Renal denervation for the management of hypertension.  
Joint position statement from the SEH-LELHA and the ACI-SEC

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ABSTRACT

Hypertension is the most prevalent cardiovascular risk factor. Despite pharmacological treatment, a high percentage of patients do not achieve an adequate blood pressure control. Renal sympathetic denervation is a minimally invasive intervention for the management of hypertension involving the interruption of the renal artery sympathetic nervous system using a catheter-based approach. The early studies showed promising results, but the controversial results coming from the SYMPLICITY HTN-3 trial sent this technique into oblivion. Over the last 3 years, new clinical trials have appeared including new devices used in different populations, which definitively proves the effectiveness of renal sympathetic denervation.

This joint position statement from the Spanish Society of Hypertension-Spanish League for Combating High Blood Pressure (SEH-LELHA), and the Interventional Cardiology Association of the Spanish Society of Cardiology (ACI-SEC) reviews the evidence available on the efficacy and safety profile of renal sympathetic denervation for the management of hypertension. Based on the results of clinical trials, recommendations have been established on what patients may be eligible for renal sympathetic denervation and under what circumstances.

Keywords: Hypertension. Renal sympathetic denervation. Blood pressure.

Denervación renal en el tratamiento de la hipertensión arterial.  
Posicionamiento conjunto de la SEH-LELHA y la ACI-SEC

RESUMEN

La hipertensión arterial es el factor de riesgo cardiovascular más prevalente. A pesar del tratamiento farmacológico, un alto porcentaje de pacientes no consiguen un adecuado control. La denervación renal es una intervención mínimamente invasiva para el tratamiento de la hipertensión que implica la interrupción de los nervios simpáticos renales mediante un abordaje con catéter. Los estudios iniciales mostraron resultados prometedores, pero los controvertidos resultados del ensayo SYMPLICITY HTN-3 llevaron al abandono de la técnica. En los últimos 3 años han aparecido los resultados de nuevos ensayos clínicos, con nuevos dispositivos y en diferentes poblaciones, que demuestran definitivamente la eficacia de la denervación renal.

En este documento de posicionamiento conjunto de la Sociedad Española de Hipertensión-Liga Española para la Lucha contra la Hipertensión Arterial (SEH-LELHA) y la Asociación de Cardiología Intervencionista de la Sociedad Española de Cardiología (ACI-SEC)
se revisa la evidencia disponible sobre la eficacia y la seguridad de la denervación renal en el tratamiento de la hipertensión. A partir de los resultados de los ensayos clínicos, se generan recomendaciones sobre qué pacientes y en qué condiciones podrían ser candidatos a una denervación renal.


**Abreviaturas**

- ABPM: ambulatorio de presión arterial.
- BP: presión arterial sistólica.
- DBP: presión arterial diastólica.
- HMOD: hipertensión mediada por órganos dañados.
- HTN: hipertensión arterial.
- RSD: denervación renal.
- R-HTN: hipertensión resistente.
- SBP: presión arterial sistólica.
- ABPM: monitorización ambulatoria de la presión arterial.
- ACEI: inhibitor de la enzima convertidora de angiotensina.

**INTRODUCCIÓN**

El sistema nervioso simpático desempeña un papel en la patofisiología de la hipertensión arterial. En 2007, se abordó el problema de la hipertensión resistente (HTN) con el primer ensayo clínico aleatorizado de denervación renal percutánea (RSD). Cada ensayo clínico recoge datos sobre la eficacia del procedimiento, así como las posibles complicaciones. Aunque el camino todavía está por recorrer, el nuevo evidencia ha proporcionado un marco claro para las próximas investigaciones.

**CLINICAL EVIDENCE ON THE ROLE OF RENAL SYMPATHETIC DENERVATION IN THE MANAGEMENT OF HYPERTENSION**

El suplemento muestra las características epidemiológicas del HTN (sección 1), así como el papel del sistema nervioso simpático en el manejo del HTN (sección 2), lo que mejora nuestro entendimiento de los ensayos clínicos. La tabla 1 del suplemento muestra los principales estudios en los que se informó de la eficacia de RSD.

