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Mini Review

Does Renal Sympathetic Denervation Decrease Sympathetic Nerve Activity?

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Abstract

One major development in the field of sympathetic nerve research is the recent invention of catheter-based Renal Sympathetic Denervation (RSD) for the treatment of resistant hypertension. A large number of clinical trials have shown the effectiveness of RSD in lowering blood pressure. However, the recent Symplicity HTN-3 trial, the first trial on RSD with a single-blinded and sham-controlled design, failed to show a blood-pressure-lowering effect of RSD. One of reasons explaining this discrepancy may be that sympathetic denervation in some patients is not complete. Therefore, investigating methods to verify the completeness of RSD has high clinical importance. This article reviewed the correlation between RSD and the noradrenaline content/spillover as well as Muscle Sympathetic Nerve Activity (MSNA), discussed the value of using noradrenaline and MSNA in predicting blood pressure response to RSD, and pointed out some future directions.

Keywords: Blood pressure; Muscle sympathetic nerve activity; Noradrenaline; Renal sympathetic denervation

Introduction

In hypertensive patients, renal sympathetic nerve activity is increased and high renal sympathetic nerve activity may be a major mechanism for the development of hypertension [1]. One major development in the field of sympathetic nerve research is the recent invention of catheter-based Renal Sympathetic Denervation (RSD) for the treatment of resistant hypertension. Since the first clinical trial on RSD was published in 2009 [2], a large number of clinical investigations have shown the effectiveness of RSD in lowering blood pressure. However, the recent Symplicity HTN-3 trial, the first trial on RSD with a single-blinded and sham-controlled design, failed to show a blood-pressure lowering effect of RSD [3]. One major limitation in the current clinical trials on RSD is the lack of a method to verify the completeness of sympathetic denervation in the renal artery [4]. The Simplicity catheter is required to be moved and rotated ≥4 times to cover the circumference of the renal artery, which makes RSD operator-dependent [4]. In addition, long-term side effects of RSD are not yet known [5-7]. Therefore, investigating methods to verify the completeness of RSD has high clinical importance [8-10]. This article reviewed the correlation between RSD and the noradrenaline content/spillover as well as Muscle Sympathetic Nerve Activity (MSNA), and discussed the value of using noradrenaline and MSNA in predicting the response of blood pressure to RSD.

Renal Sympathetic Denervation

Resistant hypertension is blood pressure that remains above the reduction goal despite concurrent use of three antihypertensive drugs at optimal doses, including a diuretic. Resistant hypertension contributes to an increased risk of cardiovascular events [11], and affects ≈ 6 million people in the United States [12,13]. Patients with resistant hypertension had few therapeutic options before 2007.

Renal sympathetic nerves include efferent and afferent nerves which lie adjacent to the adventitia layer of the renal artery [14]. Renal sympathetic nerves are crucial for production of catecholamines which can lead to hypertension [14]. Increased renal efferent sympathetic nerve activity can increase renin secretion and increase sodium absorption [15,16], consequently leading to increased fluid retention and hypertension. In addition, an increase in renin can activate the renin-angiotensin-aldosterone system, which contributes to the formation of hypertension [15,16]. On the other hand, increased renal afferent nerve activity can stimulate central sympathetic outflow, which can increase systemic vascular resistance and hypertension [15,16].

RSD is a catheter-based endovascular procedure to disconnect renal sympathetic nerves in the renal arteries. Therefore, RSD may lower blood pressure of hypertensive patients where renal sympathetic nerve activity is commonly increased [1]. This hypothesis was first investigated in 2007 by Krum et al. [2]. In this proof-of-principle Symplicity HTN-1 trial (N=45) [2], the authors showed that RSD decreased office systolic blood pressure by 22 mm Hg at 6 months in patients with resistant hypertension, and similar results were observed in the randomised but not sham-controlled nor blinded Symplicity HTN-2 trial (N=106) in 2010 [17]. The results of these two trials brought hope for patients with resistant hypertension. Subsequently, RSD has become a treatment option for resistant hypertension in many countries. It is increasingly clear that not every patient will respond to RSD. For example, the non response rate (a decrease in office systolic blood pressure of < 10 mm Hg) at 12 months was 15% in the Symplicity HTN-1 trial [18]. The randomised Symplicity HTN-3 trial (N=530), the first trial on RSD with a single-blinded and sham-controlled design, recently showed that RSD failed to lower blood pressure in patients with resistant hypertension 6 months after the procedure [3]. The reasons for the discrepancy between the Symplicity HTN-3 trial and a large number

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Table 1: Effects of RSD on the NA content and spillover.

