Journal of College of Medical Sciences-Nepal, 2012, Vol-8, No-2, 58-63 *Review Article*

Catheter based renal sympathetic denervaton: treatment option for resistant hypertension

B. M Dhital[1], Ou Yang Mao[1], J. P. Deep[2], V. K. Rauniyar[2]
[1]Third Xiangya Hospital. [2]First Xiangya hospital of Central South University, China

ABSTRACT

Essential hypertension being a major public health problem with an atrocious toll. Furthermore resistant hypertension has increased morbidity and mortality in spite of using three or more antihypertensive medication, including one diuretic at their optimal doses to achieve the target blood pressure. Renal artery with its sympathetic afferent and efferent nerve signaling has substantial role in elevating and sustaining blood pressure. Blunting the overt sympathetic activity, catheter based renal sympathetic nerve denervation has become new treatment approach for the treatment of resistant hypertension. So in this review we address the current aspect and development of renal sympathetic denervation in the management of difficult to control hypertension.

Key words: antihypertensive medications, afferent nerve, efferent nerve, renal sympathetic nerve.

Introduction

Hypertension representing a global disease has enormous morbidity and mortality leading to extra burden for worldwide health care system. Despite of many efforts in controlling and preventing the most common killer disease, there has been increasing prevalence in the developed and developing countries.[1] Hypertension and its related conditions like stroke, coronary artery disease, heart failure, and chronic kidney disease are rising despite of optimal management. Resistant hypertension defined as the uncontrolled hypertension (systolic blood pressure e" 160) in spite of using three antihypertensive medication including one diuretics at their maximum and tolerated dosages. Many factors, patient adherence, polypharmacy, doctor's inertia and secondary causes should be ruled out before tagging resistant hypertension. One of the study documented 18% to 27% patients with difficult to control hypertension has been treated with less than three antihypertensive medications.[2] Even though the treatment modalities like life style modification, DASH diet and antihypertensive medications are used but still the prevalence of resistant hypertension is about 5% to 15%.[3,4] To address these patients, their morbidity and mortality, renal sympathetic denervation is new treatment modality for the resistant hypertension.

Correspondence: B. M Dhital
E-mail: bishnumd@hotmail.com

History

It has been seen from preclinical and clinical experiments that renal sympathetic nerve activity play vital role in the hypertension and its complications. Since 1930 therapeutic splanchnicectomy and radical

sympathectomy were used for the treatment of hypertension. Dropping of the blood pressure was achieved but with enormous preoperative and long term complications like postural hypotension, orthostatic tachycardia, palpitation, anhidrosis, breathlessness, atelectasis, bowel, bladder, erectile dysfunction[5,6]attributed to non-specific sympathetic denervation of the viscera and lower extremity vasculature. Along with blood pressure decrease, drug sensitivity was also increased in about half of these patients undergoing procedure. [7] In the era of hypertensive drugs these procedures were only preserved for those not responding and tolerating these medications. Development of the renal sympathetic denervation from the concept of the old procedure has been milestone in the intervention for the treatment of resistant hypertension.

Pathophsiology

It has been widely accepted that the symapathetic over activity is the leading cause of essential hypertension and its complex pathophsiology yielding heart failure, progressive renal disease. [8,9] This neurogenic hypertension mostly depends upon the renal afferent and efferent sympathetic nerves stimulation and the flooding of norepinephrine in the blood circulation from the nerve endings. Activation of renin agiotensin aldosterone system starts with minimal frequency of stimulation of sympathetic nerves in the juxtaglomerulus cell and with the increment of the frequency less excretion of sodium from the renal tubules, finally higher frequency of stimulation leads to vasoconstriction in the small, resistance vessels with decrease in renal blood flow and glomerular filtration rate via smooth muscle present in the vessel wall.[10]Then the clinical scenario like hypertension, chronic kidney disease (vasoconstriction lead small vessel injuries), edema, heart failure ensues.

