Renal denervation and glucose metabolism: another burst bubble?

Jan Vaclavik

See related article, pp. 246-50.

In recent years, few, if any, therapeutic methods have enjoyed such immense rise in popularity and subsequent fall as catheter-based renal denervation. In this procedure, a radiofrequency ablation catheter is inserted via the femoral artery into the renal arteries. Then with the Symplicity flex catheter used in most studies, a radiofrequency current is applied at several point lesions from the luminal side of the artery with the goal of interrupting the sympathetic nerve fibres running in the vascular adventitia[1]. Sympathatic denervation of kidneys is predicted to lead to decrease in arterial blood pressure due to increased renal blood flow, decrease in plasma renin activity and reduced afferent stimulation of the hypothalamus by thekidneys[1].

The results of the first trials were very promising and gave rise to great enthusiasm among hypertension specialists and cardiologists worldwide. In the first non-randomized proof-of-concept study, Symplicity HTN-1 in patients with resistant arterial hypertension, the office blood pressure (BP) decreased 6 months after the procedure by 27/17 mm Hg (ref.[2)]. In the following randomized study, Symplicity HTN-2, the office BP 6 months after renal denervation was 33/11 mm Hg lower than in the control group treated by continuing pharmacotherapy, without any excess adverse events in the intervention group[3]. Regrettably, ambulatory blood pressure monitoring (ABPM) was performed in less than half of the patients (20 denervated and 25 controls) with a more modest reduction of mean 24-hour ABPM by 11/7 mm Hg in the interventional vs. 2/1 mm Hg in the control group[3]. Any secondary etiology of hypertension in these patients was not investigated. Nor was their adherence to treatment.

Several further denervation catheters and systems emerged on the market and their effect on BP in uncontrolled trials appeared to be similar to the above Symplicity 1 and 2 trials[4]. A later trial conducted by 10 European hypertension centres of excellence, comprising 109 patients with resistant hypertension reported an office BP reduction after renal denervation by 17,6/7,1 mm Hg but the mean 24-hour BP decreased by only 5,9/3,5 mm Hg (ref.[5]). The authors of the ESH/ESC European hypertension guidelines regarded renal denervation as promising but stressed the need for additional data from properly designed long-term comparison trials to conclusively establish its safety and persistent efficacy vs. the best possible drug treatments[6]. Despite this, many European countries approved this therapeutic method and in some countries, the procedure was even reimbursed by health insurance.

To approve this method, the American Food and Drug Administration agency (FDA) required further study. 535 patients were randomized in the U.S. in the Symplicity HTN-3 trial in a 2:1 ratio to undergo renal denervation with the Medtronic Flex catheter or a sham interventional procedure without renal denervation[7]. This study was terminated prematurely in the early 2014 because of its failure to meet the primary efficacy endpoint. Difference between the decrease in office systolic BP between renal denervation and sham procedure was only 2.39 mm Hg after 6 months (P = 0.26) and the difference in systolic BP on ABPM was only 1.96 mm Hg (P = 0.98) (ref.[7]). Further, there were no significant differences in safety between the two groups.

Many experts now argue about what could cause such an immense discrepancy between the results of Symplicity 1, 2 and 3 trials. Recent retrospective analysis of Symplicity HTN-3 showed that the decrease of office systolic BP was negligible in Afro-Americans (higher BP reduction in sham procedure by 2.3 mmHg), while in other ethnic groups the BP there seemed a significant reduction of office systolic BP in favour of renal denervation (by 6.6 mm Hg) though the changes in ABPM BP did not differ significantly for various ethnic groups[8]. The American centres had only minimal previous experience with renal denervation and the majority of investigators had only performed one or two procedures before starting treating the study patients. A retrospective radiologic analysis found that in the majority of patients treated by renal denervation (74%), complete ablations in all 4 quadrants of both renal arteries encompassing the whole 360° of artery circumference were not performed, and more pronounced BP decrease was noted in patients with a larger number of renal artery ablations (12 and more ablations) (ref.[8]). However, based on their retrospective character, all the above are only hypotheses generating results which have to be confirmed by further studies.

