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# Resistant hypertension and renal denervation: Who's kidding whom?

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The renin–angiotensin–aldosterone system (RAAS) plays an important role in the homeostasis of blood pressure regulation. Its role in the pathophysiology of hypertension is, however, complex. Over-activation of the RAAS in severe and accelerated phase hypertension is generally recognised but its role in drug-resistant hypertension less clear. This is one question being addressed by the British Hypertension Society PATHWAY Trial Programme ([www.bhsoc.org](http://www.bhsoc.org)).

The interrelationships between the RAAS and the sympathetic nervous system are also complex and extend from the central nervous system to the periphery, including post-ganglionic nerve endings, the adrenal gland and the kidney. It was therefore of considerable interest to note the impressive blood pressure reduction observed in early studies of renal denervation (RDN) in patients with apparent drug-resistant hypertension and observe to what extent neurohumoral changes accompanied the falls in blood pressure.

By way of background, resistant hypertension is defined as blood pressure remaining above goal in spite of the concurrent use of three antihypertensive agents of different classes. Ideally one of these agents should be a diuretic, and all agents should be prescribed at optimal doses. Its true prevalence is unknown, but observational studies and clinical trials suggest that it is a common clinical problem. In an analysis of National Health and Nutrition Examination Survey (NHANES),<sup>1</sup> of participants being treated for hypertension only 53% were controlled to a blood pressure <140/90 mmHg. In those with diabetes or chronic kidney disease the percentage controlled was considerably less. Similar figures (63%) for all treated patients have recently been reported by the Health Survey for England<sup>2</sup> but, of course, many of the participants in these surveys were not receiving optimal treatment for their hypertension.

Resistant hypertension comprises a heterogeneous group of patients including those with undiagnosed secondary hypertension, inaccurate blood pressure measurement, white coat hypertension and poor adherence with prescribed medication. In the author's experience true resistant hypertension is uncommon. Thus, in the evaluation of patients with apparent resistant hypertension, a

comprehensive management algorithm should be applied which includes investigations to rule out secondary causes, confirmation of appropriate treatment (drugs and doses), including a trial of spironolactone, and formal assessment of drug compliance. This should include observed drug ingestion in the clinic followed by blood pressure monitoring for up to 4 hours and 24 hour ambulatory blood pressure monitoring thereafter. The post-dosing period of observation for 4 hours in the clinic is a precaution for cases where substantial falls in blood pressure occur in the hitherto non-compliant or poorly compliant patient. If the facility is available, urinary drug assays provide additional information on non-compliance.

Only after the diligent exclusion of the majority of patients referred with so-called resistant hypertension can true resistant hypertension be diagnosed with confidence.

In a series of 35 patients referred to a specialist clinic, all of whom claimed to be taking their medications as prescribed, and in whom secondary causes for their hypertension had been eliminated and optimal treatment, including a trial of spironolactone, had been prescribed, following observed drug ingestion and 24-hour ambulatory blood pressure monitoring (ABPM), 60% achieved a blood pressure of <140/90 mmHg and 80% <150/90 mmHg.<sup>3</sup> The original series has now been extended to over 100 patients and the outcomes will shortly be available.

It is therefore manifest that poor drug compliance is the major contributing factor to apparent resistant hypertension, and without its systematic evaluation resistant hypertension will be grossly over-diagnosed.

It is against this background that we can now look at the history of trials of RDN. In both Symplicity HTN-1 (an uncontrolled study)<sup>4</sup> and Symplicity HTN-2 (a non-intervention controlled study),<sup>5</sup> impressive reductions of clinic blood pressure (circa 30 mmHg systolic) were reported following RDN, and these reductions maintained during extended follow-up for up to 3 years. Other European Centres have reported similar impressive reductions in blood pressure in uncontrolled studies,<sup>6</sup> and two meta-analyses have been published.<sup>7,8</sup>

There have been additional reports that the reductions in blood pressure have been accompanied by a fall in

plasma catecholamines,<sup>9</sup> improvements in insulin sensitivity,<sup>10</sup> reductions in plasma renin,<sup>11</sup> (although this has not been a consistent finding<sup>9</sup>) and regression of left ventricular hypertrophy.<sup>12</sup>

In general the technique has, however, been uncritically accepted and practised worldwide. Specialist centres, including the author's, receive weekly referrals from practising physicians for consideration of RDN in apparent treatment-resistant hypertension.

