



## **Sökning i databaser för vetenskaplig evidens: Denervering av sympatiska neuron i njurartärerna vid terapieresistent högt blodtryck**

### **Frågeställning**

Vilken vetenskaplig evidens finns för denervering av sympatiska neuron i njurartärerna med radiofrekvensablation vid behandling av högt blodtryck som inte svarar tillräckligt på läkemedelsbehandling

### **Bakgrund**

Denervering innebär att nerver skärs av eller förstörs på annat sätt. Renal denervering d.v.s. denervering av sympatiska neuron i njurartärerna (RSD) sker genom att katetrar förs in i njurartärerna från lumsken och radiovågor används för att förstöra de sympatiska neuronerna i artärväggen. Njurarna och sympatiska nervsystemet har stor betydelse för blodtrycket som efter RSD behandling kan låta sig styras med läkemedelsbehandling.

### **Metodrådets sammanfattande bedömning**

RSD är en metod som sänker blodtrycket uppmätt på mottagningen (d.v.s. utan placebokorrektion) (Esler, Krum et al. 2010) medan dygnsblodtrycket sjunker begränsat (ca 5-8 mmHg systoliskt) (Dorenkamp, Bonaventura et al. 2013). Behandlingsmetoden används vid högt blodtryck som inte svarat tillräckligt på livsstilsförändringar och läkemedelsbehandling. Det har rapporterats gynnsamma effekter bl a på glukosmetabolismen, hjärtats funktion och på sömnapné (Witkowski, Prejbisz et al. 2011; Brandt, Mahfoud et al. 2012). Medicinsk och teknisk kompetens samt infrastruktur finns redan för metoden i Sydöstra sjukvårdsregionen och komplikationsfrekvensen i samband med ingreppet är låg enligt rapporter från andra centra (1-3 %). Behandlingseffekterna och biverkningarna de första två åren är klarlagda men uppföljning av långtidseffekterna på blodtrycket och möjliga senkomna biverkningar av metoden saknas (Doumas and Douma 2010). Studier av effekten av RSD på de allra viktigaste effektmåtten - dödlighet och sjuklighet i hjärt- kärlsjukdomar saknas (Andersson, Herlitz et al. 2013). Följaktligen är metodens kostnadseffektivitet inte fastlagd. Det finns skäl till försiktighet i tolkningen av befintliga studieresultat rörande RSD eftersom flertalet studier av effekterna av RSD har varit sponsrade av berörda medicinskt-tekniska företag och då man nästan uteslutande saknat kontroll av placeboeffekter.

Högt blodtryck är bland de viktigaste orsakerna till sjuklighet och dödlighet (Lewington, Clarke et al. 2002). Det är därför avgörande att patienter som inte svarar tillräckligt på livsstilsförändringar och läkemedelsbehandling kan erbjudas en kompletterande behandling. RSD skulle kunna vara en behandlingsmöjlighet, men behöver studeras bättre avseende patientnyttan, gärna i nationella/internationella randomiserade och kontrollerade studier. Det är särskilt viktigt att säkerställa långtidseffekterna.



## Sökning i HTA (Health Technology Assessment) databaser (2013-12-15)

SBU - Kunskapscentrum för hälso- och sjukvården <http://www.sbu.se/sv/>

En träff på ”Renal sympathetic denervation”; HTA rapport från HTA-centrum Västra Götalandsregionen; Renal sympathetic denervation in patients with therapy resistant hypertension. (Andersson, Herlitz et al. 2013). Författarna drar följande slutsatser: ”RDS är en effektiv, kostnadseffektiv och etisk behandlingsmetod vid hypertoni som inte svarar på läkemedelsbehandling. Det saknas dock i dagsläget långtidsresultat (längre än två år) av behandling med RDS”.

*Socialstyrelsen – nationella riktlinjer*

<http://www.socialstyrelsen.se/riktlinjer/nationellariktlinjer>

Ingen träff på ”Renal Sympathetic Denervation” eller på ”denervation” i aktuella sammanhang.

*TRIP databasen* <http://www.tripdatabase.com/search/advanced>

211 resultat på ”renal sympathetic denervation”, varav 11 ”Evidence Based Synopsis” 5 ”Systematic Reviews”, 19 ”Guidelines” och 57 kontrollerade kliniska studier.