Afferent sympathetic nerve

The origin of afferent sympathetic nerves from the renal pelvic wall which are confined with mechanoreceptors and chemoreceptors, respond to stretch and ischemia respectively. Different kind of stimulus contributing renal pathology are the triggering factors for afferent sympathetic activity.[11]Ascending limb of afferent nerve makes its way from pelvis to renal root ganglia and finally to the central nervous system where there is production of vasopressin and oxytocin from the pituitary gland and then evoke central sympathetic response.[12,13] The sole pathophsyiology depends upon the activation afferent sensory fibers which in turn form a viscous cycle with overt sympathetic output from brain to kidneys, heart and blood vessels. Ablating this circuit can control the hypertension with decreasing its related diseases and their complications like coronary artery disease, left ventricular hypertrophy, sudden cardiac death, strokes and end stage renal disease.[14,15]

Efferent sympathetic nerve

Network of efferent sympathetic nerve begins from thoracic and lumbar sympathetic trunk merging into vertebral sympathetic ganglion, and lastly the post ganglion fiber emerge as renal efferent sympathetic nerve which innervates the juxtaglomerulus apparatus, renal tubules and the blood vessels of the kidney. These three components play vital role in the genesis of the hypertension with overt sympathetic outflow via central nervous system is seen diseased state with overproduction of renin and decrease in sodium excretion, blood flow and GFR in the kidney. So to overcome and break this pathophsyiology, renal

sympathetic denervation is in experimental and clinical trial to treat the essential resistant hypertension.

Percutaneous catheter based renal artery sympathetic denervation

Treatment goal of hypertension is to prevent end organ damage and reduce the cardiac morbidity and mortality. Antihypertensive drugs with lifestyle modification and low sodium, high potassium diet are the first line treatment for the arterial hypertension but if it fails to control the sympathetic drive than the catheter based therapy seems to have good results in ablating the circuit between afferent, efferent nerves in kidney and central nervous system. This novel and newly developed procedure mainly has a catheter connected to radiofrequency generator which is introduced in renal arteries with the percutaneous approach from the femoral artery. Angiography is done to define the anatomy of the renal vessels and the catheter (Symplicity™, Ardian/Medtronic Inc., California, USA) guided to renal artery with the help of DSA (digital substraction angiography) and 3D mapping system (eg. Carto, en site). Ablation of sympathetic nerve fibers in adventia of renal arteries, lasting ≤ 2min in 4 to 6 different longitudinal and rotational positions, distal to proximal site, is done using 50 to 70 degree Celsius by means of high-frequency (maximum 6-8 W) energy. Simplicity HTN-1 and HTN-2 are studies to proof the safety and efficacy of the procedure.

The simplicity HTN-1 study

The pioneer of the catheter based treatment of hypertension introduced simplicity HTN-1 study including 45 number of hypertensive patient at the beginning and later extended follow up of 153. Criteria to be adopted before a patient can be considered for interventional renal denervation were (a) Office systolic blood pressure e" 160 mm Hg (e"150 mm Hg for patients with diabetes mellitus type 2). (b) Intake of 3 antihypertensive substances (true resistance in patients with good compliance).(c) Exclusion of secondary causes of hypertension. (d) Normal or only slightly reduced renal function (estimated glomerular filtration rate e" 45 mL/min/1.73 m^2). (e) Suitable renal artery anatomy: no previous renal artery interventions, no significant stenosis or other abnormalities of the renal arteries. In this proof of principal trial, the patients (n-45) were on three or more anti hypertensive medications (average 4.7) including diuretics and have mean blood pressure 177/101 mmHg. Efficacy in lowering BP and long term safety of the procedure were the two primary end points, similarly post procedural renal functions test and norepinephrine spill over were considered as secondary endpoints. Measurements of blood pressure done at 1, 3, 6, 9 and 12 months after study showing significant decrease in blood pressure by 14/10, 21/10,22/11, 24/11 and 27/17 mmHg respectively, similarly at more than 24 months, the extended group in their follow up have significant decrease in their blood pressure .[16,17] . Additionally the reduction of blood pressure (-33/-19 mmHg) was seen in 3 years follow up (updated in march, 2012 ACC Scientific Sessions) with no late procedural safety events, and 100% patients has been classified as responders (>10mmHg reduction in blood pressure), while at 6 months of study there were only 71% responders. To proof the safety of the study renal angiography was done pre, post and at one moth of the procedure to rule out any dissection, aneurysm, pseudo aneurysm and stenosis. Among 45 Patients, two suffered complications, one having renal artery dissection and other pseudo aneurysm at the femoral

