Catheter-based renal denervation in hypertension: heading for new shores

HHS Public Access

Author manuscript

J Hypertens. Author manuscript; available in PMC 2018 May 24.

Published in final edited form as:

J Hypertens. 2018 January ; 36(1): 41–42. doi:10.1097/HJH.0000000000001614.

Catheter-based renal denervation in hypertension: heading for new shores

Felix Mahfoud[a,b], **Michael Böhm**[a], and **Elazer R. Edelman**[b,c]

[a]Klinik für Innere Medizin III, Saarland University Hospital, Homburg, Saarland, Germany

[b]Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge

[c]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Autonomic imbalance, the loss of equilibrium between the sympathetic and parasympathetic nervous systems, is thought to play an important role in the pathophysiology of hypertension [1]. The activation of renal sympathetic fibers, which reside throughout the kidney and abound in the hypertensive state, leads to an increased and excessive secretion of renin, increased sodium reabsorption in the proximal tubule, and decreased renal perfusion [2]. In the not so distant past, these observations seemed to support and promote the use of surgical sympathectomy in patients with severe hypertension, including individuals with end-organ damage, and indeed was associated with significant reduction in blood pressure (BP) accompanied by reduced mortality [3]. Surgical approaches requiring major operative approach became a method of last resort and then a neglected relic of the past until catheter-based approaches promised minimally invasive targeting of renal nerves. An ablation catheter introduced through the femoral or radial artery can be advanced into the renal arteries under fluoroscopic guidance, in which radiofrequency or ultrasound energy can be deployed to ablate the sympathetic nerves [4]. Alternative approaches use chemical denervation by injection of alcohol or other neurotoxic agents in the adventitia of the renal arteries. Although minimal invasiveness was proved and early data seemed promising, unambiguous BP lowering with noninvasive renal denervation (RDN) remains elusive, especially in light of the well executed trials [5].

In this issue of the Journal, Völz *et al.* [6] present the first results of the nationwide Swedish Registry for Renal Denervation. Their analysis included 260 consecutive patients, who were scheduled for RDN with six different catheter systems from 2011 to 2015. A total of 252 patients with resistant hypertension (average number of antihypertensive drugs 4.5 ± 1.5) underwent the procedure and were followed for 36 months (6 months: $n = 206$, 12 months: $n = 204$, 24 months: $n = 79$, 36 months: $n = 27$). Office and ambulatory BP was significantly

Correspondence to PD Dr Felix Mahfoud, FESC, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, 66421 Homburg, Saarland, Germany. Tel: +49 6841 16 15911; fax: +49 6841 16 15910; felix.mahfoud@uks.eu.

Conflicts of interest

There are no conflicts of interest.

reduced at 6-month follow-up by 15/6 and 8/5 mmHg (n = 206), and persisted to 36 months. No significant changes in medication were documented, with the caveat that no objective adherence assessments were included in study protocol. Procedural adverse events were ~3% and included two renal and one femoral artery dissection, one retroperitoneal bleeding, and four local hematomas. Although not provided, it would have been valuable to elucidate, if dissections were treated conservatively or required additional invasive/surgical treatment. Renal function, measured by estimated glomerular filtration rate, remained unchanged over time.

These data are in line with positive results of major registries [7], for example, from the United Kingdom [8], Austria [9], and Greece [10]. Such observational data are key to appreciate the efficacy and safety of real-world patients undergoing RDN outside of controlled clinical studies. Yet, they cannot answer the central question raised by randomized, controlled studies as to whether BP lowering with RDN is effect and cause or driven by nonspecific placebo or Hawthorne effects and the like. Thus, the recently published SPYRAL-OFF Medication Study [11] is especially enlightening. Here patients with uncontrolled, mild–moderate hypertension without concomitant antihypertensive medication were randomized to RDN with a multielectrode catheter or sham procedure. At 3 months, RDN significantly reduced office (−7.7/−4.9 mmHg, P <0.01) and ambulatory BP (−5.0/−4.4 mmHg, P <0.05) more than sham treatments.

