Renal sympathetic denervation after Symplicity HTN-3 and therapeutic drug monitoring in patients with resistant hypertension to improve patients’ adherence

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Renal sympathetic denervation (RDN) has been proposed as a new treatment modality in patients with apparent treatment-resistant hypertension (TRH), a condition defined as persistent blood pressure (BP) elevation despite prescription of at least three anti-hypertensive drugs including a diuretic. However, the large fall in BP reported after RDN in Symplicity HTN-2, the first randomized study, and in multiple observational studies has not been confirmed in five subsequent prospective randomized studies. The reduction in BP may be mostly due to non-specific effects, such as improvement of drug adherence in initially poorly adherent patients (the Hawthorne effect), placebo effect and regression to the mean. The overall BP lowering effect of RDN seems rather limited and the characteristics of the true responders remain largely unknown. Accordingly, RDN is not ready for clinical practice. In most patients with TRH, drug monitoring and subsequent improvement of drug adherence may prove more effective and cost-effective to achieve BP control. In the meantime, research should aim at identifying characteristics of those few patients adherent to drug treatment who has TRH and may respond to RDN.

Keywords Hypertension • Anti-hypertensive Drugs • Renal Denervation • Drug Monitoring

Introduction

The Lancet has been instrumental in publishing studies on renal sympathetic denervation (RDN) in hypertension and, accordingly, has strongly contributed to the promotion of this technology to be applied in patients with apparent treatment-resistant hypertension (TRH).1-3 However, with the recent publication of the Symplicity HTN-3 study in the USA4 the world has seemingly overcome in doubt whether RDN lowers blood pressure (BP) at all. The editor of another distinguished journal5 published his reflections and stated that the Symplicity HTN-3 results came as a shock to the world. A single, but large and properly designed prospective randomized clinical trial could on its own neutralize hundreds of mostly observational studies, case reports and other enthusiastic publications emphasizing the amazing effects of RDN, not only in patients with resistant hypertension but also in a host of other diseases and conditions. During first half of 2014, a total of four prospective randomized studies of RDN with modest results on BP in patients with TRH have been published or presented. Other recent studies showed that patients with TRH have surprisingly low drug adherence. The aim of this review is to explain the rise and decrease of RDN in TRH, and to highlight the issue of poor drug adherence in patients with apparent TRH and therapeutic drug monitoring (TDM) as a cost-effective modality to control BP and improve prognosis in this subset of difficult-to-treat high-risk hypertensive patients.

The rise and fall of renal denervation in treatment-resistant hypertension

The initial enthusiasm followed by the setback of RDN can probably be summarized by a handful of reflections and putative explanations: (i) The role of the sympathetic system in the pathophysiology of
Hypertension is substantiated by a wealth of experimental and clinical arguments. On this background, enthusiasm surged when an intervention in this system seemed to lower BP drastically. (ii) Industry ensued that RDN would replace medical treatment of hypertension in a large number of patients and driven by this prospect lased an aggressive course in development and marketing without providing evidence from randomized controlled trials. (iii) Subsequently, pitfalls in apparent treatment-resistant hypertensive patients were suddenly forgotten including well-described phenomena such as the placebo effect, regression to the mean, poor drug adherence and the Hawthorne effect, that is, patients changing behaviour.

The history of the rise and demise of RDN, initially presented as a miracle treatment for millions of hypertensive patients, deserves a more in-depth analysis. The first and for a long time the only prospective randomized clinical trial in this field, the Symplicity HTN-2 study, was monitored by Ardian (Medtronic) who collected and processed the data. Usually, when such a task is delegated to industry, all measures are taken to secure blinding and a properly randomized and controlled design. However, Symplicity HTN-2 was an open trial, making the trial particularly vulnerable to patient-, physician-, and sponsor-related biases. In a recent editorial, Shun-Shin et al. nicely stated that ‘measurement of a noisy variable by un-blinded optimistic staff is a known recipe for calamitous exaggeration’. It is unfortunate that the selection of patients enrolled in Symplicity HTN-2 and the evaluation of efficacy were based on office rather than ambulatory blood pressure (ABPM). ABPM is state of the art particularly in resistant hypertension. ABPM reduces observer bias and measurement error, minimizes the white-coat effect and has greater reproducibility, and therefore provides a better estimate of a patient’s usual BP and cardiovascular prognosis.

