

Effectiveness of Renal Denervation for Treatment of Resistant Hypertension: an Evidence-based Case Report

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ABSTRAK

Tujuan: menentukan efektivitas dari renal sympathetic – nerve ablation dibandingkan dengan penggunaan kombinasi obat anti hipertensi dalam menurunkan hipertensi resisten. **Metode:** pencarian literatur secara terstruktur dilakukan dengan menggunakan PubMed sesuai dengan pertanyaan klinis. Pemilihan artikel dilakukan berdasarkan kriteria inklusi dan eksklusi. Lima artikel yang terpilih kemudian dinilai kualitasnya dengan kriteria yang mencakup validity, importance dan applicability. **Hasil:** salah satu studi menunjukkan tidak efektifnya denervasi renal terhadap penurunan tekanan darah pada pasien dengan hipertensi resisten, namun ke empat studi lainnya menunjukkan hasil yang signifikan. **Kesimpulan:** literatur yang memiliki tingkat bukti yang paling tinggi menunjukkan bahwa tidak ada hubungan antara prosedur renal-sympathetic nerve ablation dan penurunan tekanan darah. Namun, masih ada kelemahan metodologi yang mungkin mempengaruhi hasil sehingga harus dilakukan studi selanjutnya.

Kata kunci: denervasi renal, hipertensi resisten.

ABSTRACT

Aim: to determine whether the renal sympathetic – nerve ablation method is more effective compared to multiple anti – hypertensive drug among patients with resistant hypertension. **Methods:** a search was conducted on PubMed. The selection of title and abstract was conducted using inclusion and exclusion criteria, which led to five relevant articles. The selected studies were critically appraised for its validity, importance and applicability. **Results:** one of studies showed that renal denervation is not effectively reduced blood pressure in patients with resistant hypertension; nevertheless other studies showed significant results. **Conclusion:** literature with strongest evidence showed that there is no relationship between renal sympathetic-nerve ablation procedure and reduction of blood pressure. However, as there is still some methodological flaw on the literature, we recommend doing another study that may find the appropriate results.

Key words: renal denervation, resistant hypertension.

INTRODUCTION

The increasing rate of the aging population in Indonesia leads to an increase in the number of hypertensive patients. In clinical practice, it is estimated that 10% of hypertensive patients are suffering from resistant hypertension. Resistant hypertension is defined as systolic blood pressure that is higher than 140 mmHg even though they consume three maximally tolerated antihypertensive medication class, including diuretics at an appropriate dose.¹ There are many complications of resistant hypertension such as left ventricular hypertrophy, increased incidence of retinal hemorrhage and kidney damages.²

Pharmacological treatment for resistant hypertension is currently available. However, the effectiveness of pharmacological treatment for resistant hypertension is low.³ Many failure of this pharmacological therapy is mainly attributed to low-adherence of pharmacological therapy. In which patient do not realize the seriousness of this asymptomatic disease and do not consume anti-hypertensive drug routinely.³ New approach in form of therapeutic intervention may be needed.

Renal denervation is based on a hypothesis that essential hypertension is caused by an elevated rate of norepinephrine spillover, the number of norepinephrine that is not taken by neuronal uptake and distributed to general circulation.⁴ The first proof-of-concept experiment involving ablation of sympathetic nerve was done by Schlaich in 2009. This experiment reduced blood pressure from 161/107 mmHg to 127.81 mmHg.⁵

CASE ILLUSTRATION

A 57 years old man came to our clinic for a general medical check up. He did not have an any complaints. However, during physical examination we found that his blood pressure is 152/94. From his medical records, he has consumed three different hypertensive drugs: captopril 25 mg 3 times a day, hydrochlorothiazine 25 mg twice a day and amlodipine 10 mg once a day. At first, we thought that this patient has a compliance problem. However, his wife reassured us that he was compliant in consuming his anti-hypertensive drugs. Having heard renal denervation procedure that can reduce blood

pressure in patient with resistant hypertension, we were wondering whether this procedure can be done in patient.

CLINICAL QUESTION

In a population with resistant hypertension, does renal sympathetic-nerve ablation effective in reducing blood pressure compared to people that only get combined- anti-hypertensive drugs?

