

**HYPERLIPIDEMIA & HYPERTENSION UPDATE**

## Hypertension: Renal Denervation: Hype After Initial Hope/Lessons to be Learned From its Fall/Other Methods Influencing the Autonomic Nervous System

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**ABBREVIATIONS**

BP = blood pressure  
RDN = renal denervation

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The unexpected announcement of Symplicity HTN-3 trial by the sponsor company that renal sympathetic denervation (RDN) failed to meet its primary efficacy end-point at 6 months raised concerns regarding the extent of blood pressure (BP) lowering results of the procedure.<sup>1</sup> But the answer to the “burning” question of whether we should stop research and clinical implementation of RDN based on the results of one trial needs a cautious approach.<sup>2</sup>

The revolutionary therapy of RDN has resulted in significant office BP reduction in all previous studies.<sup>3–10</sup> The mean office systolic BP reduction across trials is on average 20–30 mmHg and shows sustainability up to 3 years.<sup>3–10</sup> In some patients there is delay in the BP response to RDN and there is a gradual drop of BP post-denervation suggesting that the adverse vascular and cardiac remodeling characterizing resistant hypertension cannot be reversed in all patients in relatively short period of time.<sup>10</sup> Thus, differences in BP modulation by RDN over time could not be excluded by Symplicity HTN 3 that was focused on the 6 months end-point.<sup>11</sup>

Symplicity HTN-3 is the first to include a sham intervention arm<sup>11</sup> mimicking the Rheos Pivotal Trial designed to assess the efficacy of baroreflex activation therapy.<sup>12</sup> Patients with the device inactivated exhibited a mean decrease in systolic BP of  $9 \pm 29$  mmHg that did not differ with the reduction of  $16 \pm 29$  mmHg in the active group from month 0 to 6 months ( $p=0.08$ ).<sup>12</sup> However, in this study the 12 month follow-up revealed greater reduction in BP in both active ( $25 \pm 32$  mmHg) and cross-over group ( $25 \pm 31$  mmHg).<sup>12</sup> Due to the lack of studies with placebo groups in resistant hypertension the sham-effect should be interpreted with caution. Moreover, controls in the randomized Symplicity HTN-2 trial had no systolic BP change but there was no placebo provided.<sup>6</sup> Pooled data from intentional BP lowering trials reveal that there is 12.8 mmHg difference in systolic BP levels from baseline in the placebo group and the achieved systolic BP difference between active therapy and placebo is 11.8 mmHg.<sup>2</sup> The lowest prespecified systolic BP deviation from baseline in RDN patients was 15 mmHg that is close to expected placebo-sham-effect; it reveals the inherent weakness of the trial design in terms of assessing the true differential to sham RDN efficacy.<sup>2,11</sup>

The procedure per se could have an adverse impact on RDN-induced BP changes. There is large operator variability and a steep learning curve with the use of the single tip ablation catheter which in addition to the small average number of procedures in the 87 medical centers involved could result in ineffective ablation of the renal artery.<sup>1,2</sup> Having no marker of RDN success the interventionalist’s experience is needed for

maximizing effective ablation.