What then sets the SPYRAL-OFF apart from previous trials? Three major distinctions were introduced in the patient population, catheter technology employed, and concomitant treatment. SPYRAL-OFF excluded patients with isolated systolic hypertension, as this phenotype has an attenuated response to RDN [12], and used a modified multielectrode catheter with a revised ablation technique of distally focused treatment allowing a more circumferential and complete RDN [13]. Moreover, patients had to be off medication; therefore, resistant hypertensive individuals were not included. Adherence to the study protocol and especially the lack of antihypertensive medication intake at follow-up was confirmed by toxicological analyses allowing a proper intention to treat and per protocol analysis [14].

The SPYRAL-OFF Medication study provides biological proof of principle for BP lowering by RDN but must be seen in proper context. Early reports in resistant hypertensive patients documented greater BP drops following RDN compared with changes in mild–moderate hypertensive patients [15,16]. In the Swedish Registry [6] and other reports, baseline BP predicted future change, which could be related to regression to mean but also to higher sympathetic activity with higher baseline BP. The relationship between baseline office SBP and decrease in BP at 6-month follow-up correlates (Fig. 1) and guides assessing efficacy across studies in different patient populations. In this regard, there is not much difference between results of the Swedish Registry and randomized, sham-controlled SPYRAL-OFF Medication study, is there?

RDN remains therefore an attractive but elusive potential therapy – supported by real-world registries, but with more inconsistent findings in well executed controlled trials. What have we learned? It is in part because we know so little of RDN and even of autonomic imbalance

that we cannot converge on a definitive resolution of value assignation. The issues are complex, and high-quality research is needed to understand the potential of new device-based technologies for the treatment of hypertension. Are we sure we understand and characterize hypertension properly and discriminate patients with and without sympathetic overactivation and autonomic imbalance? Do we really have the means to control applied denervation and document effect? In addition, can we indeed consider in aggregate the efficacy and safety profile of many different devices as if there was a single class effect? Further preclinical analyses [17] are mandated as we have much to learn, now more than ever we need to continue in-depth analysis. Several new studies in resistant and more importantly in untreated hypertensive patients is steering RDN to new shores – let us see, where we end up.

References

1. Esler M. Sympathetic nervous system moves toward center stage in cardiovascular medicine: from Thomas Willis to resistant hypertension. Hypertension. 2014; 63:e25–e32. [PubMed: 24420544]
2. DiBona GF. Physiology in perspective: the wisdom of the body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol. 2005; 289:R633–R641. [PubMed: 16105818]
3. Smithwick RH. Surgical treatment of hypertension. Am J Med. 1948; 4:744–759. [PubMed: 18856769]
4. Böhm M, Linz D, Ukena C, Esler M, Mahfoud F. Renal denervation for the treatment of cardiovascular high risk-hypertension or beyond? Circ Res. 2014; 115:400–409. [PubMed: 25035133]
5. Mahfoud F, Böhm M, Azizi M, Pathak A, Durand Zaleski I, Ewen S, et al. Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. Eur Heart J. 2015; 36:2219–2227. [PubMed: 25990344]
6. Völz S, Spaak J, Elf J, Jägrén C, Lundin C, Stenborg A, et al. Renal sympathetic denervation in Sweden: a report from the Swedish registry for renal denervation. J Hypertens. 2018; 36:151–158. [PubMed: 29210862]
7. Böhm M, Mahfoud F, Ukena C, Hoppe UC, Narkiewicz K, Negoita M, et al. First report of the global SYMPLICITY registry on the effect of renal artery denervation in patients with uncontrolled hypertension. Hypertension. 2015; 65:766–774. [PubMed: 25691618]
8. Sharp AS, Davies JE, Lobo MD, Bent CL, Mark PB, Burchell AE, et al. Renal artery sympathetic denervation: observations from the UK experience. Clin Res Cardiol. 2016; 105:544–552. [PubMed: 26802018]
9. Zweiker D, Lambert T, Steinwender C, Weber T, Suppan M, Brussee H, et al. Effects of renal denervation documented in the Austrian National Multicentre Renal Denervation Registry. PLoS One. 2016; 11:e0161250. [PubMed: 27529426]
10. Tsioufis C, Ziakas A, Dimitriadis K, Davlouros P, Marketou M, Kasiakogias A, et al. Blood pressure response to catheter-based renal sympathetic denervation in severe resistant hypertension: data from the Greek Renal Denervation Registry. Clin Res Cardiol. 2017; 106:322–330. [PubMed: 27957627]
11. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet. 2017; Epub ahead of print. doi: 10.1016/S0140-6736(17)32281-X
12. Mahfoud F, Bakris G, Bhatt DL, Esler M, Ewen S, Fahy M, et al. Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. Eur Heart J. 2017; 38:93–100. [PubMed: 28158510]