METHODS

A search of PubMed® was performed on May 29th, 2014 using the key words “renal denervation”, “resistant hypertension”, “treatment” with its synonyms and related terms. (**Figure 1**) A search Cochrane® was also attempted using the same key words. The results were not included since only 2 articles were found, which were already on the PubMed® list.

Search strategy, results, the inclusion and exclusion criteria are shown in the flowchart. They were articles on clinical trials, systematic reviews, published within 5 years, and performed on humans. After literature selection, critical appraisal was done using several aspect based on Center of Evidence-Based Medicine, University of Oxford for therapy study (**Table 1** and **Table 2**).

RESULTS

This evidence-based case report will review the effectiveness of renal denervation in reducing blood pressure of patients with resistant hypertension. The primary endpoint was reduction of blood pressure compared to baseline at 6 months follow-up.

From the search criteria mentioned above, 13 journals met the inclusion and exclusion criteria. Through further selection process, five studies, which included two RCTs, two cohorts, and one systematic review, were eligible for this evidence-based case report. All included trials were appraised for its validity and relevance (**Table 1** and **Table 2**). The summary of all included studies are depicted in **Table 3**.

Four articles discussed populations with resistant hypertension while Ott et al investigated patients with moderate-resistant hypertension.



Figure 1. Flow chart of search strategy

Table 1. Critical appraisal of the 10 studies based on criteria by centre of evidence medicine University of Oxford

Articles	Year	study design	number of patients	Validity					Relevance				
				randomization	similarity treatment & control	blinding	comparable treatment	intention to treat	domain	determinant	measurement of outcome	levels of evidence*	
Bhatt et al ⁶	2014	RCT	535	+	+	+	+	+	+	+	+	+	2
Krum et al ⁷	2014	cohort	88	-	-	-	+	-	+	-	-	+	3
Ott et al ⁸	2013	cohort	54	-	+	-	+	+	-	-	-	+	3
Esler et al ⁹	2010	RCT	106	+	+	-	+	-	+	+	+	+	2

+ stated clearly in the article; - not being done; ? not stated clearly; * levels of evidence based on The Oxford Center of Evidence Based Medicine 2011

Table 2. Critical appraisal of a systematic review

Authors	Validity					Level of evidence
	PICO	Appropriate searching	Relevant study included	Quality assessment of trials	Heterogeneity	
Davis et al ¹⁰	+	+	+	+	+	3

Based on the literature, resistant hypertension is defined as systolic blood pressure of at least 160 mmHg, to be taking maximally tolerated doses, one of which had to be a diuretic at an optimum dose, while moderate-resistant hypertension is defined as office BP \geq 140/90 mmHg and

<160/100 mmHg with at least 3 anti-hypertensive drugs, including a diuretic, in adequate dose.⁶⁻¹⁰ Studies by Bhatt et al, Esler et al, Ott et al, and Davis et al had a follow-up period for 6 months, whereas Krum et al assessed the trials for 36 months.