One of the acknowledged drawbacks of RDN trials is the considerable discrepancy between average office BP and average 24-h BP at baseline and the marked difference in the magnitude of BP reduction during follow up.<sup>13</sup> In the series of Symplicity, ambulatory BP was performed only in a small subset of patients: (12/45 patients in Symplicity HTN-I and 20/106 patients in Symplicity HTN-II) and BP reduction was only 41% and 34% of office BP reduction in the two studies.<sup>6,8</sup> Contrariwise, by antihypertensive drug therapy ambulatory BP reduction is at least 65% of the reduction seen in office BP.<sup>14</sup> Similar disparities have also been noted in the EnligHTN I trial in which office BP was reduced significantly and substantially in the first month (-28/-10 mmHg) and remained at the same levels for up to 6 months.<sup>9</sup> Ambulatory BP measurement was performed in all patients and demonstrated a-10/-5 mmHg reduction in average 24-h BP, which also remained the same until the 6 month follow-up.<sup>9</sup> Recently a larger study specifically examined the BP response to RDN as measured by ambulatory BP monitoring.<sup>15</sup> In patients with true treatment resistant hypertension (n=303) there was a significant reduction in 24-h systolic BP (-10/-10/-12 mmHg, p<0.001) and diastolic BP (-5/-5/-7 mmHg, p<0.001), at 3, 6 and 12 months, respectively.<sup>15</sup> There was no effect in pseudo-resistant patients (n=43), while office BP was reduced to a similar extent.<sup>15</sup> In a study including the experience of 10 European expert centers revealed a more modest decrease in office systolic/diastolic BP after RDN (-17.6/-7.1 mmHg) that was accompanied by -5.9/-3.5 mmHg drop in 24-h BP.<sup>16</sup> Moreover, although criticizing the RDN method, a very recent work comparing RDN versus impedance cardiography adjusted-drug treatment revealed an ambulatory BP reduction of -10/-7 mmHg in the RDN group that could not by any means be considered clinically unmeaningful.<sup>17</sup>

Based on the above, knowing the exact difference of office and ambulatory BP in the Symplicity HTN-3 inclusion phase as well as the drops of these BP parameters is essential in order to assess RDN efficacy. Moreover, due to that reduction of 24-h hemodynamic load is more closely related to target organ damage and cardiovascular prognosis compared to office BP,<sup>14</sup> future RDN studies should focus on the reduction of ambulatory BP and hard-end points instead of plain office BP.

However, apart from the efficacy BP lowering issues, Symplicity HTN-III fulfilled the ethical precept of medicine '*primum non nocere*' by successfully meeting the primary safety end-point.<sup>1</sup> RDN according to all trials is overall a safe procedure<sup>3-10</sup> and regarding renal function it is preserved even in patients with baseline renal failure.<sup>18,19</sup> Vascular complications are rather rare, while renal stenoses are infrequent and related to energy delivery in sites of previous atherosclerosis.<sup>3-10</sup> Moreover, the neural cardiovascular reflexes remain intact during exercise<sup>20</sup> and upright posture<sup>21</sup> after RDN.

Importantly, the most promising aspect of this method

of sympathetic neuromodulation is its pleiotropic nature.<sup>22</sup> Several reports have shown favorable impact of RDN on cardiac mass assessed by echocardiography and magnetic resonance.<sup>23,24</sup> Additionally RDN seems to improve glucose status,<sup>25,26</sup> arrhythmias,<sup>27,28</sup> obstructive sleep apnea syndrome<sup>26</sup> by reducing insulin resistance, end-diastolic left ventricular and atrial pressures as well as by causing better natriuresis.<sup>22-28</sup> Most interestingly, in certain models of experimental hypertension not accompanied by excess sympathetic activation, RDN causes BP drop not by reducing sympathetic outflow but mostly due to left shift of pressure-natriuresis curve.<sup>22,29</sup> These pathophysiological considerations for fundamental co-impact of RDN on sodium balance should be assessed in future clinical trials. The use of different catheters and energy modalities (i.e. radiofrequency, ultrasound, cryotherapy or combination)<sup>3,30-34</sup> ensuring more complete ablation of renal nerves would perhaps influence BP, metabolic and cardiovascular parameters up to a higher degree.

In this context, we strongly believe that there is an emerging need to discuss on the appropriate design/methodology of randomized trials for the true role of RDN in the therapy of hypertension and cardiovascular diseases. The key point is that RDN is a method that has substantial pathophysiological background with experimental and clinical studies supporting its effects.<sup>22,34</sup> Finally, the lesson to be learned is that when a "negative" trial like Symplicity HTN-3 is published (as it will be when you read these lines) one should not only be skeptical to RDN but also to the trial itself.

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