Renal Denervation Therapy in a Resistant Hypertensive Patient-Report of First Case in Bangladesh

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Introduction:

Arterial hypertension affects nowadays approximately 25% of the global adult population and its prevalence and consequent health cost is predicted to rise to 1.5 billion hypertensive patients in 2025.[1] There is a linear relationship between blood pressure (BP) values and cardiovascular risk [2,3] and according to a worldwide analysis 7.6 million premature deaths (about of 13.5% of total deaths), 54% of strokes and 47% of events due to ischemic heart disease are attributed to high BP[4]. Most importantly even modest BP reduction is accompanied by significant attenuation of the overall cardiovascular morbidity and mortality, irrespective of the starting BP level.[5–8] Despite appropriate antihypertensive treatment BP goals are not achieved in a large proportion of patients, the so-called resistant hypertensive patients. Percutaneous catheterbased transluminal renal ablation [from now on referred to as renal denervation (RDN)] by delivery of radiofrequency energy is emerging as a new approach to achieve sustained BP reduction in patients with resistant hypertension.[9-12]

Case report:

Mr. X of 52 yrs, a remote smoker, hypertensive, diabetic, hypothyroid with diagnosed case of obstructive sleep apnoea, hailing from Kallyanpur, Dhaka, was presented to us with the complaints of mild headache and sleep disturbance for the last three weeks and consulted with the physician. His BP was found uncontrolled (180/100 mm of Hg) and the medication was adjusted and prescribed to take Losartan potassium 100mg plus Hydrochlorthiazide 12.5mg, Atenolol 100 mg, Amlodipin 5 mg. After three weeks he was reassessed and BP was not under control. Then Amlodipin was increased to 10mg and Prazocin 3mg was added and ask to come after 3week. During the follow up showed no abnormality in renal function. After 3 weeks Spirenolactone was added and still his BP was not under control. Then he was asked for renal denervation therapy which was made available in Bangladesh by this time.

He was diabetic since 1992 and on insulin therapy and hypertensive since 1993 and treated with Amlodipin initially. He developed ischemic stroke with left side weakness in 2007 and he recovered well. He was in hypothyroid state since 2008 and on Levothyroxin replacement.. Sleep apnoea was diagnosed in 2009 and he was on C-PAP therapy regularly. On May 2011 he suddenly developed left sided chest pain and was admitted in private cardiac hospital and CAG done and revealed single vessel disease (LCX 90%) and PCI with stenting was done to LCX with DES.

Procedure:

Preprocedural investigation was normal including thyroid function status and his estimated GFR was 69.83 ml/min/1.73 m^2. Before going into the procedure, we had the advantages of evaluation of

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the renal arteries as we had the renal angiogram CD done about one year back. Otherwise we had to do assessment of renal arteries by doing CT angiogram. The renal arteries were suitable for RDT with length of both arteries > 20mm and diameter was around 5mm. His blood pressure was 155/95 mmHg in the morning of intervention.

After informed consent, the patient was brought to the catheterisation laboratory and premedication is applied intravenously in the presence of an anesthesiologist. As the ablation of the afferent nerves during application of the radiofrequency energy is painful, premedication with Midazolam (5 mg IV) and morphine (3 mg IV) was given. Unfractionated heparin was given 5000U intravenously and activated clotting time was maintained (ACT) of > 250 seconds. Right femoral approach was used. A 6 Fr guiding catheter was introduced and placed in right renal arteries and 100 ìg nitroglycerine was introduced through the guiding catheter before the procedure in order to avoid vasospasm. The Simplicity catheter system was used and ablation was started from distal to proximal direction. The first ablation was done 5 mm proximal to the bifurcation of the renal artery. On the right side we given 4 ablations and the last one was done just after the origin. The catheter was engaged on the left side and 100 ìg nitroglycerine was introduced. On that side we done six ablations were done and the last 2 ablations were done with half strength energy near the origin. Detail information of the ablations were given in the box-1 and 2 and success criteria for ablation (>10% decrease in the resistance) was met in all ablations.

