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# Recent advances in the management of resistant hypertension

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## Abstract

And suddenly, following the preliminary results of renal denervation and carotid baroreceptor stimulation, a big interest in resistant hypertension rose, and all interventionists, many of them with no previous experience with hypertension, fell in love with hypertension and especially resistant hypertension. In the European Society of Hypertension/International Society of Hypertension (ESH/ISH) 2014 Joint Hypertension meeting in Athens, there were no more than four to five sessions related to resistant hypertension and renal denervation, while in the 2014 EuroPCR meeting there were more than 60 renal denervation sessions!

In light of the growing scientific interest in the treatment of this patient group, an update on the treatment available and some concerns regarding the definition and treatment of resistant hypertension is presented.

## Introduction

Hypertension is the most common risk factor for cardiovascular events, affecting up to 50% of the global adult population and becoming more prevalent as this population ages [1]. Untreated hypertension leads to the development of left ventricular hypertrophy, increased intima media thickness, microalbuminuria, coronary heart disease, heart failure (HF) and atrial fibrillation. Resistant hypertension is defined as resistance to treatment, that is, when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs of different classes at adequate doses (but not necessarily including a mineralocorticoid receptor antagonist) fails to lower systolic and diastolic blood pressure values below 140 and 90 mm Hg, respectively [2].

The prevalence of resistant hypertension among hypertensives has been extensively debated, and conflicting data have been presented ranging from 10 to 50% in nephrology clinics. In a subgroup analyses of large clinical trials, its prevalence may be up to 38% [3], although, not all the trials were designed to identify resistant hypertension, and further large-scale observational studies will be needed to better elucidate its magnitude.

In a recent study, uncontrolled hypertension was found in 35.9% of patients, but only 2.2% were resistant hypertensives [4]. Patients with resistant hypertension are likely to benefit from evaluation by a hypertension team to assure proper patient identification, diagnostic work-up, and therapeutic management [5].

## Treatment

Before starting any drug treatment, clinicians should exclude pseudoresistant hypertension (which results from nonadherence to medications or from white coat hypertension), other related causes, and secondary forms of hypertension. The next step should be a combination of lifestyle changes and medical treatment.

### *Lifestyle changes*

Previous studies have shown that lifestyle changes (salt restriction, weight loss, physical exercise, moderate alcohol consumption, healthy diet, and smoking cessation) are very effective in blood pressure reduction in combination with drug treatment in patients with resistant hypertension (Class I, level A,B) [2]. Kokkinos *et al*. have shown that, in patients with severe hypertension, physical activity was accompanied by blood pressure reduction with regression of left ventricular hypertrophy [6], while in a recent study the same group showed that the progression from normal blood pressure to resistant hypertension is attenuated with physical activity [7]. Lifestyle changes in patients with resistant hypertension are associated not only with blood pressure reduction but also with a lower risk of cardiovascular events [8].

### *Medical treatment*

Physicians should prescribe drugs with a long duration of action and high trough-to-peak ratio because not only will this improve the blood pressure control but also the adherence of the patient. Treatment should include two drugs plus a diuretic and, according to the current ESH/European Society of Cardiology (ESC) guidelines [2], this will be a combination of a renin-angiotensin system (RAS) blocker with a calcium channel blocker and a diuretic, unless there are specific conditions. In a previous study by our group the addition of a diuretic or a calcium channel blocker provided significant antihypertensive effects that were superior to the combination of an angiotensin receptor blocker with an angiotensin-converting enzyme (ACE) inhibitor, emphasizing the importance of the combination of drugs with different mechanisms of action [9].

The role of the diuretic is crucial. In patients with resistant hypertension, volume overload due to salt and water retention is the most common mechanism leading to increased blood pressure. So, it is important for any antihypertensive treatment to be accompanied by salt restriction. In addition, antihypertensive drugs are more effective when patients are under salt restriction [10]. Loop diuretics should only be considered in patients with a glomerular filtration rate (GFR) <30 ml/min, and in all other cases thiazide-type diuretics are recommended. Recently, there has been a lot of debate about which diuretic is the best: Hydrochlorothiazide (HCTZ) chlorthalidone or indapamide? Two recent meta-analyses have shown chlorthalidone to be more potent than HCTZ in terms of efficacy and reduction of cardiovascular events [11,12], but in all meta-analyses there is no head-to-head comparison, and also, in the MRFIT trial (Multiple Risk Factor Intervention Trial), chlorthalidone had been used in higher doses than HCTZ. Based on the ESH/ESC guidelines, no recommendation can be made in favor of a particular diuretic agent.