**År 2013:** HTA rapport från HTA-centrum Västra Götalandsregionen; Renal sympathetic denervation in patients with therapy resistant hypertension (Andersson, Herlitz et al. 2013) (se ovan).

**År 2012:** Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension från National Health Service (NHS 2012). Rapporten slår fast att RDS är en effektiv behandlingsmetod för terapiresistent högt blodtryck och att komplikationsfrekvensen är låg. Långtidsresultat saknas.

Renal sympathetic denervation as treatment of resistant hypertension (Merino and Rozas 2012) – en Galicisk HTA- rapport på 105 sidor som drar slutsatsen att det i dagsläget inte finns tillräckligt vetenskaplig evidens för införande av RSD i sjukvården.

**År 2010:** Renal sympathetic denervation for the treatment of resistant hypertension (HealthPACT 2010), en HTA – rapport från Australia and New Zealand Horizon Scanning Network (ANZHSN). Inkluderar slutgiltigt enbart två studier. Rekomenderar bevakning av metoden.

*The Cochrane Library* <http://www.thecochranelibrary.com/view/0/index.html>

En träff på ”Renal sympathetic denervation”

**År 2013:**

Gosain et al. "Renal sympathetic denervation for treatment of resistant hypertension: a systematic review (Gosain, Garimella et al. 2013). Slutsatsen är att korttidsstudier visar en



tydlig gynnsam effect av RSD hos utvalda patienter och att biverkningar är sällsynta. Långtidsstudier av betydligt större patientpopulationer saknas.

*Clinical Evidence* <http://www.clinicalevidence.com/x/index.html>

En träff på ”Renal sympathetic denervation” – handlade om behandling av diabetisk hypertoni men inte direkt om RSD.

International Network of Agencies for Health Technology Assessment <http://www.inahta.net/>

Fem träffar på “Renal sympathetic denervation”

#### **År 2013:**

Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension (Dorenkamp, Bonaventura et al. 2013) visar att RSD är kostnadseffektiv upp till 78- års ålder hos män och upp till 76 års ålder hos kvinnor.

Gosain et al. "Renal sympathetic denervation for treatment of resistant hypertension: a systematic review (Gosain, Garimella et al. 2013). Slutsatsen är att korttidsstudier visar en tydlig gynnsam effekt av RSD hos utvalda patienter och att biverkningar är sällsynta. Långtidsstudier av betydligt större patientpopulationer saknas.

Renal sympathetic denervation in patients with therapy resistant hypertension. (Andersson, Herlitz et al. 2013) (se ovan).

#### **År 2012:**

Renal sympathetic denervation as treatment of resistant hypertension (Merino and Rozas 2012) – en Galicisk HTA- rapport på 105 sidor som drar slutsatsen att det I dagsläget inte finns tillräckligt vetenskaplig evidens för införande av RSD i sjukvården.

#### **År 2010:**

Renal sympathetic denervation for the treatment of resistant hypertension (HealthPACT 2010), en HTA – rapport från Australia and New Zealand Horizon Scanning Network (ANZHSN). Inkluderar slutgiltigt enbart två studier. Rekomenderar bevakning av metoden.

*Nasjonalt kunnskapssenter for helsetjenesten, Norge* <http://www.kunnskapssenteret.no/>

Ingen träff på ”Renal sympathetic denervation”. Ingen relevant treff på ”blodtryck”.

#### ***Annan vetenskaplig evidens***

Under perioden april 2011–april 2012 behandlades 22 patienter med terapiresistent hypertoni med kateterbaserad radiofrekvensablation av njurens sympatiska nerver på Sahlgrenska universitetssjukhuset (Rundqvist, Völz et al. 2013). Under uppföljningsperioden förekom inga biverkningar och ingen påverkan på njurfunktionen. En månad efter ablationen observerades



en minskning av viloblodtrycket på i medel 22 mm Hg systoliskt och 7 mm Hg diastoliskt) med ytterligare reduktion tre månader efter ingreppet.

En svensk consensusrapport inom området ”Utredning av terapiresistent hypertoni och indikation för renal denervering: rekommendationer från svenska arbetsgruppen för renal denervering” utkom 2013 (Andersson and Spaak 2013).