It is very likely that the substantial BP decrease registered in the original Symplicity HTN-1 and 2 trials is result of bias and placebo effect. A recent metaanalysis of hypertension clinical trials performed after 2000 found a significant decrease in office BP in placebo treated patients by 5.92/5.40 mm Hg (ref.[9]). In the trials of resistant hypertension, the BP decrease in placebo arms was even more pronounced, reaching 8.76/3.70 mm Hg (ref.[9]). Three factors may explain the magnitude of the placebo effect. Firstly, the "regression to mean" – high biological variability of BP often leads to enrolment of patients at the "big-day" when their BP is high, and on next visits the BP is lower due to its variability. Secondly, clinical

observers have a tendency to repeat the BP measurement to approximate the BP to expected values, thus producing an "unintentional observer bias". Thirdly, improvement in patient compliance may play an important role due to better education and more thorough follow-up, manifesting in larger BP decrease in placebo arms in patients using more antihypertensive drugs at enrolment[9].

In 2011, Mahfoud et al. reported improvement in glucose metabolism and insulin sensitivity 3 months after renal denervation in 37 patients with resistant arterial hypertension[10]. Of these, 17 were enrolled in the controversial Symplicity HTN-2 trial. Fasting glucose was reduced by renal denervation from 118 mg/dL (6.56 mmol/L) to 108 mg/dL (6.0 mmol/L, $P = 0.039$). Insulin levels were decreased from 20.8 to 9.3 mIU/L ($P = 0.006$) and C-peptide levels from 5.3 to 3.0 ng/mL ($P = 0.002$). After 3 months, homeostasis model assessment–insulin resistance decreased from 6.0 to 2.4 ($P = 0.001$). Mean 2-hour glucose levels during the oral glucose tolerance test (OGTT) were reduced significantly by 27 mg/dL (1,5 mmol/L, $P = 0.012$) (ref.[10]).

In a recently published DREAMS study, 29 patients with metabolic syndrome who used a maximum of 1 antihypertensive or 1 antidiabetic drug or both, underwent renal denervation, which did not lead to a significant improvement in insulin sensitivity 6 and 12 months after treatment[11]. Neither did fasting glucose change significantly during the follow-up (baseline 7.2 mmol/L, at 6 months 7.4 mmol/L and at 12 months 7.0 mmol/L, $P = 0.34$), or fasting insulin (20.9, 20.1 and 19.6 mIU/L, $P = 0.53$) or fasting C-peptide (1319 pmol/L baseline, 1306 pmol/L at 12 months, $P = 0.82$) (ref.[11]). The results of OGTT were also not significantly changed. As the only explanation for the difference, the suggestion was made that the patients in the Mahfoud study had possibly higher baseline sympathetic activation because of resistant hypertension[11].

Remarkably, the authors of the DREAMS study also observed that renal denervation did not alter sympathetic activity as assessed by muscle sympathetic nerve activity and heart rate variability[11], contrary to previous reports. It seems that the currently used catheter does not adequately lower sympathetic nervous system activity and thus cannot produce the desired effects, mainly in lowering BP.

In this issue of Biomedical Papers, Matous et al. present their data on the effect of renal denervation on glucose metabolism in 51 patients with resistant arterial hypertension[12]. They too found no positive effect of renal denervation 12 months after the procedure using the Medtronic Flex catheter. Fasting glucose level significantly increased at 12 months (from 7.4 to 7.8 mmol/L; $P = 0.032$), glycated hemoglobin (from 46.1 to 47.6 mmol/mol; $P = 0.079$) and C-peptide level also showed a trend towards increase (1178 to 1271 pmol/L; $P = 0.098$) (ref.[12]). In patients with type 2 diabetes mellitus (n = 25; 49%) fasting glucose significantly increased (from 8.6 mmol/L to 9.5 mmol/L; $P = 0.033$). In patients without diabetes mellitus (n = 26; 51%) there were no statististicaly significant changes in any parameter[12].

The baseline patient characteristics in both the Matous and Mahfoud studies were very similar, including a similar proportion of diabetic patients, and this cannot explain the different results of these trials. 84% patients in the recent Matous study underwent standard RDN according to common protocol - i.e. bilateral denervation with at least 4 applications of radiofrequency to each renal artery (proximal, distal, anterior, posterior - controlled by biplane X-ray). In 4 patients of this study, changes were made in oral antidiabetic medication or insulin dosage during the 12-months follow-up but this would more likely lead to improved, not worsened glucose control. Although not reported in more detail, Matous et al. found a relatively high level of non-compliance to the antihypertensive medication in these patients based on assessment of serum levels of antihypertensive drugs, and they assume the same applies to peroral antidiabetic medication.

In an experimental trial in rats, surgical renal denervation affected neither weight gain nor plasma glucose levels, but it increased urinary glucose by 45% and diuresis by 68% in diabetic rats ($P < 0.05$), probably due to reduced levels of cortical and medullar GLUT1 protein in the kidneys[13]. Surgical renal denervation also had no effect on mean arterial pressure in this study[13]. A more recent study from this group in rats, also showed no effect of renal denervation on glucose values and metabolism[14].