Notwithstanding the well-known major contribution of poor drug adherence to apparent resistant hypertension, in Symplicity HTN-2, drug adherence was not thoroughly monitored, either at baseline or during follow-up. This made the study vulnerable to the Hawthorne effect. Twenty-four hour ambulatory and home BPs were reported in a subgroup only, without providing baseline data. Participants in the intervention group may have started taking their drugs as prescribed, in response to the intervention and massive attention devoted to them. Patients in the control group might have been less adherent in order to meet the 6 months criteria for RDN. Finally, regression to the mean and placebo effect must also be taken into account. Simply by recruiting patients with the highest BPs at the outset would yield more BP decrease at follow-up. Noteworthy, the placebo effect is small by using ABPMs. However, ABPMs remain as sensitive to the Hawthorne effects as office BP.

**Figure 1** Hawthorne was an electrical power plant in Chicago (en.wikipedia.org/wiki/Hawthorne_Works). Some investigators discovered already in the 1920s that the employees worked much harder if lights were turned brighter. But the workers had been informed of the experiment and it was after a while understood that they did not respond to the lights being improved, but simply changed their behaviour because they were under observation. In no other field of medicine is this phenomenon more powerful than in hypertension research. Simply teaching people to take their own blood pressure is changing their behaviour and improving their drug adherence. It is thus no surprise that apparent treatment-resistant hypertensive people who have a mixed motivation for taking their drugs, to a certain degree explaining why they appear as drug resistant, start taking their drugs following renal sympathetic denervation, with a subsequent dramatic, but largely non-specific blood pressure fall.
The role of device industry in promoting renal denervation

Symplicity HTN-2 was a small open study with suboptimal design including only 106 patients followed up for 6 months. In spite of this limited evidence, RDN was adopted in hundreds of centres worldwide. Medtronic Inc.10 (Minneapolis, MN, USA) paid $800 million to purchase Ardian10 (Mountain View, CA, USA), the company that had developed the technology,5 and more than 10 companies developed their own RDN systems, five of which obtained the CE mark. ‘CE’ is an acronym standing for the French words ‘Conformité Européenne’ (European Conformity). CE marking means that the product is assessed before being placed on the market and meets EU safety, health and environmental protection requirements. However, CE marking is unrelated to medical indication at variance with the USA where FDA approves a medical device only when it has been tested and proved effective for a certain medical condition. The procedure was quickly reimbursed in Germany, subsequently also in Switzerland, Sweden, and the Netherlands. While RDN remained an investigational procedure in the USA, at least 8000,28 possibly 15 000–20 000 procedures were performed in Europe and in the rest of the world in <4 years, most of them using the Ardian-Medtronic® catheter.

Medtronic established a separate autonomic division of the company for all activities globally, marketing and research, related to the use of their RDN catheters. The incomes generated by selling the Symplicity catheters to hundreds of invasive centres in Europe directly financed research projects elsewhere and in particular these incomes paid for the largest trial, Symplicity HTN-34 in the USA. This more stringent designed trial was required to document BP lowering effects by the Food and Drug Administration in the USA. This more stringently designed trial was required to document BP lowering effects by the Food and Drug Administration in the USA before the device could be approved there for clinical use. In Symplicity HTN-3,4 blinding of patients through the use of a sham procedure and more extensive use of ABPM measurement balanced and limited the impact of the Hawthorne, white-coat, placebo, and regression-to-the-mean effects in both treatment arms. Thus, the true size of BP decrease attributable to RDN became evident and it was <2.1 mmHg systolic based on 24-h ABPM monitoring.

The complexity and multifactorial character of hypertension, in addition to the possible biases in previous trials, led us to the working hypothesis that RDN would fail to normalize or substantially reduce BP in most patients with TRH, and this was discussed prior to the announcement that Symplicity HTN-3 had failed to meet its primary endpoint (www.tctmd.com/show.aspx?id=123265). We29–31 and others19,25 had predicted that the true effect of RDN may have been overestimated, and that BP reduction would be considerably less in properly designed studies,1,9 that is, ‘one size may not fit all’.26 In the preliminary analysis of the European Network Coordinating research on Renal Denervation (ENCoREd)32 there was large inconsistency between the 17.6 mmHg decreases in office systolic BP vs. only 5.9 mmHg for 24-h systolic BP.