**Metodrådet i Sydöstra sjukvårdsregionen den X februari 2014**

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### **Litteraturreferenser**

Andersson, B., M. Herlitz, et al. (2013). Renal sympathetic denervation in patients with therapy resistant hypertension. Göteborg, Region Västra Götaland, HTA-centrum.

It is still not known if sympathetic renal denervation has any long-term adverse effects, or whether there will be a reinnervation to such an extent that the effect on blood pressure will be diminished. It is also not known if there are significant interactions between RDN and pharmacological interventions that may affect renal hemodynamics. Finally, we lack long-term safety aspects on how RDN treated patients can cope with conditions of salt restriction or severe hypovolemia. Ethical aspects: A large group of hypertensive patients are possible candidates for RDN. Thereby, this invasive method could compete with other cardiovascular interventions and may lead to a shortage of overall interventional capacity. The long-term risks and benefits of RDN are still unknown. In contrast to pharmacological blood pressure lowering the effects of RDN on blood pressure cannot be reversed by withdrawal of the intervention. Is it ethically justified to introduce such treatment on a large scale in the clinical routine before possible long term risks are known?

Economical aspects: The average cost per patient treated with renal sympathetic denervation is 85 000 SEK. The annual cost of combined drug treatment varies between patients but could be exemplified by a typical 4-drug combination that costs 1600 SEK per year. During 30 years of treatment this corresponds to a total medication costs of 48 000 SEK in 2012 year's prices. In an American health economy analysis, RDN was estimated to a discounted lifetime incremental cost-effectiveness ratio of \$ 3071 per QALYs (quality-of-life-adjusted life-year), which corresponds to about 20 000 SEK.

Concluding remarks: Renal sympathetic denervation is a catheter-based endovascular technique for patients with uncontrolled therapy resistant hypertension. It reduces blood pressure and left ventricular hypertrophy significantly (GRADE ⊕⊕OO), and improves insulin sensitivity (GRADE ⊕OOO). It is uncertain whether it affects renal function. Even though follow-up data for more than two years are still lacking, present data suggest that the technique may be safely used, and may be a valuable treatment alternative for patients with therapy resistant hypertension.

Andersson, B. and J. Spaak (2013). Utredning av terapiresistent hypertoni och indikation för renal denervering: rekommendationer från svenska arbetsgruppen för renal denervering. Göteborg, Svenska arbetsgruppen för renal denervering inom Svensk förening för hypertoni, stroke och vaskulär medicin.

Brandt, M. C., F. Mahfoud, et al. (2012). "Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension." *J Am Coll Cardiol* **59**(10): 901-909.

**OBJECTIVES:** This study investigated the effect of catheter-based renal sympathetic denervation (RD) on left ventricular hypertrophy (LVH) and systolic and diastolic function in patients with resistant hypertension. **BACKGROUND:** LVH and diastolic dysfunction are associated with elevated sympathetic activity and increased morbidity



and mortality. The effect of RD on LVH and LV function is unclear. **METHODS:** Forty-six patients underwent bilateral RD, and 18 patients served as controls. Transthoracic echocardiography was performed at baseline, and after 1 month and 6 months. **RESULTS:** Besides reduction of systolic and diastolic blood pressure (-22.5/-7.2 mm Hg at 1 month and -27.8/-8.8 mm Hg at 6 months,  $p < 0.001$  at each time point), RD significantly reduced mean interventricular septum thickness from 14.1 +/- 1.9 mm to 13.4 +/- 2.1 mm and 12.5 +/- 1.4 mm ( $p = 0.007$ ), and LV mass index from 53.9 +/- 15.6 g/m(2.7) (112.4 +/- 33.9 g/m(2)) to 47.0 +/- 14.2 g/m(2.7) (103.6 +/- 30.5 g/m(2)) and 44.7 +/- 14.9 g/m(2.7) (94.9 +/- 29.8 g/m(2)) ( $p < 0.001$ ) at 1 month and 6 months, respectively. The mitral valve lateral E/E' decreased after RD from 9.9 +/- 4.0 to 7.9 +/- 2.2 at 1 month and 7.4 +/- 2.7 at 6 months ( $p < 0.001$ ), indicating reduction of LV filling pressures. Isovolumic relaxation time shortened (baseline 109.1 +/- 21.7 ms vs. 85.6 +/- 24.4 ms at 6 months,  $p = 0.006$ ), whereas ejection fraction significantly increased after RD (baseline: 63.1 +/- 8.1% vs. 70.1 +/- 11.5% at 6 months,  $p < 0.001$ ). No significant changes were obtained in control patients. **CONCLUSIONS:** Besides the known effect on blood pressure, our study showed for the first time that RD significantly reduces LV mass and improves diastolic function,



which might have important prognostic implications in patients with resistant hypertension at high cardiovascular risk.