access site, during the procedure. Further at 6 months follow up Magnetic resonance angiography have good results advocating the safety of study. Considering secondary endpoints norepinephrine spill over was decreased by 75% and 48% from right and left kidney respectively. There was significant blood pressure reductions (22/12) at six months compared with the whole body norepinephrine spill over decline by 47% (n-10) giving the insight of low sympathetic activity playing a vital role in the essential hypertension. The major limitations of this study were small sample size, lack randomization and placebo control group, no proper and strict recruitment criteria, no ambulatory blood pressure monitoring, and secondary hypertension has not been ruled out. In spite of these restrictions, this innovative study safely and effectively lowerd the resistant blood pressure without any serious complications in its follow up.

The simplicity HTN-2 study

The next catheter based renal sympathetic denervation study was the simplicity HTN-2, which was multicenter, randomized, prospective trial with control group conforming the previous study .Out eligible 190 patients ,those with resistant hypertension (systolic blood pressure ≥160 mmHg and with diabetes mellitus type 2 ≥ 150mmHg), 106 were randomized to renal denervation (n=52) or control (n=54) group. The baseline mean systolic blood pressure was 178/96 mmHg in spite of taking antihypertensive medication (mean=5.2). After six month of the study the denervation group had significantly decreased the blood pressure by 32/12 mmHg (P<0.0001), while the control group blood pressure did not differ from the baseline.[18] similarly 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10mmHg or more, compared with 18 (35%) of 51 controls (P <.0001). Office, home, ambulatory blood pressure and the dosage, number of antihypertensive medication were also decrease in denervated group at 6 months and later extended follow up. Similarly, average blood pressure reduction of (-28/-10 mmHg) was sustained to 12 months in extended follow up the previous study (updated in march, 2012 ACC Scientific Sessions). In terms of these findings, this study supports the previous proof of principal study. Out 52 patients who underwent catheter denervation, seven have intraprocedural bradycardia relieved by atropine, one femoral artery pseudoaneurysm, one urinary tract infection, one post procedural blood pressure drop, one case of back pain, and one parasthesias. Renalfunctions test (assessed by serum creatinine, estimated glomerular filtration rate, cystatin-C concentration and albumin-to creatinine ratio) and angiogram (to rule out stenosis ≥ 60% of occlusion) done at six months showed no statically significant change with control group supporting the post procedural long term safety. In this study, no procedural related serious complications were observed but some patients in follow up have some serious adverse events including angina, transient ischemic attack, hypertensive and hypotensive episodes, nausea and edema, and were managed staying with the guidelines. The occurrence of adverse events didn't differ between the groups. Even though every procedure has its drawbacks, but outcome in terms of lowering blood pressure was remarkable. Again the limitations were small small size, short 6 months follow up period (later extended to 12 months), more percentage of males, high rate of diabetes and coronary artery disease, included in denervated group compare to control group.

Discussion

So for the two studies showed renal sympathetic denervation has promising outcome in term of blood pressure reduction, safety and efficacy. Renal afferent fibers along with sympathetic fibers are mainly ablated, and pain during the procedure indicates affarent C fibers to CNS were injured with high frequency energy. The reduction in blood pressure in 6, 12 and 34 months of study also proved that no regeneration and growth of ablated nerve fibers with no activation of barorecptor reflex which were the main pathophsyiological mechanism of the essential hypertension. Recently the new concept of device therapy for resistant hypertension are in clinical trial in which the baro receptor stimulation of the afferent leads to activate the parasympathetic fibers of the vagus nerve are used to control the blood pressure with lowering the heart rate, but the endpoints for procedural safety and acute phase response were not achieved.[19] Over sympathetic drive is related to the component of metabolic syndrome, and the insulin resistance has been improved with decrease in glucose and insulin concentration, at the mean time increase in insulin sensitivity has been observed with the renal sympathetic denervation,[20]which can add additional benefit in treatment of resistant hypertension with diabetes mellitus Type 2. Similarly, the catheter based treatment might be useful in other disease having overt sympathetic activity like chronic heart failure, end stage renal disease, cardiorenal syndrome, liver failure with cirrhosis and ascites.[21]Since catheter based renal sympathetic denervation is innovative new technique having significant safety efficacy profile in lowering the blood pressure needs further large randomized, multicenters clinical trials with longer follow up periods to be practiced as evidence based medicine in every hypertension clinic and higher referral cardiac centers .The future is not so far when essential hypertensive patients can be cured and the resistant hypertension can be easily controlled with this novel intervention.