However, if improvement of blood pressure control in highly compliant patients is the therapeutic target, at least two other classes of antihypertensive drugs are available in our armamentarium: beta-blockers (the ones with vasodilatory effects, such as nebivolol and carvedilol, seem preferable) and aldosterone antagonists. According to the ESH/ESC guidelines, the combination of either an angiotensin II receptor blocker or ACE inhibitor with a beta-blocker is not a first-line one, probably due to limited efficacy. Nevertheless, in a recent study, Giles *et al*. have shown that a nebivolol and valsartan fixed-dose combination is an effective and well-tolerated treatment option for patients with hypertension [13]. Things are completely different in patients with clinical organ damage (i.e. coronary artery disease or congestive HF where this particular combination is very effective and should be regarded as a gold standard.

In some patients with resistant hypertension, plasma aldosterone levels are significantly higher, suggesting a role in blood pressure control resistance [14]. An increasing body of evidence has suggested benefits of mineralocorticoid receptor antagonists, such as spironolactone or eplerenone, in improving blood pressure control in patients with resistant hypertension, regardless of circulating aldosterone levels [15]. Although approximately 70% of patients with uncontrolled resistant hypertension have an estimated GFR greater than 50 ml/min and serum potassium levels less than 4.5 mEq/L (which is associated with a low risk for hyperkalemia), only a minority of them receive mineralocorticoid-receptor antagonists. Recent data have shown that baseline potassium levels of <4.5 mEq/L, older age, body mass index and high baseline systolic blood pressure were associated with improved blood pressure control in patients with resistant hypertension [16]. Thus, this class of drugs remains an alternative treatment for patients whose blood pressure remains elevated after treatment with three drugs to maximum-tolerated doses.

### *Interventional therapies*

In patients who still have uncontrolled hypertension despite receiving triple drug treatment, including a diuretic at an adequate dose, carotid baroreceptor stimulation or renal denervation can be considered.

#### *Carotid baroreceptor stimulation*

Carotid baroreceptors play a key role in blood pressure regulation and impairment in their function has been associated with development and maintenance of

hypertension [17]. Chronic electrical stimulation of carotid sinus nerves via implantable devices has shown significant reduction in both systolic and diastolic blood pressure. In the Rheos Pivotal, Device Based Therapy in Hypertension (DEBuT-HT), and Rheos Feasibility Trials, blood pressure either in clinic or with ambulatory blood pressure measurement (ABPM) was reduced significantly [18-20]. However, longer-term observations have involved only a restricted number of patients and further data on larger numbers of patients are needed to confirm the efficacy and safety of the method. One of its main limitations is the surgical procedure, the need for general anesthesia, and the size of the device. Although newly unilateral devices have limited the implantation procedure to one side only, the potential beneficial effects of the method should be balanced against the invasive nature of the procedure, and against the need for periodical control and the replacement of the generator battery or reintervention in case of device failure.

#### *Renal denervation*

Renal denervation is the bilateral destruction of renal nerves travelling along the renal artery by radiofrequency ablation catheters, inserted percutaneously through the femoral (and lately the radial) artery. The sympathetic nervous system innervates the kidney via efferent fibers, and provides regulation of the central nervous system via afferent fibers. Key events after efferent stimulation of the kidneys are the effects of the sympathetic system on renal vascular resistance, reduced renal blood flow, renin release, and sodium reabsorption. In renal denervation, a wide range in the blood pressure lowering effect has been reported. In the Symplicity HTN-1 trial, 45 patients receiving a mean number of 4.7 antihypertensive drugs with uncontrolled hypertension underwent catheter-based renal denervation [21]. They noticed a significant reduction of systolic and diastolic blood pressures of 14 and 10 mm Hg, respectively after 4 weeks, 27 and 17 mm Hg after 12 months ($P$<0.026), and 33 and 19 mm Hg after 36 months ($P$<0.1), but there are long-term data for only 24 patients [22]. In the following Symplicity HTN-2 trial, they included 106 patients randomized 1:1 to receive the intervention or serve as a control group [23]. After 6 months of treatment, office systolic and diastolic blood pressures were reduced by 32/12 mm Hg ($P$<0.0001), home blood pressures by 20/12 mm Hg ($P$<0.001), and ABPM blood pressures by 11/7 mm Hg ($P$<0.007) but only for 20 patients. Other studies have shown improvement in arterial stiffening, regression of left ventricular hypertrophy, and improvement of diastolic dysfunction, glucose tolerance and renal protection.