Dorenkamp, M., K. Bonaventura, et al. (2013). "Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension." Eur Heart J **34**(6): 451-461.

**AIMS:** Recent studies have demonstrated the safety and efficacy of catheter-based renal sympathetic denervation (RDN) for the treatment of resistant hypertension. We aimed to determine the cost-effectiveness of this approach separately for men and women of different ages. **METHODS AND RESULTS:** A Markov state-transition model accounting for costs, life-years, quality-adjusted life-years (QALYs), and incremental cost-effectiveness was developed to compare RDN with best medical therapy (BMT) in patients with resistant hypertension. The model ran from age 30 to 100 years or death, with a cycle length of 1 year. The efficacy of RDN was modelled as a reduction in the risk of hypertension-related disease events and death. Analyses were conducted from a payer's perspective. Costs and QALYs were discounted at 3% annually. Both deterministic and probabilistic sensitivity analyses were performed. When compared with BMT, RDN gained 0.98 QALYs in men and 0.88 QALYs in women 60 years of age at an additional cost of euro2589 and euro2044, respectively. As the incremental cost-effectiveness ratios increased with patient age, RDN consistently yielded more QALYs at lower costs in lower age groups. Considering a willingness-to-pay threshold of euro35 000/QALY, there was a 95% probability that RDN would remain cost-effective up to an age of 78 and 76 years in men and women, respectively. Cost-effectiveness was influenced mostly by the magnitude of effect of RDN on systolic blood pressure, the rate of RDN non-responders, and the procedure costs of RDN. **CONCLUSION:** Renal sympathetic denervation is a cost-effective intervention for patients with resistant hypertension. Earlier treatment produces better cost-effectiveness ratios.

Doumas, M. and S. Douma (2010). "Renal sympathetic denervation: the jury is still out." Lancet **376**(9756): 1878-1880.

Esler, M. D., H. Krum, et al. (2010). "Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial." Lancet **376**(9756): 1903-1909.

**BACKGROUND:** Activation of renal sympathetic nerves is key to pathogenesis of essential hypertension. We aimed to assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension. **METHODS:** In this multicentre, prospective, randomised trial, patients who had a baseline systolic blood pressure of 160 mm Hg or more ( $\geq 150$  mm Hg for patients with type 2 diabetes), despite taking three or more antihypertensive drugs, were randomly allocated in a one-to-one ratio to undergo renal denervation with previous treatment or to maintain previous treatment alone (control group) at 24





participating centres. Randomisation was done with sealed envelopes. Data analysers were not masked to treatment assignment. The primary effectiveness endpoint was change in seated office-based measurement of systolic blood pressure at 6 months. Primary analysis included all patients remaining in follow-up at 6 months. This trial is registered with ClinicalTrials.gov, number NCT00888433. FINDINGS: 106 (56%) of 190 patients screened for eligibility were randomly allocated to renal denervation (n=52) or control (n=54) groups between June 9, 2009, and Jan 15, 2010. 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 controls were assessed for the primary endpoint at 6 months. Office-based blood pressure measurements in the renal denervation group reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg,  $p < 0.0001$ ), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg [21/10], baseline of 178/97 mm Hg,  $p = 0.77$  systolic and  $p = 0.83$  diastolic). Between-group differences in blood pressure at 6 months were 33/11 mm Hg ( $p < 0.0001$ ). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls ( $p < 0.0001$ ). We noted no serious procedure-related or device-related complications and occurrence of adverse events did not differ between groups; one patient who had renal denervation had possible progression of an underlying atherosclerotic lesion, but required no treatment. INTERPRETATION: Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients. FUNDING: Ardian.