Table-I

Right renal artery ablation protocol

No of ablation	Time(s)	Energy(W)	Temperature	Baseline Resistance(Ù)	Reduction of resistance
1	120	8	65	320	15%
2	120	8	70	310	20%
3	120	8	60	275	25%
4	120	8	65	290	16%

Table-II

Left renal artery ablation protocol

No of ablation	Time(s)	Energy(W)	Temperature	Baseline Resistance(Ù)	Reduction of resistance
1	120	8	55	300	15%
2	120	8	65	315	20%
3	120	8	66	275	25%
4	120	8	66	285	18%
5	60	8	50	265	10%
6	60	8	50	260	10%

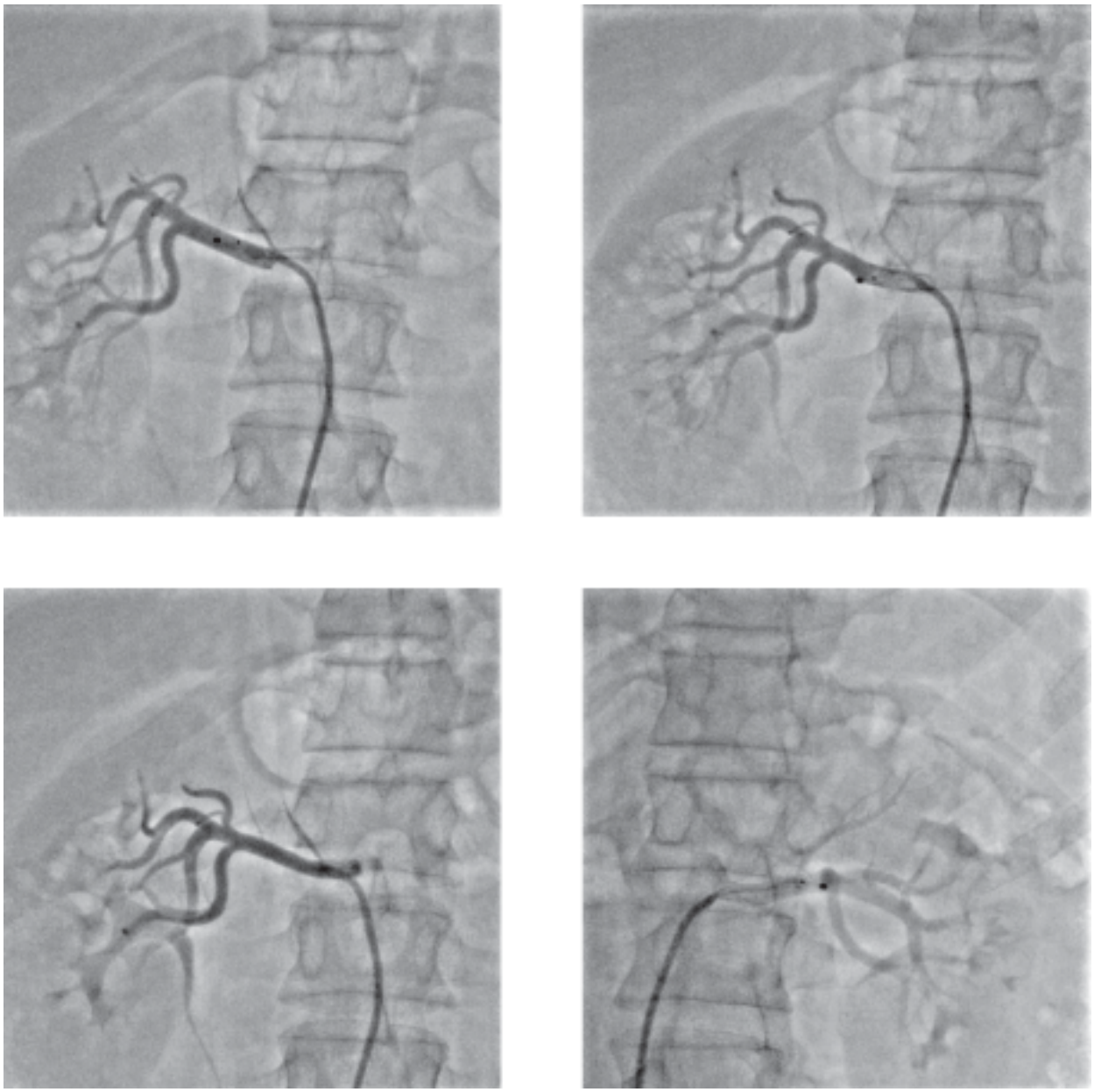

Fig.-: *a. Ablation catheter placed in the right renal artery. b. Catheter positioned in the right renal with appropriate contact c. Right renal artery after completion of ablation. d. First ablation in progress left renal artery. Note the position of the catheter tip just proximal to bifurcation of the renal artery.*

No complication was noted during the whole procedure including no puncture site complication. The patient felt mild pain during ablation and it was managed with adjustment of dose of morphin and midazolam.