Clinical trials in Europe,33 we had thus clearly in mind the limitations of previous studies. We needed a simple and practical way to deal with pitfalls in the recruitment of patients with resistant hypertension into a study protocol. After extensively ruling out secondary hypertension, and improving drug treatment, patients had to qualify for the RDN protocols by having elevated daytime ABPMs after witnessed intake of their prescribed anti-hypertensive medications.30 This was a convenient way to identify the true treatment-resistant hypertensive patients and to exclude patients with white-coat resistant hypertension or those non-adherent patients whose BP normalized after witnessed drug intake. Meanwhile, a leading hypertension centre in Germany34 published a small but well-documented series of patients whose BP remained unchanged after RDN. For many hypertension experts in Europe, this was a clear sign of what was to come. We were thus not surprised when we found no change in either office or ABPMs following RDN, first in an open series of six patients,30 later followed by a randomized study, the Oslo-RDN trial.35 Patients who were randomly assigned to further improvement of drug treatment guided by non-invasive haemodynamic monitoring had normalized BPs. In contrast, patients exposed to RDN experienced only a small and probably partly placebo-induced fall in office and ABPMs (Table 1). The decreases averaged 20 mmHg more for office and 9 mmHg more for daytime ambulatory systolic BP in the haemodynamically guided drug treatment (control) group compared with the RDN group.

The pitfalls with renal denervation in treatment-resistant hypertension

In the absence of solid evidence of efficacy, how can we explain the uncontrolled deployment of RDN in Europe and worldwide (with the notable exception of the USA where RDN remained an investigational procedure)? Of course, publications of the Symplicity studies and of multiple observational studies, and enthusiastic editorials and reviews in the Lancet1 – 3 and other top-ranking journals such as Circulation36 and JACC37 had a substantial impact, and the lack of strict rules for introduction of device-based therapies in Europe facilitated the large-scale implementation of the technique. However, this phenomenon would have remained limited without the huge promotion by device-producing industry. Probably never before has industry launched a stronger campaign to market a new technology. A multitude of national and international advisory boards organized educational meetings, developed website (www.poweroverpressure.com) and produced guidelines. Medical journals were swamped by reviews and meta-analyses showing the powerful BP lowering effects as recorded in observational studies and in the single available randomised study, Symplicity HTN-2. Comments pointing out the defects and inconsistencies in such meta-analysis encountered great delay in getting published.38 Physicians were invited to training sessions and the sponsor promoted RDN in large as well as in small hospitals, public and private clinics and facilitated with all means the recruitment of patients to physicians and centres who would perform the procedure. Many never questioned whether RDN should be implemented, but when it should start in an institution. By all means, the purpose was to disseminate the enthusiasm for RDN from the technically oriented invasive radiologists.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Symplicity HTN-2</th>
<th>Oslo RDN</th>
<th>HTN-3</th>
<th>PRAGUE-15</th>
<th>French Dener-HTN</th>
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<tr>
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<td>Plasma drug concentrations</td>
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<td>No. of drugs at baseline</td>
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<td>RDN Drug adjustment</td>
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<td>180</td>
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<td>159</td>
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<tr>
<td>Baseline (mmHg)</td>
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<td>−14.13</td>
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<td>−15</td>
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<tr>
<td>ΔFU—6 months (mmHg)</td>
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<td>−28</td>
<td>−11.74</td>
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<td>ΔRDN—control (mmHg)</td>
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<td>−2.39</td>
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<td>+9</td>
<td>−1.96</td>
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SBP, systolic blood pressure; RDN, renal denervation; 6 months, 6-month follow-up; −ΔRDN—control in favour of renal denervation group, +Δ in favour of control group; ?*, baseline ambulatory BP values were not given in this study; ** results is given just for the difference between 20 patients in renal denervation group and 25 patients in control group.
and cardiologists who usually had little interest or experience in the treatment of hypertension to the ‘hypertension establishment’. The European Society of Hypertension issued specific guidelines,39,40 but maintained reservations that more data were needed, and eventually it had to be proved that RDN would lower morbidity and mortality before being generally accepted in the treatment of true or apparent TRH.

Unfortunately, the most enthusiastic proponents of RDN do not seem to have fully accepted the lessons of Symplicity HTN-3. In the aftermath of Symplicity HTN-3, a campaign has been set up to criticise the study because of including inexperienced investigators, of whom many did few procedures partly with insufficient delivery of ablation energy, and enrolling too many African-American patients who took more anti-hypertensive drugs in the course of the study.38,41 Symplicity HTN-3 may have had its weaknesses; however, no subgroup analysis was statistically significant and all the hypotheses explaining the failure of Symplicity HTN-3 by showing a difference in BP were post hoc and speculations. It has been suggested that the lack of demonstrated efficacy of RDN in Symplicity HTN-3 may be due to lack of statistical power or even to chance42 or that the trial was well conceived but not rigorously executed.41 Furthermore, the Symplicity HTN-3 results are diluted by non-scientific comparisons with the Medtronic registry14 which is hampered by all the weaknesses touched upon in this commentary, and even more as it is a pure industry-ran activity. Finally, while RDN will not become available in the USA, and ongoing research in Asia was stopped, Medtronic and other companies continued making their catheters available for clinical use in Europe and did not restrain marketing of RDN happened in the way it did. We must make sure that nobody in this field should let things like the commercial pressure of RDN be the only driver of research and development. By a careful estimate, 20 000 renal arteries have been exposed to ablation in people with hypertension (www.medpagetoday.com/MeetingCoverage/TCT/47688) in a study released as an abstract at the transcatheter cardiovascular therapeutics meeting in Washington, DC on September 16, 2014. This German study investigated the effect of Symplicity® Flex Catheters (Medtronic Inc., Minneapolis, MN, USA) and could detect no significant difference in ABPMs while offices BPs were not measured.