Gosain, P., P. S. Garimella, et al. (2013). "Renal sympathetic denervation for treatment of resistant hypertension: a systematic review." *J Clin Hypertens (Greenwich)* **15**(1): 75-84.

HealthPACT (2010). Renal sympathetic denervation for the treatment of resistant hypertension. Canberra, Department of Health and Ageing.

Lewington, S., R. Clarke, et al. (2002). "Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies." *Lancet* **360**(9349): 1903-1913.

BACKGROUND: The age-specific relevance of blood pressure to cause-specific mortality is best assessed by collaborative meta-analysis of individual participant data from the separate prospective studies. METHODS: Information was obtained on each of one million adults with no previous vascular disease recorded at baseline in 61 prospective observational studies of blood pressure and mortality. During 12.7 million person-years at risk, there were about 56000 vascular deaths (12000 stroke, 34000 ischaemic heart disease [IHD], 10000 other vascular) and 66000 other deaths at ages 40-89 years. Meta-analyses, involving "time-dependent" correction for regression dilution, related mortality during each decade of age at death to the estimated usual blood pressure at the start of that decade. FINDINGS: Within each decade of age at death, the proportional difference in the risk of vascular death associated with a given absolute difference in usual blood pressure is about the same down to at least 115 mm



Hg usual systolic blood pressure (SBP) and 75 mm Hg usual diastolic blood pressure (DBP), below which there is little evidence. At ages 40-69 years, each difference of 20 mm Hg usual SBP (or, approximately equivalently, 10 mm Hg usual DBP) is associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from IHD and from other vascular causes. All of these proportional differences in vascular mortality are about half as extreme at ages 80-89 years as at ages 40-49 years, but the annual absolute differences in risk are greater in old age. The age-specific associations are similar for men and women, and for cerebral haemorrhage and cerebral ischaemia. For predicting vascular mortality from a single blood pressure measurement, the average of SBP and DBP is slightly more informative than either alone, and pulse pressure is much less informative. INTERPRETATION: Throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.

Merino, A. and M. C. Rozas (2012). Renal sympathetic denervation using endovascular radiofrequency ablation for the management of resistant hypertension. Santiago de Compostela, Galician Agency for Health Technology Assessment (AVALIA-T).

NHS (2012). Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension, National Institute for Health and Clinical Excellence.

Rundqvist, B., S. Völz, et al. (2013). "Kateterbaserad renal denervering: ny metod vid resistent hypertoni. Betydande blodtrycksminskning, visar initiala erfarenheter av ingreppet." Läkartidningen **110**: 86-88.

Witkowski, A., A. Prejbisz, et al. (2011). "Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea." Hypertension **58**(4): 559-565.

Percutaneous renal sympathetic denervation by radiofrequency energy has been reported to reduce blood pressure (BP) by the reduction of renal sympathetic efferent and afferent signaling. We evaluated the effects of this procedure on BP and sleep apnea severity in patients with resistant hypertension and sleep apnea. We studied 10 patients with refractory hypertension and sleep apnea (7 men and 3 women; median age: 49.5 years) who underwent renal denervation and completed 3-month and 6-month follow-up evaluations, including polysomnography and selected blood chemistries, and BP measurements. Antihypertensive regimens were not changed during the 6 months of follow-up. Three and 6 months after the denervation, decreases in office systolic and diastolic BPs were observed (median: -34/-13 mm Hg for systolic and diastolic BPs at 6 months; both  $P < 0.01$ ). Significant decreases were also observed in plasma glucose concentration 2 hours after glucose administration (median: 7.0 versus 6.4 mmol/L;  $P = 0.05$ ) and in hemoglobin A1C level (median: 6.1% versus 5.6%;  $P < 0.05$ ) at 6 months, as well as a decrease in apnea-hypopnea index at 6



months after renal denervation (median: 16.3 versus 4.5 events per hour;  $P=0.059$ ). In conclusion, catheter-based renal sympathetic denervation lowered BP in patients with refractory hypertension and obstructive sleep apnea, which was accompanied by improvement of sleep apnea severity. Interestingly, there are also accompanying improvements in glucose tolerance. Renal sympathetic denervation may conceivably be a potentially useful option for patients with comorbid refractory hypertension, glucose intolerance, and obstructive sleep apnea, although further studies are needed to confirm these proof-of-concept data.