A recent autopsy finding in a woman with resistant hypertension who died 9 days after catheter-based renal denervation on aortic dissection found that renal denervation did not lead to complete interruption of the continuity of all adventitial nerve bundles around the renal arteries[15]. Around both arteries, adventitial and periadventitial nerve bundles of variable calibre were noted at distances from 1 to 4 mm from the luminal surface but the damage from renal denervation did not penetrate deeper than 2 mm from the luminal surface[15].

In conclusion, it seems that currently used techniques of catheter-based renal denervation have either very limited or no effect on either blood pressure or glucose metabolism. For these reasons, it is time for renal denervation to return from the bedside to the laboratory and more effective modalities of this procedure should be developed. Then, before adoption into clinical practice, their effect must be assessed in meticulously designed prospective, randomized, blinded, sham-controlled trials.

REFERENCES

1. Krum H, Sobotka P, Mahfoud F, Böhm M, Esler M, Schlaich M. Device-based antihypertensive therapy: Therapeutic modulation of the autonomic nervous system. Circulation 2011;123(2):209-15. doi:10.1161/CIRCULATIONAHA.110.971580
2. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009;373(9671):1275-81. doi:10.1016/S0140-6736(09)60566-3
3. Symplicity HTN-2 Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm 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. doi:10.1016/S0140-6736(10)62039-9
4. Oparil S, Schmieder RE. New approaches in the treatment of hypertension. Circ Res 2015;116(6):1074-95. doi:10.1161/CIRCRESAHA.116.303603

5. Jin Y, Persu A, Staessen JA. Renal denervation in the management of resistant hypertension: current evidence and perspectives. Curr Opin Nephrol Hypertens 2013;22(5):511-8. doi:10.1097/MNH.0b013e3283640024
6. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281-1357. doi:10.1093/eurheartj/eht151
7. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393-401. doi:10.1056/NEJMoa1402670
8. Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, Flack JM, Katzen BT, Lea J, Lee DP, Leon MB, Ma A, Massaro J, Mauri L, Oparil S, O'Neill WW, Patel MR, Rocha-Singh K, Sobotka PA, Svetkey L, Townsend RR, Bakris GL. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J 2015;36(4):219-27. doi:10.1093/eurheartj/ehu441
9. Patel HC, Hayward C, Ozdemir BA, Rosen SD, Krum H, Lyon AR, Francis DP, di Mario C. Magnitude of blood pressure reduction in the placebo arms of modern hypertension trials: implications for trials of renal denervation. Hypertension 2015;65(2):401-6. doi:10.1161/HYPERTENSIONAHA.114.04640
10. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: A pilot study. Circulation 2011;123(18):1940-6. doi:10.1161/CIRCULATIONAHA.110.991869
11. Verloop WL, Spiering W, Vink EE, Beeftink MM, Blankestijn PJ, Doevendans PA, Voskuil M. Denervation of the renal arteries in metabolic syndrome: the DREAMS-study. Hypertension 2015;65(4):751-7. doi:10.1161/HYPERTENSIONAHA.114.04798
12. Matous D, Jiravsky O, Nykl I, Branny M. Effect of renal denervation on glucose metabolism after a 12 month follow-up. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2015;159(2):246-50. doi:10.5507/bp.2015.030
13. D'Agord Schaan B, Lacchini S, Bertoluci MC, Irigoyen MC, Machado UF, Schmid H. Impact of renal denervation on renal content of GLUT1, albuminuria and urinary TGF-beta1 in streptozotocin-induced diabetic rats. Auton Neurosci 2003;104(2):88-94. doi:10.1016/S1566-0702(02)00295-3
14. Dias LD, Casali KR, Leguisamo NM, Azambuja F, Souza MS, Okamoto M, Machado UF, Irigoyen MC, Schaan BD.Renal denervation in an animal model of diabetes and hypertension: impact on the autonomic nervous system and nephropathy. Cardiovasc Diabetol 2011;10:33. doi:10.1186/1475-2840-10-33
15. Vink EE, Goldschmeding R, Vink A, Weggemans C, Bleijs RLAW, Blankestijn PJ. Limited destruction of renal nerves after catheter-based renal denervation: results of a human case study. Nephrol Dial Transplant 2014;29(8):1608-10. doi:10.1093/ndt/gfu192