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Article

The efficacy of renal sympathetic denervation as a treatment for heart failure

Eficácia da denervação simpática renal como tratamento para a insuficiência cardíaca

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ABSTRACT: Heart failure (HF) has become increasingly frequent in the population, due the importance of this disease worldwide so several studies evaluate new treatment options, such as renal sympathetic denervation (RDN), to inhibit kidney-stimulated cardiac activation. The aim of this study is to understand whether RDN is a feasible treatment for heart failure and its advantages. An integrative literature review was conducted with a search in the PubMed and Scielo databases, using the descriptors "Sympathectomy", "Denervation" and "Heart failure", found in DeCS. We searched for articles published in the last 10 years, in English, Spanish and Portuguese, available in full, excluding studies with experimental models. A total of 188 articles were found and of these 23 were selected, which have demonstrated relevance to the objective of the article. RDN consists of interrupting the renal nerve, suppressing sympathetic activity and the renin-angiotensin-aldosterone system. Despite being a delicate technique, RDN is safe, presenting complications inherent to invasive procedures, however of low to moderate severity, and few adverse effects. Thus, RDN proved to be a promising treatment for HF, promoting the remission of important symptoms, but it did not represent a cure for this disease.

KEYWORDS: Sympathectomy; Denervation; Heart Failure.

RESUMO: A insuficiência cardíaca (IC) tem se tornado cada vez mais frequente na população e, dada a importância dessa doença a nível mundial, diversos estudos avaliam novas formas para tratá-la, como a denervação simpática renal (DSR), com o intuito de inibir a ativação cardíaca estimulada pelos rins. O objetivo desse estudo é compreender se a DSR é um tratamento factível para a insuficiência cardíaca e quais são suas vantagens. Foi realizado uma revisão integrativa da literatura com busca nas bases de dados PubMed e Scielo, utilizando os descritores "Sympathectomy", "Denervation" e "Heart failure", encontrados no DeCS. Buscou-se por artigos publicados nos últimos 10 anos, em inglês, espanhol e português, disponíveis na íntegra, excluindo estudos com modelos experimentais. Foram encontrados 188 artigos e destes 23 foram selecionados. A DSR consiste em inativar o nervo renal, suprimindo a atividade simpática e do sistema renina-angiotensina-aldosterona. Apesar de ser uma técnica delicada, a DSR é segura, apresentando complicações inerentes a procedimentos invasivos, porém de baixa a moderada gravidade, e poucos efeitos adversos. Dessa forma, a DSR demonstrou ser um promissor tratamento para a IC, promovendo a remissão de sintomas importantes, como controle de arritmias e remissão de edemas periféricos, contudo não representou a cura para essa doença.

PALAVRAS-CHAVE: Simpatectomia; Denervação; Insuficiência Cardíaca.

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INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by distinctive symptoms such as dyspnea, swelling in the ankles, and fatigue, which may be accompanied by elevated jugular venous pressure, pulmonary rales and peripheral edema. These symptoms may be caused by structural and/or functional cardiac abnormalities, which result in decreased cardiac output and/or elevated intracardiac pressures at rest or during stress[1].

HF is the fastest-growing cardiovascular condition in the world, imposing a significant strain on healthcare systems globally. With a growing elderly population and advancements in HF treatment, older adults can now live with HF for longer than ever, making it necessary to enhance healthcare systems to ensure effective chronic disease management, improved health outcomes, and reduced healthcare expenses[2].

In heart failure, several compensatory mechanisms are activated to maintain adequate tissue perfusion. Consequently, inadequate or excessive activation of the sympathetic nervous system has been recognized as an exacerbating factor and even a potential cause of heart disease[3].

In this context, chronic sympathetic nervous system (SNS) overactivity is one of the key pathophysiological mechanisms operative in HF. In the acute phase, this upregulated SNS activity is an essential compensatory response initiated to counteract reduced contractility. However, in the long-term, it becomes one of the main contributors to cardiac dysfunction, as it promotes maladaptive cardiac hypertrophy and cell death[4]. Therefore, the sympathetic nervous system becomes a source of deterioration and a target for therapeutic intervention[5].