En 2009, el primer estudio de RSD en pacientes con HTN resistente (R-HTN) fue realizado. El estudio SYMPLICITY HTN-1 fue publicado. Este estudio sugirió una eficacia significativa de RSD frente a un grupo control. Aunque el camino aún está por recorrer, la nueva evidencia proporciona una guía clara para el manejo de pacientes con HTN.

A pesar de la brevedad del tiempo que ha transcurrido desde la publicación de estas guías, los datos proporcionados no han disuadido el uso de RSD. A pesar de la brevedad del tiempo que ha transcurrido desde la publicación de estas guías, los datos proporcionados no han disuadido el uso de RSD. A pesar de la brevedad del tiempo que ha transcurrido desde la publicación de estas guías, los datos proporcionados no han disuadido el uso de RSD.
with the medication burden or with an increased number of antihypertensive drugs. RSD has proven to be safe and has a low rate of complications associated with the procedure.10 The GLOBAL SYMPLICITY registry, with over 2900 patients is the largest and longest duration analysis to this date of renal sympathetic denervation to show the efficacy and safety profile of RSD in a real-life scenario.11 Table 2 of the supplementary data shows a summary of different registries on RSD.

RSD has been confirmed as a safe intervention. The incidence rate of both immediate complications associated with the procedure and renal and vascular complications in the short- and mid-term (6-12 months) is very low and is mainly associated with local problems at the puncture site; serious renal complications (renal artery dissection or stenosis) are anecdotal. Table 3 of the supplementary data summarizes the safety data from the main randomized clinical trials that often have a short-term clinical follow-up.

**POSSIBLE INDICATIONS FOR RENAL SYMPATHETIC DENERVATION WITH DATA FROM THE LATEST CLINICAL TRIALS**

Data from both randomized clinical trials and registries prove that the RSD procedure is safe and effective reducing BP, which is consistent across different populations including high-risk subgroups, and with different devices. Section 3 of the supplementary data reviews various consensus documents and recommendations previously published by different scientific societies prior to the publication of the SPYRAL HTN and RANDIANTE-HTN clinical trials.

RSD can be considered in patients with resistant HTN (BP > 140/90 mmHg despite lifestyle changes treated with ≥ 3 antihypertensive drugs at optimal doses, one of them being a diuretic or HTN controlled with ≥ 4 drugs), and also in patients with uncontrolled HTN (BP > 140/90 mmHg in patients with poor therapeutic compliance), and high cardiovascular risk.

**Renal sympathetic denervation in patients with resistant hypertension**

Patients with R-HTN were the first group in whom the role of RSD was assessed. The SYMPLICITY HTN-3 trial failed to demonstrate the increased efficacy of RSD vs sham control in patients with R-HTN.9 However, subsequent analysis revealed design and execution limitations that cast doubts on the reliability of the results.12 In the recently published RADIANCE-HTN TRIO trial, patients with R-HTN treated with a standardized triple combination pill experienced a drop in their BP levels 2 months after RSD compared to a sham procedure.13 If the BP lowering effect and the safety of RSD are maintained in the long term, RSD might be an alternative to the addition of more antihypertensive medications in patients with R-HTN.

**Renal sympathetic denervation in patients with uncontrolled hypertension**

The new evidence available introduces a paradigm shift for a technique that was initially conceived for the management of R-HTN when all other therapeutic options fail, and is currently an option that should be taken into consideration in patients with persistent BP > 140/90 mmHg despite drug treatment.

