minute walk distance. Gao et al (2016) state that using the larger catheter (5f) instead of smaller catheters used in the past likely led to the better penetration of vessels. This new catheter along with a refined technique may be responsible for the improvement of EF and left
ventricular volume as shown by echocardiography in this study. This study also shows that RDN may be more useful for patients with hypertensive heart failure due to the SNS activity decrease and its effects on BP.

The authors of this study conclude that “RDN using a 5F ablation catheter can improve cardiac function, reduce HF symptoms and signs, and enhance exercise tolerance in patients with HF” however a larger scale study should be performed to confirm these findings.


This most recent study was single-centre, prospective, randomized and controlled study. This study was performed by 3 of the authors in the previous Gao et al (2016) study. This study looked at patients with chronic systolic HF and targeted the role of excess SNS activity. This study enrolled 60 patients to randomly receive RDN or to be in the control group. “All patients performed a 6-minute walk test, echocardiography, blood pressure measurement, and biochemical test, at both baseline and in a 6-month follow up.” Patients with renal artery stenosis, TIDM, recent MI or CVA (6 months), possible pregnancy or severe valvular heart disease were excluded from this study. Patients were included if they had NYHA functional class II or III chronic systolic HF. Patients included were over 18 years of age, had LVEF <40% on echocardiography or NT-proBNP > 125 pg/mL, GFR >45 mL/min/1.73 m² and systolic BP >100 mmHg.

This study randomized 30 patients to receive RDN and they were pre-treated with chewable enteric coated aspirin 300 mg or clopidogrel 300 mg. The patients were also given IV heparin 6000-8000 U. The catheter used in this study was a “6 F radiofrequency ablation catheter (Ablation instrument [39D-72X]: Johnson Medical
Instrument Co. Ltd.) in temperature control mode (8–10 W, 50°C).” After the procedure patients were evaluated with renal arteriography. All patients were kept on their current medication regimen with maximum tolerated doses and after ablation, meds were adjusted according to common practice.6

Patients were followed for 6 months post procedure and efficacy and safety endpoints were followed through this time. The efficacy endpoints were LVEF (via echocardiography), NT-proBNP level, NYHA class and six-minute walk test. Of these endpoints, all parameters showed improvement. Distances in the 6-minute walk test increased by 75 meters on average which is estimated from figure 3 in the study.6 The safety endpoints of GFR, BP and heart rate showed no significant changes and no procedure driven incidents occurred. The authors of this study conclude that RDN is an effective and safe treatment for HF and especially the treatment of HF in the setting of HTN.6

DISCUSSION

The studies4–6 have shown promise of RDN as a treatment for HF. The results collectively showed improvement across a wide range of endpoints and lacked significant issues of safety. The data compiled should be enough to set in motion a larger study to truly capture the effect of RDN on the patient and exercise tolerance.
This is an exciting time in the course of RDN research. While the results for its effect on hypertension (HTN) has not shown significant benefit, the previous research has solidified the safety of the treatment even if it is used for a relative disease process. Even better, if we are able to use RDN in common practice with greater benefit being in patients with concomitant HTN, then the past research for its use in HTN serves an even greater purpose.

There could be apprehension from researchers to proceed with full motion into trials of RDN for HF due to the experiences had with HTN. This may lead to a delay in studies being performed or bias in some way. On the other hand, this is promising research and will hopefully lead the charge into a larger study being conducted.

Many benefits in biochemical markers, exercise tolerance, and changes in NYHA functional class have been shown in the studies reviewed here. If these results could be shown over the long term and with a larger sample size then this may just be a way to treat past the symptoms and lessen some of the disability that comes with advanced heart failure.

**CONCLUSION**

RDN is a potential treatment for increasing exercise tolerance in patients with HF. Hopefully, the lack of benefit shown in patients with HTN will not steer research away from RDN. The research in this realm is too young to be able to recommend RDN as a mainstream treatment. With enough clinical evidence, this could be a beneficial option for patients with HF and especially with a hypertensive variety. Further clinical research
is needed to determine the efficacy of RDN in patients with HF but this treatment should be considered in the appropriate settings.
References

1. Heart failure- ClinicalKey. *Heart failure.*:53.


Table 1: Quality Assessment of Reviewed Articles

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<tr>
<th>Study</th>
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ᵃ There was no patient or provider blinding.
ᵇ The Patel et al was partially funded by Medtronic who developed the catheter used in the study.
ᶜ Study lacks control group and blinding.