Could there be responders to renal denervation in hypertension?

Does the failure of Symplicity HTN-3 mean the end of RDN? Not necessarily. Indeed, as already mentioned, RDN is based on a solid rationale substantiated by over 50 years of meticulous research of the sympathetic nervous system and its involvement in the pathophysiology of hypertension.6–12 Furthermore, it has been shown in cohorts recruited from the third (the effect of progressive sympathectomy on BP, Walter Bradford Cannon 1931, www.ncbi.nlm.nih.gov/pubmed/2204236) until the fifth decade of the last century13,14 that abdominal sympathectomy associated to splanchectomy is effective in the treatment of severe hypertension. Finally, many centres report major responses to RDN in a minority of patients.30,32,35 Accordingly, research should go on to find out the minority of patients who are true responders to RDN, and identify predictors of effective RDN (Figure 2); among others it may be an opportunity in middle aged patients with grades 1 and 2 hypertension and no heavy target organ damage. European Network Coordinating Research on Renal Denervation is set up to include patients in randomized trials, observational studies, and registries independent of industry. Some early results32,46 from this joint effort have already been published and suggest that it may be worthwhile to search for potential predictors of response to RDN. When including two prospective randomized studies that have been reported46,47 not but fully published to the three published studies,2,4,35 the overall picture may open for some optimism that some truly responding patients may be identified (Table 1).

Still, before going ahead, we have to draw the lessons of the RDN story. The wisdom hereof is first of all that no new bright idea can suddenly appear and resolve the problem of hypertension—or even resistant hypertension—as a whole. Previous knowledge has been building up through clever research by generations of investigators and hypertension cannot be resolved overnight. Hypertension is too complex and multifactorial and the size of the problem is so extensive that nobody in this field should let things like the commercial marketing of RDN happened in the way it did. We must make sure that RDN is beneficial and does no harm. Many patients have probably undergone unneeded procedures. By a careful estimate, 20 000 renal arteries have been exposed to ablation in people with hypertension and an increasing number of cases of renal artery...
stenosis after RDN are reported. Very recent news along these lines are that in Germany the insurance companies have terminated their coverage. The negative news that RDN is not for most people may reach Time Magazine and Der Spiegel but it remains to be seen whether all clinicians who treat people with hypertension in daily life understood the mistake (Figure 1).

Therapeutic drug monitoring in resistant hypertension

While non-adherence to drug therapy is a major problem in the treatment of TRH patients, TDM maybe a useful tool for detecting and reducing non-adherence and leading to effective BP control. Chung et al. have assessed cost-effectiveness of TDM using a Markov model based on German data and life statistics to evaluate life-years, quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios in TRH patients receiving either TDM optimized therapy or standard best medical therapy. Efficacy of TDM was modelled by reducing risk of hypertension-related morbidity and mortality. Cost analyses were performed from a payer’s perspective. In the age group of 60-year olds, TDM gained 1.07 QALYs in men and 0.97 QALYs in women at additional costs of €3854 and €3922, respectively. Given a willingness-to-pay threshold of €35 000 per QALY gained, the probability of TDM being cost-effective was ≥95% in all age groups from 30 to 90 years. Results were influenced mostly by the frequency of TDM testing, the rate of non-responders to TDM, and the magnitude of effect of TDM on BP. Thus, Chung et al. found that TDM presents a cost-effective health care intervention in patients diagnosed with TRH and this finding is valid for a wide range of patients, irrespective of age and sex.

It has been known for decades that poor drug adherence is a major problem among patients with apparent TRH and it was pointed out as the number one problem in an algorithm for the management of apparent TRH. Before hypertension can be considered resistant to a rational triple drug regimen in maximal doses, the physician should rule out poor adherence to the treatment regimen (including dietary and other non-pharmacological advice), adverse drug interactions, pseudotolerance (due to fluid retention), isolated office hypertension, pseudohypertension, and previously undetected secondary causes (e.g. renovascular disease, primary aldosteronism, and pheochromocytoma). Once these conditions have been excluded, haemodynamic measurements may be indicated to identify the mechanism(s) at fault so that the therapeutic regimen can be modified appropriately.