Studies	N	Patients	Findings
Symplicity HTN-1 trial [2]	45	Resistant hypertension	RSD decreased renal NA spillover by 47% (95% CI of 28-65%) in 10 patients 15-30 days after the procedure. This was associated with a mean 6-month blood-pressure reduction of 22/12 mm Hg.
Schlaich et al. [22]	1	Resistant hypertension	SBP was 161, 141 and 127 mm Hg at baseline, 1 and 12 months after RSD, respectively. Kidney NA spillover decreased by 48% in the left kidney and 75% in the right kidney at 1 month after RSD. Whole-body NA spillover was reduced by 42% at 1 month after RSD.
Schlaich et al. [23]	2	Resistant hypertension, PCOS	Office SBP decreased from 183 at baseline to 175 mm Hg at 3 months in one patient, and from 167 to 140 mm Hg in the other. Whole-body NA spillover decreased by 5% and 8%, respectively. MSNA decreased by 17% and 33%, respectively.
Schlaich et al. [24]	9	Resistant hypertension, end-stage renal disease	RSD decreased office SBP during 3-12 months. 2 patients had more complete NA spillover data. NA spillover decreased by 22% and ≈18% at 3 months, respectively.
Ezzahti et al. [25]	17		Office SBP decreased by 5.7±18.8 mm Hg (P=0.11, N=17) and 12.7±16.0 mm Hg (P=0.007, N=16) at 6 and 12 months after RSD respectively. Plasma NA decreased by 128±167 pg/ml (P=0.008, N=16) and 95±172 pg/ml (P=0.08, N=12) at 6 and 12 months after RSD respectively. Neither the baseline nor the change in plasma NA in the responders (N=7) is different from those in the non-responders (N=8).

BP: Blood Pressure; MSNA: Muscle Sympathetic Nerve Activity; NA: Noradrenaline; PCOS: Polycystic Ovary Syndrome; RSD: Renal Sympathetic Denervation; SBP: Systolic Blood Pressure

of other trials are not fully understood, although it has been suggested that incomplete sympathetic denervation of the renal artery may, at least in part, explain the failure of the Symplicity HTN-3 trial [19]. However, this needs to be investigated in the future.

The procedure of RSD is previously described [20]. In brief, a catheter connected to a radiofrequency generator is inserted percutaneously and advances into the lumen of the renal artery. The typical inserting point is the right femoral artery and anatomic eligibility for the procedure is confirmed by renal angiography. The treatment catheter is introduced into each renal artery. Then discrete radiofrequency ablations lasting up to 2 min each are applied, and catheter is required to be moved and rotated ≥4 times to cover the circumference of each renal artery [4,20].

The renal artery anatomy is one of the criteria for a patient to be eligible for RSD. The expert consensus document from the European Society of Cardiology states that eligibility of renal arteries for RSD includes no polar or accessory arteries, no renal artery stenosis, and no prior revascularization [21]. Given that RSD may lead to renal artery stenosis [6] and long-term effects of RSD are unknown, exclusion of patients with this unfavorable renal artery anatomy from RSD is crucial.

Renal Sympathetic Denervation and Noradrenaline

RSD applies radio frequency energy to the renal arterial lumen, aiming to destroy both the afferent and efferent sympathetic nerves in the renal arteries [2,3,17]. Therefore, parameters on the renal sympathetic nerve activity are important to assess the success of the RSD procedure. One such parameter is renal noradrenaline spillover. A Pubmed search for clinical trials on RSD that contained noradrenaline data was conducted and five articles were identified (Table 1) [2,22-25].

In the first case report on RSD, Schlaich et al. [22] found that both kidney noradrenaline spillover and whole-body noradrenaline spillover decreased at 1 month after RSD in a patient with resistant hypertension. Reduction in noradrenaline spillover was associated with a gradual reduction in blood pressure [22] (Table 1). The proof-of-principle Symplicity HTN-1 trial (N=45) [2] reported that RSD decreased renal noradrenaline spillover during 15-30 days after the procedure in a subgroup of patients (N=10) with resistant hypertension, which was associated with a blood pressure reduction at 6 months in these patients. Subsequently, Schlaich et al. [23] reported that whole body noradrenaline spillover decreased in 2 patients with resistant hypertension who were also complicated with polycystic ovary syndrome. The decrease in whole body noradrenaline spillover was associated with moderate reductions in blood pressure [23]. In 2013, Schlaich et al. [24] reported that renal noradrenaline spillover reduced at 3 months after RSD in 2 patients complicated with both resistant hypertension and end-stage renal disease. However, whether renal or whole body noradrenaline spillover correlates with the blood pressure change needs to be further investigated.