Table 3. Results of all studies

Author	Primary Endpoint	Result	Summary
Bhatt et al ⁶	Reduction of blood pressure compared with baseline at 6 months	Decrease in SBP* of -14.13±23.93 mmHg in the denervation group compared to -11.74 25.94 mmHg in the sham procedure group, p = 0.26 between those group. Change in 24-hour ambulatory SBP was -6.75±15.11 mmHg in the denervation group compared to -4.79±17.25 mmHg in sham-procedure group. P = 0.98	Reduction of blood pressure after 6 months post-renal denervation in this study is neither clinically significant nor statistically significant.
Krum et al ⁸	Reduction of blood pressure from baseline within 36 months	Mean reduction (95% CI) in systolic and diastolic blood pressure from baseline, p=0.01: <ul style="list-style-type: none"> • 1 month → SBP: -18.9 (-22.1 to -15.7) mmHg, DBP* -9.4 (-11.4 to -7.4) mmHg. • 6 months → SBP: -22.0 (-25.7 to -18.4) mmHg, DBP -10.2 (-12.4 to -7.9) mmHg. • 12 months → SBP: -26.5 (-30.2 to -22.8) mmHg, DBP -13.5 (-15.9 to -11.1) mmHg. • 24 months → SBP: -28.9 (-33.5 to -24.4) mmHg, DBP -14.0 (-16.9 to -11.1) mmHg. • 36 months → SBP: -32.0 (-35.7 to -28.2) mmHg, DBP -14.4 (-16.9 to -11.9) mmHg 	Significant reduction of blood pressure of blood pressure within 36 months.
Ott et al ⁸	Blood pressure reduction in moderate hypertension patient after 6 months post renal denervation therapy	<ol style="list-style-type: none"> 1. Office BP <ul style="list-style-type: none"> • At baseline in 54 patients: Systolic (151 ± 6 mmHg), Diastolic (83 ± 11 mmHg) • Three months post RDN: Systolic (146 ± 23 mmHg, p = 0.164), Diastolic (79 ± 12 mmHg, p = 0.011) • Six months post RDN: Systolic (138 ± 21 mmHg, p < 0.001); Diastolic (75 ± 11 mmHg, p < 0.001) 2. 24-h ABPM (n = 36) <ul style="list-style-type: none"> • at baseline: Systolic (151 ± 5 mmHg); Diastolic (84 ± 10 mmHg) • - Three months post RDN: Systolic (142 ± 20 mmHg, p = 0.012); Diastolic (79 ± 11 mmHg, p = 0.003) • - Six months post RDN: Systolic (133 ± 19 mmHg, p < 0.001); Diastolic (75 ± 11 mmHg, p < 0.001) 	Significant reduction of office and 24 – h ambulatory BP in patients with moderate treatment of resistant hypertension after 6 months post RDN.
Esler et al ¹⁶	Reduction of blood pressure compared to non treated patient with baseline at 6 months	<ol style="list-style-type: none"> 1. 3 months: therapy group → Office BP was reduced from baseline by 32/12 mm Hg (SD 23/11, p<0.0001). Control group → Office BP was reduced from baseline by 1/0 mm Hg [21/10], p=0.77 systolic and p=0.83 diastolic) 2. 6 months: Reduction of SBP at least 10 mmHg in therapy group (84%) compared to control group (35%) (p<0.0001) 	Reduction of blood pressure of blood pressure after 6 months. This randomised controlled trial is statistically significant
Davis et al ¹⁰	Reduction of blood pressure in controlled and uncontrolled studies at 6 months	<ol style="list-style-type: none"> 1. 12 studies included: 4 controlled studies, uncontrolled studies 2. MA* of controlled study showed significant decrease in both systolic and diastolic blood pressure (SBP and DBP): Mean difference of SBP at 3 month follow-up → -20.82 (95%CI -26.41, -15.24). Mean difference of SBP at 6 month follow-up → -28.90 (95%CI -37.20, -20.60) 3. MA of uncontrolled studies also showed significant decrease in both SBP and DBP: Mean difference of SBP at 3 month follow-up → -22.79 (95%CI -26.83, -18.76). Mean difference of SBP at 6 month follow-up → -25.01 (95%CI -29.92, -20.09) 	Renal denervation therapy resulted in substantial reduction in mean BP at 6 months in patient with resistant hypertension

*Abbreviations: ABPM (Ambulatory Blood Pressure Monitoring); SBP (Systolic Blood Pressure); DBP (Diastolic Blood Pressure); MA (Meta Analysis)

Study by Bhatt showed no significant reduction of blood pressure in post renal denervation therapy, however, other studies concluded the contrary results.⁶⁻¹⁰

DISCUSSION

Since the inception of renal denervation, this method has been hailed as a novel way to combat resistant hypertension.⁴ It is a relatively new finding, in which proof of concept study was done in 2009 by Schlach.⁵ Even though it is a relatively new study, as many as 4 RCT and cohort studies and one systematic reviews (**Table 2**) were found in this topic. This may be caused by high prevalence and morbidity that may be caused by resistant hypertension.²

From five studies that we analyzed in this EBCR, we found two cohorts and one RCT that found that renal denervation procedure effectively reduce both systolic and diastolic blood pressure. The reduction of systolic blood pressure ranged from 10 mmHg to 32 mmHg.^{7,8} Whereas the reduction of diastolic blood were more modest ranged from 10 mmHg to 17 mmHg.^{7,11} Two studies showed decreased blood pressure of >10mmHg however both these studies were more aimed at the safety hence limited number of participant and heterogeneity and no randomization performed.^{12,13}