Follow up after 2 hours of procedure BP was 110/70 mmHg and after 4 hours it was 140/80mmHg and on the next day BP was 150/90 mmHg. Just after the procedure BP reduced probably due to effects of premedication and it usually needs at least one month for the response of blood pressure following RND therapy.

One month after the procedure, the patient was reasonably well and alphapress was omitted and now his BP was ranges around 130/80 mmHg.

Table-III

Unmet needs in RDN[44]

• Randomized blinded studies
• Use of 24-h ABPM to enroll patients and to assess BP reduction
• Comparison of RDN efficacy and safety when using different procedures
• Long-term maintenance of efficacy and safety
• Impact in morbidity and mortality reduction
• Cost-benefit balance studies
• Standardized certification of RDN centers

Table-IV

Today recommendations[44]

First step: Exclude

- False resistant hypertension (peudoresistance) by using 24 h ambulatory blood pressure monitoring (ABPM) and home BP monitoring.
- Secondary arterial hypertension
- Causes which maintain high BP values and might be removed (obstructive sleep-apnea, high salt intake, BP raising drugs, severe obesity)

Second step:

Optimize antihypertensive treatment with at least three (or better four) tolerated drugs including a diuretic and an antialdosterone drug (if clinically possible, e.g. after re-evaluating renal function and the potential risk of hyperkaliemia) and check for effective BP control using ABPM before giving indication for RND

Third step:

Consider anatomic contraindications due to unresolvesd safety issues (avoid RDN in case of multiple renal arteries, main renal artery diameter of less than 4mm or main renal artery length less than 20mm, significant renal artery stenosis, previous angioplasty or stenting of renal artery). Likewise, eGFR should be > 45 ml/min/1.73m2

Overall:

- Perform the procedure in very experienced hospital centers, such as hypertension excellence centers
- Use devices which have demonstrate efficacy and safety in clinical studies

Discussion:

The Joint National Committee 7 and European Society of Hypertension (ESH)/European Society of Cardiology (ESC) defines resistant hypertension as failure to achieve goal BP (<140/90 mm Hg for the overall population and <130/80 mm Hg for those with diabetes mellitus or chronic kidney disease) when a patient adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic.[5-6] The exact prevalence of resistant hypertension is difficult to determine but depending on the population and the hypertension center considered it ranges from 5 to 30%.[13–16] Failure to reach BP goals despite therapeutic interventions accelerates target organ damage and sets patients at high risk for major cardiovascular events.[5,6,17]

Along these lines, developing additional approaches to the current management of resistant hypertension consisting of lifestyle modification combined with poly-pharmacotherapy is a clinical priority. Within the past year, the innovative method of RDN has progressively entered clinical practice in many countries, for the treatment of

resistant hypertensive patients. The potential for its clinical use is based on the role of sympathetic overactivity in the maintenance of high BP values.

Increased sympathetic activity has been shown to characterize all hypertensive phenotypes including essential hypertension,[18–20] white-coat and masked hypertension,[18,21] associated with either dipping, extreme dipping, nondipping, or reverse dipping conditions.[22] This is also the case for pregnancy-induced hypertension,[23] some secondary types of hypertension[24] and resistant hypertension.[25] Most notably, sympathetic nervous system overactivity involves the kidney[26] and increases progressively and in parallel with hypertension severity stages.[25,27,28] The sympathetic innervation of the kidneys is achieved through a dense network of postganglionic neurons that innervate the kidney.[29,30] The axons of preganglionic neurons exit the thoracic and lumbar sympathetic trunk and reach the pre and paravertebral sympathetic ganglia. Renal postganglionic nerves run alongside the renal artery and enter the hilus of the kidney. Thereafter, they divide into smaller nerve bundles following the blood vessels and penetrate the cortical and juxtamedullary areas. Renal sympathetic nerve activation enhances noradrenaline production and release from nerve endings, leading to renal vasoconstriction, enhanced renin secretion, increased sodium and fluid reabsorption, renal vasoconstriction, and decrease in renal blood flow and glomerular filtration rate.[31]