The concept of uncontrolled HTN includes a high percentage of hypertensive patients (maybe even > 60%) with highly heterogenous clinical characteristics and cardiovascular risk. Given the invasive nature of the RSD procedure, and until more information becomes available on the reduction of cardiovascular events in more specific subgroups of patients, there are some high-risk situations in which BP control is essential to reduce the risk of cardiovascular events:

a) **Patients with frequent hypertensive crises.** Hypertensive crises with SBP levels > 180 mmHg and/or DBP levels > 110 mmHg can cause brain, cardiac or microvascular damage. Emergency visits for hypertensive crises exceed 4% of all visits to the emergency room.14 Even in the absence of hypertension-mediated organ damage (HMOD), episodes of hypertensive crisis can have long-term implications to the extent that these patients may have a 50% higher risk of suffering cardiovascular events compared to controlled hypertensive patients. Nonetheless, outside the crisis setting they show similar BP levels.15

b) **Patients with low compliance to pharmacological treatment.** Pharmacological treatment of HTN is generally a long-term option and in most cases, for life. Poor compliance is a common problem to the extent that almost one third of all hypertensive patients do not start a new prescription of antihypertensive drugs,15 and around 50% become non-compliant within the first year after starting treatment.16 In the SPYRAL HTN trials, the 24-hour ABPM levels showed decreased BP levels throughout the entire 24-hour period in patients treated with RSD compared to no changes in the control group in the absence of drugs or incomplete control in the presence of drugs.4,5 Furthermore, in the SPYRAL HTN OFF-MED trial, the treatment group experienced an average reduction of 9.2 mmHg in office SBP levels.5 A meta-analysis of 123 studies including 613,815 patients showed that a drop of office SBP levels of 10 mmHg was associated with a significantly lower risk of cardiovascular events.14 Poor compliance is a serious problem of public health since these patients in whom an adequate BP control is not achieved, even due to poor therapeutic compliance, have a high cardiovascular risk.17 However, we should stress that RSD alone cannot bring BP levels down enough to achieve BP control in most patients. In the RADIANCE-HTN SOLO trial, the 24-h ABPM only 25% of the patients treated with RSD reached values < 130/80 mmHg.18 In these non-compliant patients, the main strength of RSD is the “always on” effect regardless of pharmacokinetics and compliance to drugs.

c) **Patients with hypertension-mediated organ damage.** The presence of HMOD identifies a group of patients with high cardiovascular risk in whom conventional treatment has failed to prevent the progression of the disease.19 Achieving the BP levels recommended is especially important in these patients because, in the early stages of the disease, some types of HMOD can be reversed; in more advanced stages, HMOD is irreversible despite adequate BP control. But this is important since it slows its progression while reducing the cardiovascular risk of these high-risk patients.17 A meta-analysis including 698 patients treated with RSD revealed an independent effect of RSD on HMOD, which advocates for the use of RSD in this group of high-risk patients.18

d) **Patients at high cardiovascular risk.** The European guidelines on the management of HTN establish the factors that influence cardiovascular risk in hypertensive patients including clinical characteristics, analytical characteristics, presence of HMOD or established cardiovascular or kidney disease. All these factors establish a 10-year cardiovascular risk that is categorized into 4 groups: low, moderate, high or very high risk to the extent that, for example, in high-risk patients the estimated cardiovascular mortality is 5% and in very high-risk patients > 10%.9 The assessment of cardiovascular risk should play an important role in the decision-making process to the extent that the higher the risk, the greater the benefits expected with better BP control. Therefore patients at high or very high-risk would be eligible for RSD whenever BP control is not adequate.
Empowering the hypertensive patient in the setting of a shared decision-making process

Over the last few years, shared decision-making process has emerged as the go-to model in the management of different conditions. In the field of RSD, a recent survey revealed that 38% of hypertensive patients who still don’t take antihypertensive medication would prefer RSD to lifelong drug therapy even knowing that it would probably not replace medication in many cases. Just this already reduces BP significantly.\(^\text{14}\) With the evidence provided in recent trials, RSD could be a valid treatment option in patients with uncontrolled HTN and high to very-high cardiovascular risk in whom, in a shared decision-making process context, consensus with the patient can be reached. In any case, we should mention that the treatment of HTN always requires the adoption of healthy lifestyle habits, and the recommendation to patients should include drug treatment as the first option.