The kidneys not only receive efferent sympathetic nerve signals from the central nervous system but also play a critical role in transmitting information via afferent sympathetic nerve fibers back to the central nervous system. The well-established role of the sympathetic nervous system in regulating blood pressure and heart failure, combined with the location and vulnerability of renal sympathetic nerve fibers when exposed to heat, prompted the development and utilization of renal sympathetic denervation in the human population[6].

Given the established association between heart failure and heightened sympathetic activity, modulating renal nerve activity becomes a convenient therapeutic approach for these patients[7].

Considering the information above, this article aims to conduct an integrative literature review to assess the feasibility of renal sympathetic denervation as a treatment for heart failure and to explore its associated benefits.

MATERIALS AND METHODS

This is an integrative literature review encompassing a bibliographic survey conducted in the PUBMED/MEDLINE, SciELO and LILACS databases, using the descriptors “Sympathectomy”, “Denervation” and “Heart failure”, aligned with the Health Sciences Descriptors (DeCS). Inclusion criteria were articles published from January 2011 and April 2021, available in English, Spanish, or Portuguese. The exclusion criteria were articles that were not available in full and research conducted with experimental models. The search, selection and analysis of articles were carried out by a team of four researchers.

RESULTS

After applying the inclusion and exclusion criteria, a total of 188 articles were identified. Among these, 151 articles were excluded as their titles, abstracts, and topics did not align with the terms of interest, and 6 articles were removed due to duplication. Consequently, 23 articles were included, encompassing both original and review studies. Of these, 22 articles were found in the PubMed database, and one was sourced from Scielo. The selected articles and their details are presented in Tables 1 and 2.

Table 1 - Original articles selected from PubMed and Scielo databases and their main characteristics.

Author	Title	Year	Database	Results
Staico, R.[8]	Renal Sympathetic Denervation: a New Catheter in a New Scenario.	2013	Scielo	Case report of a patient with Chagas disease and refractory arrhythmia. Clinical follow-up involved periodic assessment of the implantable cardioverter-defibrillator and showed no sustained ventricular arrhythmias or need for therapy by the device in the two-month follow-up.
Geng, J.[9]	Influence of Renal Sympathetic Denervation in Patients with Early-Stage Heart Failure Versus Late-Stage Heart Failure.	2018	PubMed	A total of 17 consecutive patients with HF underwent RDN. Compared to baseline, there was a significant increase in LVEF in all patients in group 1 ($P<0.05$), which did not happen in group 2. (group 1: HF duration ≤ 3 years; group 2: HF duration > 3 years).