13. Mahfoud F, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, et al. Impact of lesion placement on efficacy and safety of catheter-based radiofrequency renal denervation. J Am Coll Cardiol. 2015; 66:1766–1775. [PubMed: 26483099]

14. Mahfoud F, Schmieder RE, Azizi M, Pathak A, Sievert H, Tsioufis C, et al. Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: state of the art and considerations for the future. Eur Heart J. 2017; Epub ahead of print. doi: 10.1093/eurheartj/ehx215

15. Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet. 2014; 383:622–629. [PubMed: 24210779]

16. Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H, et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomized clinical trial. Eur Hear J. 2014; 35:1752–1759.

17. Tzafriri AR, Keating JH, Markham PM, Spognardi AM, Stanley JR, Wong G, et al. Arterial microanatomy determines the success of energy-based renal denervation in controlling hypertension. Sci Transl Med. 2015; 7:285ra65.

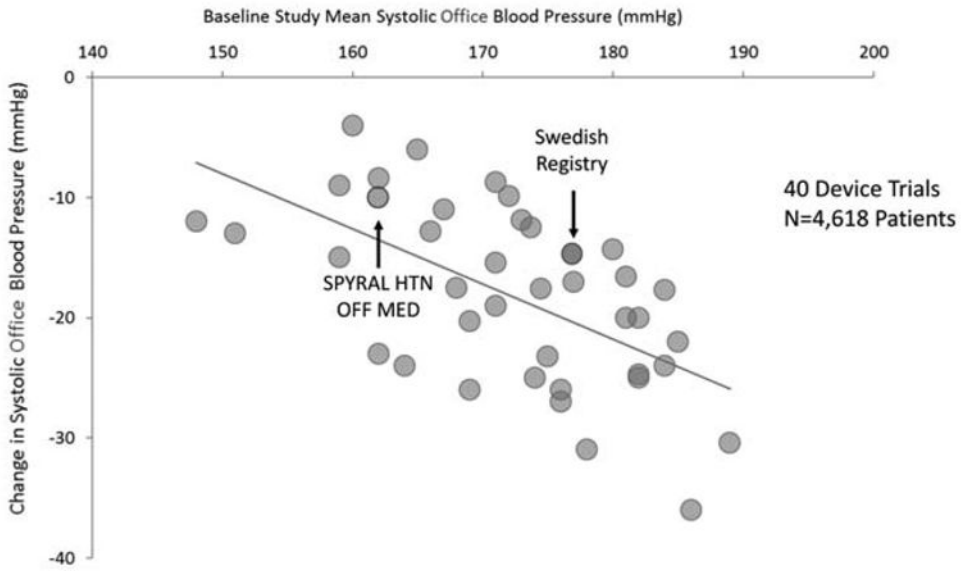

FIGURE 1.
Relationship between baseline office SBP and decrease in blood pressure at 6 months.