Along the same lines Ray W. Gifford Jr, already in October 1987 in printed material adopted from the upcoming Joint National Committee-4 Report, summarized the following 16 ground rules in the clinical assessment of patients with apparent TRH in order to promote adherence to treatment: (i) Inform patients of their BP...
level. (ii) Agree on a goal BP. (iii) Be sure patients understand that (a) BP can be controlled but not cured, (b) they cannot tell BP level by the way they feel, and (c) they should not stop treatment without discussing it with their physician. (iv) Incorporate treatment into patients’ daily lifestyles. (v) Involve patients’ families in treatment process. (vi) Encourage self-monitoring of BP in selected cases. (vii) Provide positive reinforcement. (viii) Simplify therapeutic regimen. (ix) Provide simple oral and written instruction on drug dosages, side effects, and therapeutic goals. (x) Encourage discussion of anti-hypertensive medications, side effects, problems, and concerns. (xi) Consider clinical-patient contracts. (xii) Modify dosages and change drugs to avoid side effects. (xiii) Minimize cost of therapy. (xiv) Schedule frequent counseling visits for non-adherent patients. (xv) Contact patients who miss appointments. (xvi) Collaborate with other health-care providers.

Thus, drug adherence in apparent TRH is a serious issue that has drawn the attention of experienced clinicians for many years. Recently, in a study of 84 patients taking on average five anti-hypertensive drugs it was shown by measurements that no drug was detectable in the blood in 34.5% of the patients, and 65.5% of the patients fulfilled the criteria of non-adherence.5 Other investigators have provided similar results.34–36 Beyond the clinical challenge of convincing people with severe hypertension to take their anti-hypertensive medication in order to control their high BP and improve their prognosis, changes in drug adherence over time may have major, unpredictable effects on the results of clinical trials including patients with apparent RHT. People may change their behaviour when given special attention in research (the Hawthorne-effect) (Figure 1). This may introduce important biases, as patients with assumed TRH but with poor drug adherence, may start taking their drugs when exposed to additional intervention. We postulate that much of the recent controversy in renal denervation can be explained in this way.2,4

Clinical assessment of non-adherence in routine practice is challenging.57 Drug adherence is usually investigated by patient’s diary or somewhat more sophisticated by electronic pill boxes, or blood and urine measurements of prescribed drugs. Measurements of drugs can provide interesting information,35,34–36 but it is not often used in practical clinical work especially in primary care, and the cost has been prohibitive until recently. Neither patient’s diary nor electronic pill boxes are perfectly reliable to ensure drug intake. The only methods that 100% ensures true drug intake is witnessed drug intake, an approach that may yield quite interesting results in patients with TRH.30,35,34 However, while witnessed intake of drugs may identify adherent patients for immediate inclusion into a study, this method is not particularly practical in the long run for the follow-up in clinical practice or research.

In the long run, TDM in body fluids may be the best tool for evaluation and improvement of adherence to drug therapy.58 This approach allows an objective surveillance of patient adherence by repeatedly measuring concentrations of anti-hypertensive drugs in blood and urine. Moreover, when non-adherent patients were confronted with their low or undetectable drug levels and were provided with additional counselling to overcome barriers of adherence, BP control improved considerably without intensification of therapy.58 While several studies14,34–35 focused on the objective exclusion or confirmation of non-adherence, this recent study58 utilized the information gained from TDM measurements for therapeutic purposes. The TDM results were discussed with the non-adherent patients to explore barriers to adherence and counselling was provided to overcome the specific barrier. During follow-up, SBP was reduced by 46±10 mmHg in non-adherent compared with 12±17 mmHg in adherent patients without intensification of the anti-hypertensive therapy.58

Therapeutic drug monitoring identifies and helps to resolve the key problem in many—possibly the majority—of patients with apparent TRH—that is, poor adherence to prescribed drug regimen. Weakness is that patients who are aware they will undergo the drug concentration measurement may start to take the pills just few days before especially in the case the patients do not take drugs because of the presence of side effects. As previously shown, the cost-effectiveness of this approach is supported by a solid rationale2,25 and should not be compared with similar analyses of controversial device intervention50–51,54–56 in apparent TRH patients. So far, such analyses50–52 were indeed based on Symplicity HTN-2, an un-blinded study largely open to the Hawthorne and placebo effects, whose results could not be replicated in any of five randomized trials published or presented in 2014.

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