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Author	Title	Year	Database	Results
Gao, J. [22]	Percutaneous renal artery denervation in patients with chronic systolic heart failure: A randomized controlled trial.	2019	PubMed	The improvement of exercise tolerance (RDN: 301.2 ± 139.5 m; CONTROL: 227.2 ± 65.0 m), (p = 0.01, Cohen's d = 0.66), decrease of NT-proBNP level, (RDN: 440.1 ± 226.5 pg/mL; CONTROL: 790.8 ± 287.0 pg/mL), (p < 0.001, Cohen's d = 1.14) and increase in LVEF (RDN: 39.1 ± 7.3%; CONTROL: 35.6 ± 3.3%) (p = 0.017, Cohen's d = 0.61) at echocardiography in comparison to the control group suggest the feasibility and effectiveness of RDN for the treatment of chronic systolic HF.
Patel, H. [23]	Renal denervation in heart failure with preserved ejection fraction (RDT-PEF): a randomized controlled trial.	2016	PubMed	A greater proportion of patients improved at 3 months in the RDN group with respect to VO_2 peak (56% vs. 13%, P = 0.025) and E/e′ (31%vs.13%, P=0.04). Change in estimated glomerular filtration rate was comparable between groups.
Shen, M [24]	Interventional and Device-Based Autonomic Modulation in Heart Failure.	2015	PubMed	RDT has proven to be a very promising treatment for HF in contrast to other existing methods and devices, such as the defibrillator, ventricular assist device and heart transplantation, as RDN leads to an improvement in most symptoms, rather than just addressing them partially. However, further specific studies need to be carried out, taking into account each type of HF and their particularities.
Gao, J. [25]	Effects of percutaneous renal sympathetic denervation on cardiac function and exercise tolerance in patients with chronic heart failure.	2017	PubMed	The distance achieved by the 14 patients in the 6-minute walk test increased significantly at six months after RDN, while the ejection fraction increased from 36.0±4.1% to 43.8±7.9% on echocardiography. No RDN-related complications were observed during the follow-up period.
Verloop, W [28]	Renal denervation in heart failure with normal left ventricular ejection fraction. Rationale and design of the DIASTOLE (Denervation of the renal sympathetic nerves in heart failure with normal Lv Ejection fraction) trial.	2013	PubMed	Decreased renal sympathetic nerve activity results in a clinically significant reduction in blood pressure. It is known that the SNS has a causative role in the development and prognosis of HFREF. RDN appears to be a safe and relatively easy minimally invasive technique to interfere with sympathetic nerve hyperactivity.
Berukstis, A. [32]	Impact of renal sympathetic denervation on cardiac sympathetic nerve activity evaluated by cardiac MIBG imaging.	2016	PubMed	A total of 16 patients with resistant arterial hypertension were investigated. There was a significant change in cardiac sympathetic nerve activity assessed by scintigraphy, which prevents the worsening of HF in hypertensive patients.
Yang, J. [33]	Percutaneous Renal Sympathetic Denervation for the Treatment of Resistant Hypertension with Heart Failure: First Experience in Korea.	2013	PubMed	The beneficial effect of RDN in hypertensive patients with heart failure and kidney damage are, in addition to reducing BP, repairing end organ damage.

Caption: HF (Heart Failure); RDN (Renal Sympathetic Denervation); LVEF (Left Ventricular Ejection Fraction); SNS (Sympathetic Nervous System); VO2 (oxygen volume); E/e′ (ratio between the volume of the left atrium and the left ventricle); BP (Blood Pressure); HFREF (Heart Failure with Reduced Ejection Fraction).

Table 2 - Review articles selected from PubMed and Scielo databases and their main characteristics

Author	Title	Year	Database	Summary
Singh, J. [10]	Non-pharmacological modulation of the autonomic tone to treat heart failure.	2013	PubMed	RDN, which disrupts the renal nerves from the renal artery, may alter the neurohormonal balance to facilitate favorable remodeling of the ventricles. Vagus nerve stimulation and carotid baroreceptor stimulation have been shown in separate pilot studies to improve functional status and ventricular function. Multiple clinical trials are currently evaluating the safety and efficacy of these therapeutic strategies in the treatment of HF.

