Renal denervation: A plea for wisdom

Dénervation rénale : plaidoyer pour la sagesse

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Introduction

The ‘tranquil’ world of hypertension has been disturbed by the emergence of a new interventional approach to hypertension management, namely renal denervation (RDN). Currently, RDN is only indicated for the treatment of resistant hypertension (RH), and presents a unique opportunity to control blood pressure in highly selected patients who are refractory to medical treatment (rate of control is 40% based on Symplicity-1 trial data [1]). Considering the high prevalence of hypertension, the potential indications for such therapy are huge, provided that additional evidence confirms, in the future, the benefits of RDN.

Aims of antihypertensive treatment

This new technique is, however, a source of concern for hypertension specialists because the studies performed (Symplicity HTN-1 [1] and -2 [2]) have shifted the focus onto lowering blood pressure, while for hypertension specialists, the paradigm of hypertension management relies much more on preventing cardiovascular events than on lowering blood pressure per se. This has been extensively illustrated in the past few decades by many large clinical trials and meta-analyses showing that some antihypertensive regimens may provide benefits beyond blood pressure lowering. Further, office blood pressure is now considered to be a poor surrogate for cardiovascular events, with a greater value put on central or ambulatory blood pressure.
Levels of evidence

At present, RDN is far from having the same level of evidence as medical treatment for hypertension, and we are only at the beginning of a story. This could, of course, be a source of misunderstanding between hypertension specialists and interventional cardiologists or radiologists. Indeed, ‘interventionalists’ may consider that this intervention is safe, easy and quick to perform, and that it provides a very substantial and sustainable blood pressure lowering effect (for the moment, the effect of RDN seems to persist to at least 3 years). In addition, it may solve the problems of compliance and imperfect pharmacokinetics, and it may present a radical and definitive solution. In this respect, hypertension specialists may be considered too ‘wise’ with respect to the potential benefits of this technique. However, if physicians are too keen to propose RDN, there is a risk that it will be used for cases other than RH, e.g. patient preference or treatment intolerance, that are not supported by current evidence.

Where do we stand now with RDN?

Most of our current knowledge relies on about 100 patients included in a randomized trial (Symplcity HTN-2 trial [2]). Although pivotal, this study is of limited size and has some methodological concerns. In addition, no hard endpoints were considered, and having analysed only office blood pressure may have overstated the blood pressure benefit compared with ambulatory blood pressure. An ongoing study (SYMPPLICITY HTN-3 Trial [3]) as well as the French ‘STIC’ may help to clarify the real blood pressure benefit of the technique. However, even if future studies could improve our confidence in the technique, no outcome study has yet been launched.

Why should we try other options before proposing RDN?

Resistant hypertension is associated with a greater occurrence of secondary forms; it is also frequently associated with increased aldosterone levels or volume excess that can be managed efficiently with appropriate treatment, namely diuretics. Proposing RDN in these cases would be pointless.

A three-drug-class regimen is now considered as the cornerstone of the treatment of severe hypertension. It includes renin angiotensin system blockers, calcium channel blockers and thiazide-like diuretics [4]. The absence of blood pressure control with these three treatments defines RH if high blood pressure is confirmed by ambulatory measurements in Europe. Having associated these treatments before any other option is mandatory for three main reasons:

- the pathophysiology of hypertension is complex, some forms being mainly related to volume excess and hyperaldosteronism or renin angiotensin system activation, others to hypersympathetic tone, others to vascular alteration; these different forms will not respond to treatment in the same way;
- these treatments not only improve blood pressure control, but also prevent cardiovascular outcomes;
- these treatments will likely be maintained and even reinforced after RDN; they should be fully tested before.

Another treatment, spironolactone, plays a major role in RH, and may help to control hyperaldosteronism, which is frequently associated with RH. A marked improvement in blood pressure control in this population could be obtained simply by applying this systematic approach of treatment optimization. Indeed, a recent report from France showed that only 1/4 of patients with uncontrolled hypertension receive three drugs, while the majority receive one or two drugs [5]. RDN should not take us away from this basic but efficient generalized drug-treatment approach.

It is tempting to offer patients RDN if they suffer side-effects from antihypertensive drugs. However, one has to be cautious because, over the long-term, slight ankle oedema or increased diuresis may be relatively meaningless if some harmful effect of RDN starts to be observed at an unexpectedly high frequency in the future (e.g. renal stenosis or other damage related to renal autoregulation loss). This has to be fairly considered before proposing this technique to our patients.

Why should we remain cautious towards RDN?

Essentially, we must be cautious because we do not know the real long-term consequences of this procedure on renal function. Nothing is known about the long-term effects of the kidney artery injury induced by RDN. It is conceivable that we will observe fibrotic stenosis [6], and maybe some disturbance of kidney function, particularly when autoregulation is needed. This, of course, has to be carefully followed in registries, which need to be established. For the time being, we are not able to weight the benefits and risks of RDN over the longer term, which is the time scale of primary prevention in hypertension.

Conclusions

There is a great hope for RDN, as this technique is an option for patients with RH; and the indications for RDN may be extended in the future, depending on the available evidence. For now, the medical community should be cautious about proposing RDN, and should stick firmly to the current indications, which have been delineated in a recent French consensus [4]. A wider use of this approach is not justified for now. Pharmacological treatments are the only proven way to prevent cardiovascular events, with extensive documentation of their benefit. Their tolerance is generally good (the side-effects should not be overstated), as is their efficacy, provided that the right dosages and associations, including spironolactone, are used. Not using effective antihypertensive drugs would negate several decades of research and efforts in hypertension that have led to the current optimized blood pressure lowering strategy based on solid evidence.
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However, RDN is a unique opportunity to motivate the medical community, including interventional cardiologists, to a rigorous evaluation of hypertensive patients to select the few candidates that currently can be referred for RDN [7]. It is also an opportunity to look more systematically to secondary forms of hypertension and, overall, to improve blood pressure control in the population, even if it is not through extensive use of RDN. The medical community has a major responsibility with this technique to avoid missing mandatory steps of validation — with important opportunities for prospective registries — to progressively find the true role for RDN in the management of hypertension. We hope that wisdom will prevail.

Disclosure of interest

Pierre Lantelme and Atul Pathak have been speakers for Medtronic and Saint–Jude. Atul Pathak is investigator for RECOR Medical.

References