Fadl Elmula *et al*. compared the role of optimal medical treatment with renal denervation in patients with true resistant hypertension [24]. They found that office and 24-hour blood pressure reduction with optimal medical treatment was superior to renal denervation, in patients with true resistant hypertension. And then the disappointing results from the Symplicity HTN-3 trial [25] were announced, according to which, the newer interventional therapy was no better than optimal medical treatment. In brief, 535 patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. The study failed to achieve both its primary and secondary efficacy endpoints. The mean reduction in office blood pressure was 14.1 mm Hg with active therapy and 11.7 mm Hg with placebo at 6 months, and was highly significant for both groups compared to baseline ($P$<0.001), but the between-group difference was small (2.4 mm Hg) and not significant ($P$=0.26). Similarly, the mean systolic blood pressure reduction in 24 hour ABPM at 6 months was 6.8 mm Hg with active therapy and 4.8 mm Hg with placebo compared to baseline, and the small between-group difference (2.0 mm Hg) was not significant ($P$=0.98).

## Where we stand now

#### *Identifying the true resistant hypertension patient*

As we pointed out at the beginning, the most important but commonly overlooked issue is to identify the true resistant hypertension patients. This can be done in many cases (as many studies and guidelines have suggested) in excellence centers for hypertension. In the recent ESH/ISH joint meeting in Athens, there were two important abstracts related to this topic. In the first presentation by Fadl Elmula *et al*. [24], all evaluated patients were asked to bring their blood pressure drugs with them and take them in front of the investigators. Their blood pressures were assessed with 24 hour ABPM. From the 65 patients with suspected resistant hypertension, only 10 had true resistant hypertension. These 10 patients were then randomized either to renal denervation or to optimal medical treatment. After 6 and 12 months, both office and 24 hour ABPM were lower among patients who were treated with optimal medical treatment than those treated with renal denervation. In the other study, Tomaszewski *et al*. [26] performed urine analysis in 298 consecutive patients, 17 of whom were referred for renal denervation. The mean number of drugs screened for was three, whereas the mean number of drugs detected was just 2.3, and zero in 10% of patients! Both studies showed the importance of hypertension excellence centers for the detection of true resistant hypertension before any procedure is undertaken.

#### *The Symplicity HTN-3 trial*

The Symplicity HTN-3 trial had disappointing results. This trial was carried out, even the non-procedural part of

it, by interventionists in interventional departments rather than by, or in collaboration with, hypertension centers. There was an inexplicable enthusiasm among interventionalists for the renal denervation method, in sharp contrast to the conservative and evidence-based position of the ESH/ESC in the recent published guidelines [2]: "At present, the renal denervation method is promising, but in need of additional data from properly designed long-term comparison trials to conclusively establish its safety and persistent efficacy vs. the best possible drug treatments". This is not new. If we look at the data from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation (BARI) trials [27,28], optimal medical treatment was equally effective to invasive treatment in terms of prognosis, in patients with stable coronary artery disease. The question in invasive trials is what is considered to be optimal medical treatment in hypertension. If there are currently five classes of drugs, plus aldosterone antagonists, and alpha-blockers, why is the combination of only three drugs used to define resistant hypertension? In the SymplicityHTN-3 trial, more patients in the sham group were receiving aldosterone antagonists than the renal denervation group (17 vs. 23%). Let's have a look at their comments on three variables that may have influenced the efficacy of the Symplicity HTN-3 trial.

*Drug changes and adherence*

During the trial, two out of five patients required medication changes. The question is did the trial include real resistant hypertensives or uncontrolled hypertension patients?

*Patient population*

The method was not effective in African Americans. It is important to know if the method is less effective in some ethnic groups.

*Procedure-related factors*

The number of ablations per patient was significantly related to the degree of procedure success. According to the presenters, many of the US operators had had no prior experience with the denervation catheter before treating their first on-trial patient. The question is did they have any previous experience with hypertension and the procedure? How ethical is this? Also, they found that the number of comorbidities, the higher baseline blood pressures, and male gender were associated with higher blood pressure reductions and inversely related to estimated GFR. On the other hand, non-responders were typically those taking a higher number of hypertensive drugs. The question still remains, are they the really resistant hypertensives?

## Conclusion

Resistant hypertension represents a real challenge in the treatment of hypertensive patients in everyday clinical practice. However, first of all, clinicians have to distinguish the cases of uncontrolled or pseudoresistant hypertension in order to improve the treatment and subsequent prognosis of those patients.

## Abbreviations

ACE, angiotensin-converting enzyme; ESC, European Society of Cardiology; ESH, European Society of Hypertension; GFR, glomerular filtration rate; HF, heart failure; ISH, International Society of Hypertension.

## Disclosures

The authors declare that they have no disclosures.

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