Against the hype surrounding RDN there have been few words of caution.

None of the Symplicity studies screened patients comprehensively for non- or poor compliance. Only one in five had received a trial of spironolactone, which in our experience has been shown to produce falls in blood pressure almost as great as those seen with RDN.<sup>13</sup>

In Symplicity HTN 2, the reduction in blood pressure with ABPM following RDN was only 11/7 mmHg, a far smaller reduction than one would have anticipated from the clinic recordings. As Howard and colleagues have pointed out,<sup>14</sup> in drug trials without randomisation or blinding, clinic blood pressure reductions are substantially greater than reductions in blood pressure as assessed by ABPM. However, with randomisation and blinding, reductions as measured in the clinic and by ABPM are remarkably similar. These authors predicted that this would be the case with the first randomised, controlled, sham-operated trial of RDN, Symplicity HTN 3, with an effect size nearer to 10mm Hg than 30 mmHg systolic pressure.

Interestingly Fadl Elmula and colleagues have reported, in a small series of patients undergoing RDN with treatment-resistant hypertension after witnessed intake of medication and ABPM, that no fall in either clinic or ABPM blood pressures followed RDN.<sup>15</sup> In a subsequent paper the same authors report that, after excluding poor drug compliance, adjusting drug treatment was more effective than RDN in lowering blood pressure in true resistant hypertension.<sup>16</sup>

Whilst many have urged caution over the widespread and often uncritical application of RDN to suspected cases of resistant hypertension, the technique has been extensively adopted by cardiologists and interventional radiologists in many countries, with a proliferation of device manufacturers entering an anticipated rapidly expanding and lucrative market.

Guidelines on the application of RDN for the treatment of resistant hypertension have been published by the British Hypertension Society<sup>17</sup> and other organisations,<sup>18</sup> but the strict criteria recommended prior to qualification for RDN have, in international practice, almost certainly not been adopted.

In Symplicity HTN-3 was prematurely stopped because the trial failed to meet its primary endpoint, the change in office systolic blood pressure from baseline to 6 months,<sup>19</sup> the difference in systolic pressure between the intervention

arm and the sham-operated arm being only 2 mmHg systolic pressure. This was obviously a far less impressive outcome than many would have anticipated from the earlier observational and non-sham controlled trials. The authors, however, confirmed that the procedure was safe, with few complications – an outcome similar to other earlier trials of RDN.

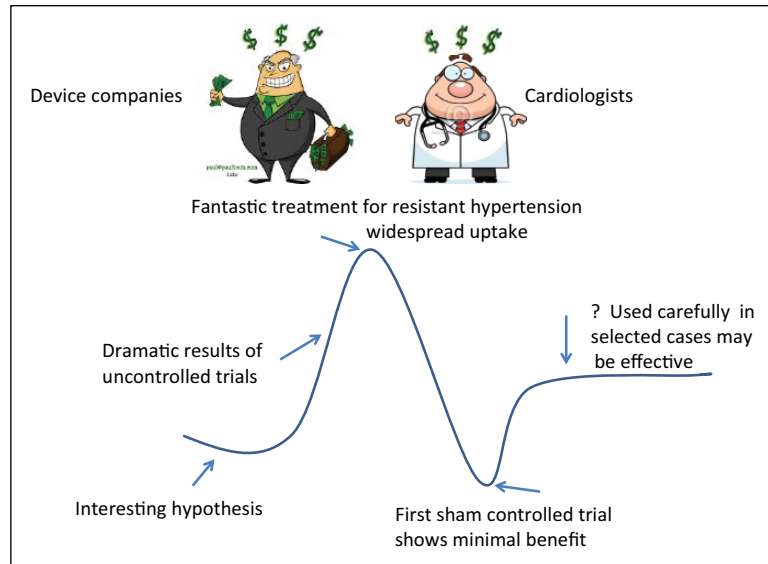
It has previously been suggested that substantial reductions in blood pressure in previous RDN trials could have been explained by better adherence to drug therapy following the procedure, during intensive follow-up under close observation by physicians.<sup>20</sup> Without doubt, from our observations in patients with resistant hypertension, and from studies of urine drug concentrations, compliance with medications is a major problem in this group of patients. It is entirely possible that in the context of a formal trial, particularly when RDN is controlled by a group undergoing a sham procedure, that improved compliance with drug taking post procedure would be similar in the two groups.