### STUDY PRIOR TO RENAL SYMPATHETIC DENERVATION

Patients should be examined in a unit specialized in HTN and vascular risk 3 months prior to the procedure in a center with proven experience.\(^\text{20}\) Table 1 summarizes the studies to be conducted in patients eligible for RSD.

Uncontrolled HTN should be confirmed through 24-hour ABPM.\(^\text{21}\) After confirming the presence of uncontrolled HTN, the clinical situations that increase BP levels such as obesity or obstructive sleep apnea should be identified and corrected. Also, substances such as salt or certain drugs that may also lead to HTN should be suspended or minimized. Non-compliance to treatment, which is very common and not always identified by the patient, if not rigorously investigated, should be ruled out.\(^\text{26}\) It is essential to rule out secondary HTN (table 2) or, if diagnosed, treat it effectively. Still, it is not an absolute contraindication to RSD.\(^\text{23}\)

### RENAL SYMPATHETIC DENERVATION PROCEDURE WITH RADIOFREQUENCY DEVICES

Section 4 of the supplementary data shows more in-depth technical aspects of RSD. Figure 1 of the supplementary data summarizes the RSD procedure.

A better knowledge of the anatomy of renal nerves\(^\text{24}\) and the development of new ablation devices have optimized the treatment technique,\(^\text{5,6}\) which is based on 3 main objectives:

#### Management of the renal artery main trunk and branches

It is common for the renal nerves to reach the kidney after bypassing the main renal artery.\(^\text{14}\) In animal models, it has also been confirmed that the application of combined radiofrequency in the renal artery main trunk and branches reduced the content of norepinephrine in the renal tissue even more, and in the cortical axonal density, both associated with the response to RSD.\(^\text{25}\)

In patients treated with RSD, the presence of untreated accessory arteries leads to a lower hypotensive response.\(^\text{26}\) Their identification and treatment is essential and, if they are amenable to treatment thanks to their diameter [minimum diameters of 3 mm], the treatment of accessory arteries is advised.

Last but not least, the perivascular space around the ostium and the proximal third of the main renal artery is often occupied by ganglia of solar plexus and by the lumbar sympathetic chain [figure 1]. Both carry innervation to the kidneys, but also to other abdominal and pelvic organs, and they could be accidentally denervated if the treatment is applied to the ostium and proximal third of the main renal artery. Therefore, until more information becomes available, it seems reasonable to be cautious when treating the most ostial portion of renal arteries.\(^\text{24}\)

#### Treatment of the 4 quadrants of the renal artery

The distribution of nerve fibers around the renal artery follows a variable pattern across different individuals.\(^\text{27}\) Preclinical studies in a porcine model have shown that the application of radiofrequency in one point produces effects on approximately 25% of the arterial circumference;\(^\text{28}\) and procedures that use multiple helically staggered ablations in the 4 quadrants are more effective reducing the norepinephrine content into the renal tissue.\(^\text{29}\)

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**Table 1.** Studies prior to renal sympathetic denervation in patients with uncontrolled hypertension