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Author	Title	Year	Database	Summary
Chatterjee, No. [12]	Novel Interventional Therapies to Modulate the Autonomic Tone in Heart Failure.	2015	PubMed	RDN is safe and tolerated in patients with HF, but its ultimate efficacy and tolerability must be tested in larger studies.
Kishi, T. [13]	Deep and future insights into neuromodulation therapies for heart failure.	2016	PubMed	The reduction of sympathetic activity by RDN is beneficial for HF. However the methodology of the procedure, selection of patients and the quality of devices require further clinical and basic research to develop a RDN procedure that is more appropriate for HF.
Pascual-Figal, D. [17]	Neprilysin and Heart Failure.	2017	PubMed	After RDN, there was a reduction in noradrenaline and neprilysin activity in the kidney, both of which are elevated in HF. The favorable outcomes of RDN in HF have also been associated with a reduction in angiotensin II concentration.
McArdle, M. [18]	Beyond Blood Pressure: Percutaneous Renal Denervation for the Management of Sympathetic Hyperactivity and Associated Disease States	2015	PubMed	RDN has demonstrated promise as a treatment, not only for resistant hypertension stemming from sympathetic nervous system alterations, but also for other conditions linked to this underlying cause. However, further studies are still needed.
Böhm, M. [19]	Renal denervation and heart failure.	2014	PubMed	Studies on renal sympathetic denervation have demonstrated the feasibility of treating heart failure-associated comorbidities, such as arrhythmias and metabolic disorders, using the advantages provided by this technique.
Böhm, M. [20]	Therapeutic potential of renal sympathetic denervation in patients with chronic heart failure.	2013	PubMed	Chronic heart failure is associated with the activation of the sympathetic nervous system, which triggers the release of norepinephrine and, consequently, promotes the regulation of the cardiovascular system. Therefore, renal sympathetic denervation offers the potential to enhance the quality of life of heart failure patients.
Sobotka, P. [21]	Sympatho-renal axis in chronic disease.	2011	PubMed	Excessive central sympathetic drive is linked to a series of complications in individuals and the kidney's afferent nerves contribute to this heightened activation. Renal sympathetic denervation leads to improvement in chronic conditions associated with this excessive stimulation. However, further studies are needed to evaluate more specific cases.
Bhat, A. [26]	An Update on Renal Artery Denervation and Its Clinical Impact on Hypertensive Disease.	2015	PubMed	All seven patients reported a significant symptomatic improvement, with significant quantitative improvement in six-minute walking distance at 6 months.
Hoogerwaard, A. [27]	Is renal denervation still a treatment option in cardiovascular disease?	2020	PubMed	Patients in the RDN group showed a significant improvement in ejection fraction, NYHA class, NTproBNP, heart rate and functional capacity. BP and renal function remained unchanged
Schwartz, P. [29]	Autonomic Modulation for the Management of Patients with Chronic Heart Failure.	2015	PubMed	All patients reported symptomatic improvement and had an increase in the 6-minute walk test.
Kanai, T. [30]	New Treatment for Old Disease: Management of Resistant Hypertension by Percutaneous Renal Sympathetic Denervation.	2013	PubMed	RDN has emerged as a promising treatment for patients with less severe hypertension, congestive heart failure, chronic kidney disease, and metabolic syndrome.
Froeschl, M. [31]	Percutaneous Renal Sympathetic Denervation: 2013 and Beyond.	2014	PubMed	Left ventricular systolic function improved, i.e., ejection fraction increased from 63.1 ± 8.1% at baseline to 69.1 ± 7.5%. Left atrial size decreased after RDN.
Schlaich M. [34]	Renal Sympathetic Denervation: A Viable Option for Treating Resistant Hypertension.	2017	PubMed	The degree of renal sympathetic nerve activity was predictive of long-term survival in patients with heart failure.

Caption: RDN (Renal Sympathetic Denervation); HF (Heart Failure); BP (Blood Pressure); NYHA (New York Heart Association); NTproBNP (N-terminal pro–B-type natriuretic peptide).

An increase in LVEF (Left Ventricular Ejection Fraction) observed in echocardiography after RDN was highlighted in 5 articles.[9,22,25,27,31] However, one study noted that the increase in LVEF is more pronounced in patients with HF for 3 years or less.[9] Another outcome highlighted, presented in 4 studies, was the increase in exercise tolerance in the 6-minute walk test[22,25,26,29.] Additionally, patients with HF who underwent RDN presented improvements in their clinical condition, including a reduction in arrhythmias and metabolic dysfunctions. This clinical improvement was reported in at least 8 studies[8,10,19,20,21,24,28,34].

DISCUSSION

Renal sympathetic denervation (RDN) was devised with the objective of serving as a safe and effective adjuvant treatment for resistant arterial hypertension. Presently, the benefits of RDN are under investigation for other clinical conditions linked to sympathetic hyperactivity[8].

Excessive activation of sympathetic nerves is a critical factor in the development and progression of heart failure[9,10]. A reduction in cardiac output activates afferent stimuli from the baroreceptors to the central nervous system cardio-regulatory centers, which, in turn, activates the sympathetic nervous pathway[11]. The efferent sympathetic nervous system emits fibers that innervate the renal cortex and end close to the macula densa, leading to increased renin secretion. Renin catalyzes the conversion of angiotensinogen into angiotensin I, which is subsequently converted into angiotensin II. Angiotensin II stimulates and enhances the response of the sympathetic nervous system and also inhibits the suppression of sympathetic tone mediated by the baroreflex. As a result, there is an increase in sympathetic tone and peripheral sympathetic activity, which can lead to elevated blood pressure cardiac overload[12].