The possibility, in Symplicity HTN-3, that RDN was ineffective in the trial, compared with sham operation, because of inadequacies in the denervation procedure is extremely unlikely. The technique is relatively simple, and those participating in the trial will have been appropriately trained in its conduct.

So what of the future?

The scientific background and the work leading up to RDN was sound, and the innovative work of Esler and colleagues commendable.<sup>21</sup> The early trials of RDN in man certainly reawakened interest in the role of the sympathetic nervous system in the pathophysiology of hypertension in general and, more specifically, in resistant hypertension. Following Symplicity HTN-3, however, we need to take a big step backwards to re-evaluate RDN. The Joint UK Societies have recommended a moratorium on RDN until the Symplicity HTN-3 outcomes have been appropriately analysed and digested.<sup>22</sup> The device companies are reviewing the development and marketing of newer catheters for RDN. In my opinion we need a further trial with a larger number of subjects than that reported by Fadl Elmula, where inclusion is restricted to those who are found to be truly treatment resistant after evaluation following observed drug ingestion. Only when such a study has been conducted can we begin to establish the future role of RDN in treatment-resistant hypertension (Figure 1).

This whole episode in the history of hypertension management raises interesting issues, the first being the necessity for properly controlled randomised clinical trials to be carried out prior to the widespread and uncritical uptake of RDN in clinical practice. This would be required for any new antihypertensive drug, so why would we not demand that similar stringent processes are adopted prior to the introduction of a novel blood pressure-lowering device? (This must certainly apply to other devices and proposed methods to treat resistant hypertension that are currently being developed.) The second is the recognition of the



**Figure 1.** Oscillations in the development of renal denervation.

enormous problem of poor compliance with drug therapy in hypertensive patients. The cost to health providers of poor compliance is substantial, not only from the wastage of drugs, but the need for more clinic visits, repeated investigations and the morbidity and mortality associated with uncontrolled blood pressure. Drug assays on urine samples are inexpensive and cost effective and expose poor compliance. They should be used routinely in the work-up of patients with resistant hypertension.

Further research is needed on the pathophysiology of true resistant hypertension, with particular reference to the role of the sympathetic nervous system, the involvement of the RAAS, and the real problems of volume overload in some patients. Again The PATHWAY programme may shed some light on this.

There may, ultimately, be a place for RDN where drug taking is problematic due to side effects or other causes of non-compliance, and further controlled trials in such subgroups would be mandatory.

The natural history of RDN mimics the teaching to many generations of British medical students, on new drugs, by the late Desmond Lawrence – unrivalled enthusiasm, followed by total rejection and then an ultimate place for use in a restricted number of patients.

Let us not forget that other interventional procedures in medicine, such as tonsillectomy and knee arthroscopy with washout, have ultimately been shown to be of little value when objectively evaluated.

On the basis of the evidence to date, I put the following question to both the physicians and their patients with ‘resistant’ hypertension – who’s kidding whom?

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