<table>
<thead>
<tr>
<th>Evaluation of pharmacological treatment</th>
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<tbody>
<tr>
<td>Type and number of drugs</td>
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<tr>
<td>Drug adequate dosage</td>
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<tr>
<td>Assess use of aldosterone antagonist</td>
</tr>
<tr>
<td>Assess lack of therapy compliance</td>
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<tr>
<td>Assess intolerance to drug therapy</td>
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<tr>
<td>24-hour ABPM study</td>
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<tr>
<td>Rule out pseudo-resistant hypertension or white coat effect</td>
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<tr>
<td>Confirm uncontrolled hypertension (SBP &gt; 130 mmHg/DBP &gt; 80 mmHg at the 24-hour levels or SBP &gt; 135/DBP &gt; 85 in the day’s levels)</td>
</tr>
<tr>
<td>Rule out secondary causes of hypertension (table 2)</td>
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<tr>
<td>Cardiovascular risk assessment</td>
</tr>
<tr>
<td>Coexistence of other cardiovascular risk factors such as dyslipidemia, diabetes or smoking</td>
</tr>
<tr>
<td>Presence of HMOD</td>
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<tr>
<td>Presence of established cardiovascular or kidney disease</td>
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<tr>
<td>Imaging of the renal anatomy by computerized tomography or nuclear magnetic resonance imaging (assessment of occlusive stenosis, accessory branches, arterial diameter)</td>
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<tr>
<td>Complementary tests recommended:</td>
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<tr>
<td>Hemogram, renal function parameters, liver and lipid profiles, and urine sediment tests to detect the presence of microalbuminuria</td>
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<tr>
<td>Specific analytical determinations:</td>
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<tr>
<td>Baseline plasma aldosterone-to-renin ratio</td>
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<tr>
<td>Thyroid hormones</td>
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<tr>
<td>Calcium-phosphorus metabolism with parathyroid hormone levels</td>
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<tr>
<td>Cortisol (basal and 24-hour urine ratios)</td>
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<tr>
<td>Catecholamines with 24-hour urinary metanephrines ratio</td>
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<tr>
<td>Polysomnography</td>
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<tr>
<td>ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure, HMOD, hypertension-mediated organ damage; SBP, systolic blood pressure.</td>
</tr>
</tbody>
</table>
Application of the maximum possible number of ablation points

A post-hoc analysis of the SYMPLICITY HTN-3 trial confirmed that patients with a greater number of radiofrequency applications reduced their BP levels even more without any associated adverse events.9 We recommend applying the maximum number of ablation points possible, always respecting a distance of 5 mm among them with a 4-quadrant distribution.

Section 4 of the supplementary data shows how to perform a RSD procedure using a tetrapolar radiofrequency catheter. Table 3 shows the precautions and contraindications regarding RSD.

Care after renal sympathetic denervation procedure

Once the procedure is finished, it is important to ensure adequate hemostasis in the femoral puncture. Usually, in the absence of complications, patients can be discharged after 24 to 48 hours with the same antihypertensive treatment they had before the procedure or with treatment adjustments in cases that show an immediate response, but still with adjustment appointments within 5 to 7 days. Of note, the effects of the intervention can take weeks to materialize.29

REQUIREMENTS OF A RENAL SYMPATHETIC DENERVATION PROGRAM

The success of a RSD program is based on the existence of a multidisciplinary team that performs a comprehensive assessment of the patient from the selection of candidates through their assessment prior to the intervention, the RSD procedure, and subsequent follow-up. This process should be carried out at specific units specialized in the management of HTN in collaboration with interventional cardiology units. Figure 2 shows the selection process of eligible patients.

We strongly discourage isolated procedures outside this controlled environment. RSD should not be performed in centers with volumes < 10 cases/year. Centers without a structured RSD program, but...
with eligible patients, should refer them to an experienced center rather than performing isolated procedures.

RSD procedures should be performed by operators experienced in the management of endovascular treatment. The SYMPLICITY HTN-3 trial post-hoc analysis showed the importance of an experienced interventional specialist given one of the factors influencing the results of the study was the operator’s lack of experience. Therefore, we recommend that procedures should be performed at centers with proven experience only and that, in centers that lack experience, should refer patients to an experienced center rather than performing isolated procedures.
this experience, the possibility of monitoring should be available including assistance during the patient selection process and supervision of the procedure until enough experience is gained to ensure optimal results.

CONCLUSIONS

This expert consensus document has reviewed the information available regarding RSD in the management of patients with HTN. Also, it has established, for the first time, the indication for RSD in cases of uncontrolled HTN, especially in patients at high cardiovascular risk with HMOD or cardiovascular disease while taking the patient’s opinion into consideration as part of a shared decision-making process, and as long as it is evaluated by a multidisciplinary team and performed by experienced operators.

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AUTHORS’ CONTRIBUTIONS


CONFLICTS OF INTEREST

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M21000235.

REFERENCES