The cell bodies of renal afferent nerves are located in the ipsilateral dorsal root ganglia (T6-L4). From there, ascending signals travel to the cardiovascular centers in the central nervous system. Renal afferent sensory nerves respond to stretch (mechanoreceptors), renal ischemia, hypoxia or other injury (chemoreceptors) by increasing renal afferent activity.[32–34] Electrical stimulation of afferent renal nerves increases BP[35] and induces mesenteric and muscle vasoconstriction.[35]Conversely, afferent renal denervation attenuates these effects and delays or prevents hypertension in several animal models. [36] Overall afferent and efferent fibers deliver an important contribution to regulation of systemic vascular resistance and BP control.[37]

In the past century, surgical splanchnicectomy that led to renal denervation among others improved survival of hypertensive patients when compared to conservative management available at that time,[38] but the interest in this invasive surgical technique faded quite suddenly with the dawn of effective antihypertensive drug therapy. Renal denervation is a percutaneous procedure, minimally invasive, characterized by short recovery times, and absence of significant systematic side effects. Evidence on the clinical effectiveness of this procedure in hypertensive patients comes from the Symplicity Clinical Trial Program consisting of a group of studies focusing on the effects of RDN in the treatment of resistant hypertension. These trials include the Symplicity Hypertension (HTN)-1 (with etextended follow-up) and the Symplicity HTN-2 study, both already published.[10-12]

This first-in-man proof-of-concept and safety study was Simplicity HTN 1which included 50 patients (mean age 58±9 years) with severe resistant hypertension (office SBP e"160mmHg with at least three or more antihypertensive medications, including a diuretic). Office SBP/DBP values after bilateral RDN were reduced by -14/-10, -21/-10, -22/-11, -24/-11, and -27/-17mmHg at 1, 3, 6, 9 and 12 months, respectively. In a small subset of patients renal noradrenaline spillover was found to be reduced by 47% thereby demonstrating the effectiveness of sympathetic renal fibers ablation. Over a longer-term follow-up of 153 patients, including 45 patients treated with RDN in the frame of Symplicity HTN-1 Study and a larger group of similar patients treated with catheter-based RDN in a nonrandomized manner (mean age 57 years, mean office SBP/DBP 176/98mm Hg in spite of an average of 5.1 antihypertension drugs), office SBP/DBP values were significantly reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14mmHg at 1, 3, 6, 12, 18, and 24 months, respectively. These findings suggest that reduction of BP is sustained at least up to 2 years after the procedure.

The long-term safety of catheter-based RND was investigated in the extended Symplicity HTN-1 cohort (n¼153) in which 97% of patients (149 of 153) had no complications. The four acute procedural complications included three groin

pseudoaneurysms and one renal artery dissection, all managed without further sequelae. In one patient, computed tomography (CT) angiography performed 6 months after the procedure revealed progression of an existing stenosis at the ostium of one renal artery that was successfully treated with stenting. However, the site of the stenosis was not in the area of energy delivery during RDN. Focusing on renal function, during the first year of follow-up, estimated glomerular filtration rate remained stable, and after the 2 years there were no cases of doubling of serum creatinine or of chronic kidney disease stage 4 or 5 development.