Measuring content and changes in plasma noradrenaline is less challenging and more practical than measuring noradrenaline spillover. The association between the noradrenaline measurements and the success of RSD was investigated by Ezzahti et al. [25]. The authors found that office systolic blood pressure decreased by 5.7 mm Hg and 12.7 mm Hg at 6 and 12 months after RSD respectively. In this study, plasma noradrenaline decreased by 128 pg/ml and 95 pg/ml at 6 and 12 months after RSD respectively, indicating that RSD decreased the plasma noradrenaline content which is consistent with the noradrenaline spillover data [2,23,24]. The next question is whether the baseline plasma noradrenaline or the change in plasma noradrenaline can predict blood pressure response to RSD in these hypertensive patients. Unfortunately, neither of these two parameters in the responders (defined as a reduction of systolic blood pressure of ≥10 mm Hg) is different from those in the non-responders (defined as a reduction of systolic blood pressure of <10 mm Hg) in the study by Ezzahti et al. [25], indicating that neither the baseline nor the change in plasma noradrenaline content is a good indicator of blood pressure response to RSD.

Renal Sympathetic Denervation and Muscle Sympathetic Nerve Activity

RSD can decrease central sympathetic outflow via disconnecting renal afferent sympathetic nerve activity [26], which may be

Table 2: Effects of RSD on MSNA.

Studies	N	Patients	Findings
Schlaich et al. [22]	1	Resistant hypertension	SBP was 161, 141 and 127 mm Hg at baseline, 1 month after RSD and 12 months after RSD respectively. MSNA was 56, 41 and 19 bursts/minute at baseline, 1 month after RSD and 12 months after RSD respectively.
Schlaich et al. [23]	2	Resistant hypertension, PCOS	Office SBP decreased from 183 at baseline to 175 mm Hg at 3 months in one patient, and from 167 to 140 mm Hg in the other. MSNA decreased by 17% and 33%, respectively.
Schlaich et al. [24]	9	Resistant hypertension, end-stage renal disease	RSD decreased office SBP during 3-12 months. 2 patients with more complete MSNA data. MSNA decreased 28% and 47% at 3 month, respectively.
Hering et al. [27]	35	Resistant hypertension	SBP was decrease decreased by 12.6±18.3, 16.1±25.6, and 21.2±29.1 mm Hg (P<0.001) at 3, 6, and 12 months after RSD, respectively. MSNA was reduced by 8±12, 6±12, and 6±11 bursts/min (P<0.01) at 3, 6 and 12 months after RSD, respectively. Neither baseline nor the change in MSNA correlated with the change in blood pressure.
Grassi et al. [28]	15	Resistant hypertension	BP decreased at 1, 3 and 6 months after RSD MSNA did not change at 1 month after RSD and decreased at 3 and 6 months after RSD. Neither baseline nor the change in MSNA correlated with BP change.
Hart et al. [29]	8	Resistant hypertension	SBP did not change at 1 and 6 months after RSD MSNA did not change at both 1 and 6 months after RSD. Individually, 4 of 7 patients responded with a decrease in MSNA (i.e. >10% fall) at 6 months after RSD. The individuals with a change in MSNA at 6 months after RSD were not necessarily those with a change in SBP. Baseline MSNA was not associated with the change in BP at both 1 and 6 months after RSD.
Brinkmann et al. [30]	12	Resistant hypertension	SBP did not change: 157±7 mm Hg at baseline vs 157±6 mm Hg at 3-6 months after RSD (P=1.0). RSD did not change MSNA (before, 34±2 bursts/ min; after, 32±3 bursts / min P=0.6). Changes in BP did not correlate with changes in MSNA.
Vink et al. [31]	12	Resistant hypertension	SBP changed from 206 ± 7 mm Hg at baseline to 186 ± 6 mm Hg at 6 months after RSD (P = 0.06). Mean resting heart rate did not change (P = 0.44). MSNA did not change: 37 ± 4 bursts/min at baseline and 43 ± 4 bursts/min at 6 months after RSD (P = 0.11). Changes in SBP did not correlate with the baseline nor changes in MSNA.
Verloop et al. [32]	29	Metabolic syndrome, using ≤ 1 antihypertensive drug	Mean 24-hour SBP decreased by 3±9 mm Hg (P=0.07) and 6±12 mm Hg (P=0.04) at 6 and 12 months MSNA did not change: 48 *vs* 48 bursts /min for baseline and at 6 months respectively; or 74 *vs* 75 bursts/100 heartbeats for baseline and at 6 months respectively. Changes in BP did not correlate with changes in MSNA.
Hering et al. [33]	25	Resistant hypertension	RSD decreased SBP by 13 mm Hg (P<0.001) at 3-month follow-up. RSD moderately decreased multi-unit MSNA (79±3 *vs* 73±4 bursts/100 heartbeats; P<0.05). RSD substantially decreased all properties of single-unit MSNA including firing rates of individual vasoconstrictor fibers (43±5 *vs* 27±3 spikes/100 heartbeats; P<0.01), firing probability (30% *vs* 22% per heartbeat; P<0.02), and multiple firing incidence of single units within a cardiac cycle (8% *vs* 4% per heartbeat; P<0.05).