One study that begs to differ from the consensus is done by Bhatt et al.⁶ This study found renal denervation did not significantly reduced blood pressure. The different conclusions between these studies were explained by superior methods that were applied by Bhatt et al.⁶ This study has the most number of patients, which were 535. In this study, we found randomization between treatment and control groups, which are lacking in all other studies. In addition, Bhatt et al used sham procedure as control in this study.⁶ Even though many researchers consider sham surgery as unethical, it is found to be more effective in testing effectiveness of procedure by performing randomized comparison.¹⁴

There are several reasons that may explain the results of the clinical trial that is conducted by Bhatt et al.¹⁵ The first explanation is that renal denervation may not be effective in human. As mentioned before, this study is the most rigorous

study that have been conducted in analyzing the efficacy of renal denervation. There may be regression-to-the-mean phenomenon that can be observed in this large sample.¹⁶ The second possible explanation is the lack of statistical power in this trial. This study's sample size is calculated based on previous study that may have overestimated clinical effect of renal denervation. This overestimation may be possible because of different baseline characteristics with other studies that have been discussed in this article: in Bhatt et al paper, the baseline hypertension in this study is 159.1 mmHg in denervation group and 159.5 mmHg in sham group. Different from other studies that have baseline blood pressure of 180 mmHg in other studies. There is evidence that renal denervation is much more effective in higher baseline blood pressure.¹⁶ The third reason is doubt that the procedure can be performed effectively in Bhatt et al trial. In this paper, it is stated that there are 88 centers of study with 535 patients participated in this trial.¹⁵ As in the supplementary section of the study it is said that all of the cardiothoracic surgeon that participated in this trial have no previous experience in doing renal denervation.^{15,16} It is likely that this procedure were not done properly. Moreover, there are no tools to assess whether renal nerve destructions has already happened. The fourth reason is the high consumption rate of vasodilators in this study.^{16,17} Vasodilators are found to be a predictor for non-response in renal denervation procedure.¹⁷

For the patient in case illustration, we cannot yet recommend renal denervation to solve his persistent high blood pressure. Even though all of the studies were conducted in patients with similar characteristics to the case: high blood pressure that is resistant with at least three drugs that includes thiazide, the lack of single conclusion between these studies prevent us to recommend this procedure. Moreover, the study that has different results was superior in term of methodology.

In addition, safety of this procedure and long-term effect of renal denervation procedure on kidney function must be also considered. Even though individual trials have explored safety profile of renal denervation procedure. A more

robust systematic review must be implemented to find the definitive results.¹⁸

Currently, renal denervation is available at the National Cardiovascular Center, Harapan Kita and Hasan Sadikin Hospital, Bandung. However, it is not yet available to the general public. So, we do not know the economical cost of this procedure in Indonesia. An analysis by Geisler et al on the cost-effectiveness of renal denervation procedure may give us some glimpse on the cost of renal denervation.¹⁹ In the analysis, the cost of renal-denervation procedure costs Rp 150.000.000,00 (assuming that 1 US\$=Rp 12.000,00) compared to Rp 10,416,000,00 of yearly combined antihypertensive drugs. According to the economic model, the cost of this procedure is US\$ 3,071 per quality-adjusted-life year.¹⁹ This expensive procedure may limit the applicability of this procedure in Indonesian society.

We should also consider genetic variations that may influence the results. A study by Dimsdale et al found that there's a significant racial difference between race and it's vascular response to norepinephrine. In this study, we found that blacks are more sensitive to autonomic nervous system changes compared to whites.²⁰ No study has found the comparison of autonomic changes in Asian population compared to white which is the subject of this research. However, as study from Asian-American showed that ACE inhibitor is less effective compared to calcium channel blocker, renal denervation may be less effective in Asian population compared to white.²¹

CONCLUSION

In conclusion, results of studies concerning the practice of renal denervation on patient with resistant hypertension are inconclusive. Randomized trials with large number of participants with intention-to-treat analysis of data will be required before an evidence-based recommendation can be provided on the benefits of this procedure.