Symplicity HTN-2 multicenter, prospective, randomized clinical trial included patients with resistant hypertension and office SBP at least 160 mmHg (or e"150mmHg for patients with type 2 diabetes.[12] Participants were randomly assigned to RDN immediately or after 6 months, without any change in the previous antihypertensive medication regimen. The primary endpoint was change in SBP at 6 months. Out of 190 patients screened for eligibility, 106 were randomized either to immediate RDN (n¼52) or to a delayed performance of the procedure (control group) (n¼54). Both groups had similar baseline characteristics and antihypertensive drug regimen, with the exception of estimated glomerular filtration rate. Office SBP/DBP values in the RDN group decreased by 32/12mmHg (baseline 178/96mmHg, P<0.0001), whereas no changes in the control group occurred. Differences in office SBP/DBP between the two groups at 6 months were 33/11mmHg (control vs. RDN group; P<0.0001). Ambulatory BP monitoring over 24 h was performed in a limited number (n¼20) of patients from both groups, showing a similar albeit less pronounced pattern of BP changes 6 months after RDN (-11/-7mmHg, ¼0.006 for SBP change, P¼0.014 for DBP change), compared to -3/-1mmHg in the control group. Differences in home SBP/DBP were 22/12mmHg (control vs. RDN; P<0.0001). At 12 months follow up, there was significant decrease in both systolic and diastolic BP in comparison to control group -28.1±24.9 and -9.7+10.6 (P<0.0001 for both).[39] Interestingly, in another substudy of Symplicity-HTN-2 including 37 resistant hypertensive patients, RDN resulted in maximum exercise SBP/DBP drop of 21/5mmHg and of 29/ 9mmHg in the recovery period, whereas heart rate response and exercise oxygen uptake were well preserved.[40]

In Symplicity HTN-2, periprocedural events requiring treatment were rare and consisted of one femoral artery pseudoaneurysm, one postprocedural drop in BP requiring a reduction in antihypertensive drugs, one urinary tract infection, one extended hospital admission for assessment of paraesthesias, and one case of back pain that was treated with analgesics and resolved after 1 month. Seven (13%) of 52 patients who underwent renal denervation had transient intraprocedural bradycardia, some of them requiring atropine. In our patients no complication developed and the whole procedure was safe. Postoperative BP reduction is probably due to premedication. One month follow up reveled marked BP reduction from baseline (-25 mmHg systolic BP and -15mmHg in diastolic BP) which is consisted with study result described above. Long term follow up is needed.

Until the beginning of 2012 only a small number of patients have been exposed to RDN, and the follow-up is rather short. Thus, several issues needs to be further elucidated. Regarding efficacy, there was no sham control group in the available trials, which is now part of Symplicity HTN-3 currently conducted in the US as well as in the Duration of Renal Sympathetic Activation and Hypertension study starting in Europe and Canada. Ambulatory blood pressure monitoring was available in a small (selected) portion of patients only and the observed degree of reduction was smaller compared to office and home BP.[15,17] Thus, the true antihypertensive effect of RDN, and particularly that on the prognostically important out of office BP, still needs to be determined. The long-term duration of the antihypertensive effect after RDN needs to be investigated since renal nerve fibers may regenerate.[41,42] It has to be emphasized that in the extended Symplicity HTN-1 trial there was no attenuation of the BP decrease throughout the follow-up period of 24 months suggesting that functional reinnervation did not take place over the time window considered. Up to now, patients with dual renal arteries and accessory arteries have been excluded and there are no systematic data on unilateral RDN effects.[10,12]

The lack of any preprocedural marker that might identify good responders to RDN (except the baseline BP) is another matter to be addressed. There is no clinically applicable technique is available to indicate successful renal sympathetic fibers ablation during the procedure. So far RDN is performed in patients with severe resistant hypertension and its effect in less severe forms of hypertension is unknown. Likewise it is also unknown whether cardiovascular endpoints are prevented and mortality reduced. Nowadays there are further experimental studies with promising results on renal sympathetic denervation performed with different techniques, using local delivery of neurotoxic drugs, cryoablation, ultrasound-induced denervation, and there are ongoing clinical trials with radiofrequency catheter using other catheter types [e.g. trials with a basket-type ablation catheter (Ablation Induced Renal Sympathetic Denervation Trial study).[43]

The above unmet needs are summarized in Box 3 and box 4 summarizes the current recommendation of RDN.

Conclusion:

Renal denervation may have beneficial effects in other conditions characterized by excessive sympathetic activation, and is currently under assessment in several clinical investigations. Until these results are available we should use RDN in patients with treatment-resistant hypertension only fulfilling the above reported criteria after careful selection in hypertension excellence centers. RDN should be performed in very experienced hypertension excellence centers by well trained interventionalists.

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