In heart failure, sympathoexcitation causes renal vasoconstriction, activation of the renin–angiotensin system, and sodium retention, resulting in an increase in blood volume[13,14]. The compensatory mechanisms of the renin-angiotensin system are initially important for maintaining cardiac output. However, in the long term, they are harmful due to their adverse impact on the structural adaptive response of the heart[10].

The effect of norepinephrine on the heart and kidneys is heightened in patients with heart failure. Specifically, heightened renal and adrenal sympathetic activity have been associated with all-cause mortality and heart transplantation in these patients[15,16].

Renal sympathetic denervation reduces afferent and efferent signals that are augmented in patients with heart failure and reduced ejection fraction. The efferent signal from the central nervous system to the kidneys results in salt and water retention along with angiotensin release. Additionally, increased venous pressure and reduced kidney perfusion increase afferent flow, resulting in an overflow of norepinephrine to the end organs, including the heart[17].

Consistent benefits of pharmacological neurohormonal blockade were observed in clinical trials of systolic heart failure, supporting the primacy of sympathetic activation in the progression of both ischemic and nonischemic dilated cardiomyopathies. However, the precise role of sympathetic nervous system activity in precipitating and exacerbating systolic heart failure remains unclear, raising questions about the potential benefits of treatment with RDN[18] .

The spillover of norepinephrine is predictive of mortality in heart failure. As RDN reduces this increased norepinephrine release, it has a positive impact on the condition, leading to improved outcomes on the 6-minute walk test[19].

The beneficial effects of RDN encompass diseases associated with HF, reducing signs and symptoms of sleep apnea, arrhythmia and metabolic diseases. This reiterates the clinical improvement promoted by RDN[20].

In HF, there is a leftward shift in the CO_2 "sensitivity" set-point of the pCO_2 receptors of the central nervous system, which results in chronic metabolic alkalosis. By reducing sympathetic tone, RDN can restore normal minute ventilation response to pCO_2, thereby reducing exercise intolerance, a consequence of heart failure[21]. A preliminary study with patients with chronic systolic heart failure suggested that exercise tolerance improved after RDN. However, the small sample size and the single-group non-blinded and non-randomized nature of the study limited the validity of its findings[22].

Recent studies propose that renal denervation might be an effective approach to treating heart failure, due to its ability to suppress the activities of the sympathetic nervous system and the renin-angiotensin-aldosterone system by blocking the renal sympathetic nerve[22]. However, there are many uncertainties about the role of renal denervation in the treatment of heart failure, including the type of technique (multi-electrode vs. single-electrode systems), the best way to apply it (number and location of ablations in the renal artery), study design, blinding and endpoint selection[23].

Techniques used in RDN

Before the RDN procedure, the patient must be thoroughly evaluated, with imaging of the renal artery and renal function tests to assess the suitability of the intervention. The procedure is performed via a standard femoral artery access, with a flexible endovascular electrode catheter connected to a generator and placed within the renal arteries to allow delivery of radiofrequency energy. Subsequently, a series of lesions are delivered along each renal artery to reduce renal sympathetic discharge from the renal nerves, located in the adventitia of the renal arteries. For safety reasons, each lesion must be at least 5 mm apart[24].

In one study, the technique used included administration of 300 mg of chewable enteric-coated aspirin or 300 mg of clopidogrel before the intervention, along with intravenous unfractionated heparin 6000 to 8000U. Following skin preparation and disinfection of the right inguinal region, the right femoral artery was punctured and a 7F catheter sheath was inserted, followed by a JR catheter for bilateral renal angiography. A 5F radiofrequency catheter was subsequently inserted for rotational ablation using a 39D72X Stockert EP Shuttle RF generator with temperature control (8-10 W, 50 °C). The effective ablation time per point was 60-90 s and 4-6 ablation points were applied to each renal artery (distance between neighboring points 0.5 cm)[25].