RECOMMENDATION

As there's still conflicting results on the efficacy of renal denervation procedure we should conduct other randomized controlled trials. The trial that we recommend should be:

- Has experienced operator, which at least have done twenty renal denervation procedure
- Has clear method to measure success of renal denervation procedure
- Baseline in lower range of blood pressure: 150-160 mmHg
- Revise calculation of sample size
- Reduce the consumption of vasodilator drug in the treatment group

REFERENCES

1. Sarafidis PA, Georgianos P, Bakris GL. Resistant hypertension: Its identification and epidemiology. *Nat Rev Nephrol.* 2013;9(1):51-8.
2. Cuspidi C, Magga G, Sampireri L, et al. High prevalence of cardiac and extracardiac target organ damage in refractory hypertension. *J Hypertens.* 2001;19(11):2063-70.
3. Pantelis A, Bakris G. Resistant hypertension: An overview of evaluation and treatment. *J Am Coll Cardiol.* 2008;52(22):1749-57.
4. Schlaich MP, Lambert E, Kaye DM, et al. Sympathetic augmentation in hypertension: Role of nerve firing, norepinephrine reuptake, and angiotensin neuromodulation. *Hypertension.* 2004;43(2):169-75.
5. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. *New Engl J Med.* 2009;361(9):932-4. PubMed PMID: 19710497.
6. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *New Engl J Med.* 2014;370(15):1393-401. PubMed PMID: 24678939. Epub 2014/04/01. eng.
7. Krum H, Schlaich MP, Sobotka PA, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet.* 2014;383(9917):622-9. PubMed PMID: 24210779. Epub 2013/11/12. eng.
8. Ott C, Mahfoud F, Schmid A, et al. Renal denervation in moderate treatment-resistant hypertension. *J Am Coll Cardiol.* 2013;62(20):1880-6. PubMed PMID: 23850901. Epub 2013/07/16. eng.
9. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet.* 2010;376(9756):1903-9. PubMed PMID: 21093036. Epub 2010/11/26. eng.

10. Davis M, Filion K, Zhang D, et al. Effectiveness of renal denervation therapy for resistant hypertension. *J Am Coll Cardiol*. 2013;62(3):231-41.
11. Worthley SG, Tsioufis CP, Worthley MI, et al. Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnlighHTN I trial. *Eur Heart J*. 2013;34(28):2132-40. PubMed PMID: 23782649. Pubmed Central PMCID: 3717311. Epub 2013/06/21. eng.
12. Ormiston JA, Watson T, van Pelt N, et al. Renal denervation for resistant hypertension using an irrigated radiofrequency balloon: 12-month results from the Renal Hypertension Ablation System (RHAS) trial. *Euro Soc Cardiol*. 2013;9(1):70-4. PubMed PMID: 23685297. Epub 2013/05/21. eng.
13. Damascelli B, Patelli G, Ticha V, et al. Catheter-based radiofrequency renal sympathetic denervation for resistant hypertension. *J Vasc Inter Radiol*. 2013;24(5):632-9. PubMed PMID: 23622036. Epub 2013/04/30. eng.
14. Kim S, Frank S, Holloway R, Zimmerman C, Wilson R, Kleburtz K. Science and ethics of sham surgery: A survey of Parkinson disease clinical researchers. *Arch Neurol*. 2005;62(9):1367-0.
15. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *New Engl J Med*. 2014;370(15):1393-401. PubMed PMID: 24678939.
16. Lüscher TF, Mahfoud F. Renal nerve ablation after SYMPPLICITY HTN-3: confused at the higher level? *Euro Heart J*. 2014.
17. Laurent S, Schlaich MP, Esler M. New drugs, procedures, and devices for hypertension. *Lancet*. 2012;380:591-600.
18. Krum H, Schlaich MP, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373(9671):1275-81.
19. Geisler B, Egan B, Cohen J, et al. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. *J Am Coll Cardiol*. 2012;60(14):1271-7.
20. Dimsdale JE, Graham RM, Ziegler MG, Zusman RM, Berry CC. Age, race, diagnosis, and sodium effects on the pressor response to infused norepinephrine. *Hypertension*. 1987;10(6):564-9.
21. Jamerson K, DeQuattro V. The impact of ethnicity on response to antihypertensive therapy. *Am J Med*. 1996;101(3 Suppl 1):22S-32S.