BP: Blood Pressure; min: minute; MSNA: Muscle Sympathetic Nerve Activity; PCOS: Polycystic Ovary Syndrome; RSD: Renal Sympathetic Denervation; SBP: Systolic Blood Pressure; *vs*: Versus

manifested as a decrease in MSNA. A Pubmed search for clinical investigations on RSD that contained MSNA data was conducted and ten studies were identified (Table 2) [22-24,27-33]. In the first case report on RSD, Schlaich et al. [22] found that MSNA decreased at 1 and 12 months after RSD respectively. The decrease in MSNA is associated with a decrease in blood pressure. Later on, Schlaich et al. [23] showed that MSNA was substantially elevated at baseline by approximately 2.5-3 folds in 2 patients with resistant hypertension, who were also complicated with polycystic ovary syndrome. Three months after RSD, MSNA decreased in these 2 patients. The decrease in MSNA was associated with moderate reductions in blood pressure [23]. In 2013 Schlaich et al. [24] reported that MSNA reduced at 3 months after RSD in 2 patients with both resistant hypertension and end-stage renal disease. In these 2 patients, blood pressure decreased up to 33 months during follow-up. In a study with a relatively larger sample size (N=35) Hering et al. [27] found that MSNA was reduced at 3, 6, and 12 months after RSD. However, neither baseline nor the change in MSNA correlated with the change in blood pressure. Grassi et al. [28] found that MSNA did not change at 1 month after RSD, but it decreased at 3 and 6 months. However, neither baseline nor the change in MSNA correlated with the change in blood pressure in this study [28].

The effect of RSD on MSNA is controversial. For example, four other studies found that RSD did not change MSNA [29-32]. These studies showed that neither baseline nor changes in MSNA correlated with change in blood pressure [29-31] (Table 2). The study by Hart et al. [29] showed that the individuals with a change in MSNA at 6 months after RSD were not necessarily those with a change in systolic blood pressure. For example, one patient whose systolic blood pressure decreased most (44 mm Hg) had an increase in MSNA (+28 bursts/100 heat beats) [29]. These studies indicate that RSD does not consistently decrease MSNA, and neither the baseline nor the change in MSNA is a good indicator of blood pressure response to RSD.

It is worthwhile to mention that all the MSNA mentioned in the above studies were multi-unit MSNA, which is routinely used and less challenging. Hering et al. [33] explored the more challenging single-unit recording and compared the change in the single-unit MSNA data with the multi-unit MSNA data. The authors found that RSD moderately decreased multi-unit MSNA by 8%; whereas it substantially decreased all properties of single-unit MSNA including firing rates of individual vasoconstrictor fibers (a 37% reduction), firing probability (a 27% reduction), and multiple firing incidence of single units within a cardiac cycle (a 50% reduction). This study [33] showed that RSD could result in the substantial and rapid reduction

in firing properties of single sympathetic vasoconstrictor fibers, this being more pronounced than multi-unit MSNA inhibition. Whether the earlier changes in single-unit firing patterns may predict long-term blood pressure response to RSD needs to be further investigated.

Summary

A limited number of studies have consistently shown that RSD decreased renal noradrenaline spillover; however, the correlation between the renal noradrenaline spillover and the extent of blood pressure reduction after RSD has yet to be assessed. RSD decreased plasma noradrenaline content; however, neither the baseline nor the change in plasma noradrenaline content correlated with the extent of blood pressure reduction after RSD. In addition, RSD did not consistently decrease multi-unit MSNA, and neither baseline nor the change in multi-unit MSNA predicts blood pressure response to RSD.

Future Directions

There are many questions needing to be addressed in the future. For example, RSD can result in a greater reduction in single-unit MSNA compared with multi-unit MSNA. Whether the earlier changes in single-unit MSNA predicts blood pressure response to RSD warrants further exploration. In addition, whether the combination of these noradrenaline and MSNA parameters can better predict blood pressure response to RSD has yet to be investigated. Moreover, other parameters or biomarkers for predicting better blood pressure response to RSD need to be urgently investigated given that (1) not every patient undergoing RSD responds to the treatment and (2) long-term side effects of RSD are unknown.

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