In the initial RDN studies, four-to-eight ablations were delivered within each renal artery, while in the last study, SPYRAL ON MED, an average of 45.9 ablation points were delivered. Not only has the number of ablations increased, but catheter design has also been enhanced. The first human trial implementing catheter-based renal artery denervation took place in 2011 and used the Medtronic Symplicity® catheter. After the success of the Symplicity, a non-randomized trial was carried out using the EnlingHTN® catheter, which consisted of an expandable electrode basket housing four Platinum-Iridium-based electrodes. Despite the risks and disadvantages, the results obtained in these studies were positive, notably in resolving resistant hypertension. After that, demand for percutaneous devices rose, driving the development of a variety of alternative catheter-based systems for renal artery denervation[26].

Second generation radiofrequency ablation catheters were multi-electrode and geometrically arranged to achieve good lesions with less manipulation. Apart from the number of ablations and catheter design, the renal nerve anatomy also played an important role in the development of the RDN technique, considering that the shape of the catheter affects ablation[27].

The use of Doppler echocardiography is important, as it allows observing whether a patient is in a severe stage of heart failure (HF) by evaluating both diastolic and systolic heart capacity. The assessment through Doppler echocardiography, both before and after RDN, serves as a relevant marker of HF regression, and consequently, of the effectiveness of the procedure[28].

Adverse effects and complications of renal sympathetic denervation

It is important to highlight that, overall, RDN seems safe and potentially effective according to exploratory clinical trials conducted with a small number of patients. However, all new technologies used to modulate the autonomic nervous system carry inherent risks due to their invasive nature. Therefore, it is important to obtain a clearer understanding of the long-term consequences of RDN[29].

No amaurosis or syncope were observed after RDN, and there was no significant difference in glomerular filtration rate and heart rate. RDN does not cause hemodynamic or renal function changes in patients with chronic systolic HF, which is a sign of its safety[22].

However, another study underscores that the procedure is not without risk, as a patient required balloon angioplasty to treat intense vessel spasm/edema, a complication that is usually managed with intra-arterial nitrate alone[23].

Complications encompassed a hypotension episode in the Symplicity HTN-1 trial, representing 0.65% of the total sample, and one in the Symplicity HTN-2 study, representing 0.94% of patients allocated to RDN. Moreover, a renal artery dissection occurred in the Symplicity HTN-1 study, as well as some pseudoaneurysms and hematomas at the femoral access site. During RDN, ablation is accompanied by visceral nonradiating abdominal pain; therefore, intravenous narcotics and sedative drugs (morphine or fentanyl and midazolam) are administered in the conscious state, 2 to 5 minutes before the first ablation[30].

It is important to note that all complications occurred in patients treated with 8 French guiding catheters. The current standard of care for the Symplicity® catheter system is delivered via a 6-French guide[31].

Renal denervation was not associated with any major long-term complications. In the period of up to twelve months after the procedure, there were no documented complications such as renal function injury, renal artery stenosis/dissection or orthostatic hypotension. However, there are still many unanswered questions regarding the long-term impact of renal artery damage in HF patients, considering that most of these patients already have declining renal function and any additional damage may have exponential repercussions. Furthermore, there may be considerable variability in the renal innervation patterns in HF patients, which may influence the effects of this procedure[9,10].

Results of Renal Sympathetic Denervation

The RDN procedure may yield positive or negative results. The research analyzed demonstrated that specific results were attainable for each type of patient, and some results were common across multiple groups of volunteers.

Patients who experienced acute myocardial infarction (AMI) showed an improvement of sodium excretion, increased cardiac output, better renal blood flow and more effective angiotensin regulation. Conversely, patients with systemic arterial hypertension (SAH) and ventricular hypertrophy showed a reduction in ventricular mass and improvement of diastolic function. Furthermore, following RDN, a noticeable decrease in norepinephrine release and enhanced renal function

contributed to the reduction of heart failure[19].