References

1. P.M. Kearney, M. Whelton, K. Reynolds et al. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365**: 217–23.

2. J. Amar, B. Chamontin, N. Genes et al. Why is hypertension so frequently uncontrolled in secondary prevention? *J Hypertens* 2003;**21**: 1199–205.

3. D. Wojciechowski, V. Papademetriou, C. Faselis et al. Evaluation and treatment of resistant or difficult to-control hypertension. Journal of Clinical Hypertension. 2008; **10**: 837–43.

4. D.A. Calhoun, D. Jones, S. Textor. et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee ofthe Council for High Blood Pressure Research. Circulation 2008; **117**: 510–26.

5. D.M. Morrissey, V.S. Brookes, W.T. Cooke. Sympathectomy in thetreatment of hypertension: Review of 122 cases. *Lancet*.1953;**1**: 403–8.

6. K.A. Evelyn, M.M. Singh, W.P. Chapman et al. Effect of thoracolumbar sympathectomy on the clinical course of primary (essential) hypertension. A ten-year study of 100 sympathectomized patients compared with individually matched, symptomatically treated control subjects. *Am J Med*. 1960;**28**: 188–221.

7. R.H. Smithwick. Hypertensive vascular disease: Results of and indications for splanchnicectomy. *J Chronic Dis*. 1955; **1**: 477–96.

8. S. Kassab, T. Kato, F.C. Wilkins et al. Renal denervation attenuates the sodium retention and hypertension associated with obesity. Hypertension. 1995; **25**:893– 7.

9. G.F. DiBona , U.C. Kopp. Neural control of renal function. *Physiol Rev*. 1997; **77**: 75–197.

10. M. Esler, G. Jennings, P. Korner et al. Assessment of human sympathetic nervous system activity from measurements of norepinephrine turnover. *Hypertension*, 1988;**11**: 3–20.

11. A. Stella, A. Zanchetti. Functional role of renal afferents. Physiological Reviews. 1991; **71**: 659–82.

12. J. Ciriello. Afferent renal inputs to paraventricular nucleus vasopressin and oxytocin neurosecretory neurons. *Am J Physiol*. 1998; **275**: 1745–54.

13. M.M. Caverson, J. Ciriello. Effect of stimulation of afferent renal nerves on plasma levels of vasopressin. *Am J Physiol*. 1987;**252**: 801–7.

14. G.F. DiBona. Sympathetic nervous system and the kidney in hypertension. *Curr Opin Nephrol Hypertens*. 2002;**11**: 197–200.

15. G.F. DiBona. Neural control of the kidney: past, present, and future. *Hypertension*. 2003;**41**: 621–4.

16. H. Krum, M. Schlaich, R. Whitbourn et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009; **373**: 1275–81.

17. Symplicity HTN-1 Investigators: Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension*. 2011; **57**: 911–7.

18. M.D. Esler, H.Krum, P.A. Sobotka et al. Renal sympathetic denervation in patients with treatmentresistant hypertension (the Symplicity HTN-2 Trial): a randomized controlled trial. *Lancet*. 2010; **376**: 1903–09.

19. J.D. Bisognano, G. Bakris, M.K. Nadim et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol*. 201; **58**: 765–73.

20. F. Mahfoud, M. Schlaich, I. Kindermann *et al.* Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation*. 201; **123**: 1940–46.

21. M. Doumas, C. Faselis, V. Papademetriou. Renal sympathetic denervation and systemic hypertension. *Am J Cardiol*. 2010; **105**: 570–6.