A significant decrease in office blood pressure (BP), improved performance in physical activities requiring long resistance and a reduction in heart rate were observed after a 6-month follow-up of patients who underwent RDN[22].

There are also important biochemical findings following RDN, including a reduction in the production of TNF-α and C-reactive Protein, which are important inflammatory markers linked to HF [9].

Despite the significant reduction in office BP, outpatient BP remained unchanged. However, in patients with insulin resistance, improved glucose metabolism was noted after the procedure[32].

Yang and collaborators have demonstrated that, in hypertensive patients with heart failure and left ventricular systolic dysfunction, the benefits of RDN might extend beyond a decrease in BP and include therapeutic implications for other syndromes in which sympathetic activation is a component of the underlying disease process. Specifically, 24% of patients experienced a 20% or more improvement in glomerular filtration rate. This occurs because conditions such as chronic heart failure and kidney damage are commonly associated with systemic sympathetic hyperactivity[33].

A notable effect of RDN is the control of arrhythmias, such as tachycardia, which are common and significant findings in patients with HF. This demonstrates yet another aspect of disease remission[26].

It was noted that there was a reduction in the daily dosage of diuretics, remission of peripheral edema, and a reduction in the dosage of beta-blockers and angiotensin II receptor blockers, which are directly related to HF and SAH[25].

A study comparing the effects of RDN and the duration of HF demonstrated that all patients experienced an improvement in ejection fraction. However, the improvement in cardiac function and the reduction in inflammatory markers were more pronounced in patients with HF for less than 3 years[9].

Clinical studies on RDN and HF with reduced ejection fraction are scarce. Available studies demonstrate that HF patients undergoing RDN experience improvement in ejection fraction, NYHA class, heart rate, and functional capacity. However, the small samples of these studies do not allow definitive conclusions. In patients with reduced EF, RDN improved left ventricular diastolic function and the ejection fraction increased at 1 and 6 months after the procedure. This improvement was attributed to the decrease in end-systolic volumes[27,31].

Large clinical trials are necessary to elucidate the results of RDN in patients with preserved EF, and the RDT-PEF study was envisioned to fulfill this role. However, it was terminated early due to difficulties in recruitment, and was unable to analyze quality of life, exercise function, biomarkers and cardiac remodeling. The RDT-PEF was only able to determine that RDN is a safe procedure[23].

Studies also show that the degree of renal sympathetic nerve activity, assessed by gold standard tracer dilution methodology, was predictive of long-term survival in patients with congestive heart failure. These findings strongly support the notion that the reduction of increased sympathetic activity is a valid therapeutic intervention[34]. Nonetheless, there is a pressing need for new clinical trials encompassing larger population samples to identify differences in results based on the etiology of HF, functional class, and ejection fraction.

CONCLUSIONS

Despite being a topic that requires more randomized clinical trials, the findings of this study showed evident benefits of renal sympathetic denervation (RDN), demonstrating that it is a feasible adjunct for the treatment of resistant arterial hypertension. Moreover, it emerges as a promising therapeutic resource for patients with HF, as demonstrated by the positive outcomes such as increased LVEF on echocardiogram, significant decrease in blood pressure, improved performance in physical activities assessed by the 6-minute walk test, effective management of arrhythmias, remission of peripheral edema, reduced dosages of beta-blockers and angiotensin II receptor blockers, and a reduction in the production of TNF-α and CRP, important inflammatory markers associated with HF.

There's no denying the existence of risks and potential adverse effects during and post the procedure. However, meticulous studies have advanced towards the development of a superior technique, aiming to attain the optimal methodology and technology. In this context, RDN is a therapeutic alternative that leads to substantial improvement in HF, and, therefore, it is a viable intervention, even though it is not precisely a cure for this disease.

Authors' contributions: Elany Maria Ferreira Portela, Jeanne Beatriz Nunes da Silva, Laís Emanuelle Lamounier, and Lara Kaiulani Lamounier - Conception and design of the study, literature research, analysis and interpretation of data, and manuscript construction; Talitha Araújo Velôso Faria - Supervision and critical revision of the manuscript.

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