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Renal Denervation, "Last Resort" or Alternative Therapy?

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Arterial hypertension represents one of the main causes of morbidity and mortality among the population with high risk of cerebral strokes, coronary heart disease.

It's arbitrarily defined as "resistant" or "refractory" when recommended blood pressure targets are not achieved, despite changes in lifestyle and treatment with adequate doses of at least three antihypertensive drugs from different classes, including a diuretic.

In a recent clinical study, it's proved a variable proportion (approximately 5-15%) of the general population of the patients with hypertension in treatment, which refer to the Centres of Excellence for the diagnosis and treatment hypertension, may be considered suffering from resistant hypertension [1]. It's evident that 5-15% of patients with hypertension, Whereas 20% of the Western population is suffering from hypertension, is easy to understand the true dimension of the phenomenon. So the choice of treatment, comes to a crossroad. Should we insist with the combination of more than three medications, or choose the path of renal denervation?

What are the main defects of drug therapy with the combination of four or more antihypertensive?

Combination of antihypertensive drugs, overcoming the limit of the three drugs, increases the risk of treating with non-beneficial, or even dangerous associations.

A typical example is the combination of a beta-blocker with an ACE inhibitor or an AT1-antagonist useful in the patient with heart failure, but absolutely not effective to improve control of blood pressure. Beta-blockers also should not be associated with the non-dihydropyridine calcium channel blockers because these drugs would add their effects chronotropic, dromotropic and inotropic effects. A dangerous association could be given from the interaction between an α1-blocker and clonidine as their effects will cancel each other and therefore blood pressure can even be increased again. Also beta-blockers and clonidine: the 'paroxysmal increase in blood pressure observed 18-36 hours after withdrawal of clonidine can be worsened by the simultaneous administration of a beta-blocker. Although it seems to overcome, increasing the number of drugs for the treatment of a chronic illness, you risk getting a poor adherence to medical therapy.

More and more often in hypertensive patients, coexist morbidities that are not compatible with the use of antihypertensive drugs: An example is the use of tiazhide-like diuretic that should be under the control of renal function in chronic renal failure and therefore it is often replaced by the loop diuretic that in terms of blood pressure control does not have the same effect daily.

Still under study, as well as the subject of debate, the renal denervation is a procedure that consists of the insert of a catheter totally similar to the one used for cardiac revascularization. It's moved forward to the renal arteries. When it is placed, the catheter sends a signal of radio-frequency which is able to destroy the nerve fibers of the artery of the sympathetic renal system and inhibits, consequently, its activity, permitting (or allowing) a significant decrease of pressure values.

Eligible patients for the procedure must have: resistant hypertension; clinical blood pressure >160/90 mmHg (>150/90 in patients with diabetes mellitus type 2) and 24-hour ambulatory blood pressure >150 /90 mmHg despite a therapy with at least three or more classes of antihypertensive drugs, and an appropriate lifestyle [2]. These limit values PA are based on the protocol applied in recent clinical studies of intervention in patients with hypertension arterial resistant. Moreover, it is appropriate that antihypertensive therapy includes at least two of the following classes of drugs: a diuretic, a drug blocker of the renin -angiotensin system and a drug with vasodilating action.

These patients own such an anatomical conformation of the renal arteries that are susceptible to treatment by denervation of the renal arteries (length>20 mm and a diameter of >4 mm), assessed by angio-TC or angio-RM.

The evidence in support of renal denervation comes from the first study, called Symplicity Hypertension-1 [3] in which 50 patients with resistant hypertension (baseline Blood Pressure values 177/101 mmHg, the mean number of antihypertensive drugs 4.7) were treated by denervation of the renal arteries and 5 patients were treated with drug therapy. At the end of the observation period of 12 months there has been a progressive and persistent reduction in systolic blood pressure values and diastolic blood pressure in patients treated with denervation of the renal arteries, while patients treated with therapy medical showed progressive increases in values pressure to the predefined time intervals (1, 3, 6, 9 and 12 months).

Another evidence comes from the second study, a multicentre, prospective, randomised, called Symplicity Hypertension-2 in which 106 (56%) of 190 patients screened for eligibility were randomly allocated to renal denervation (n=52) or control (n=54) groups between June 9, 2009, and Jan 15, 2010. 49 (of 52) patients with resistant hypertension (baseline BP values 178/97 mmHg, the mean number of drugs antihypertensive 5.2) were treated by denervation of the renal arteries and 51(of 54) patients were treated with drug therapy. At the end of the observation period of 6 months was registered a progressive and persistent reduction in systolic and diastolic BP values in patients treated with denervation of the renal arteries, while patients treated with medical therapy did not show significant changes in blood pressure the predefined time intervals (1, 3, 6 months) [4]. Regarding the safety, renal denervation was done without complications in 98% (201/206) of patients systematically followed in Symplicity-HTN1 and Symplicity-HTN2. The following complications were reported: four cases of femoral artery pseudoaneurysm, which were all able

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to be treated conservatively, and one renal artery dissection during positioning of the guiding catheter, which was successfully treated with stenting. In addition, some minor complications, including one urinary tract infection, one case of back pain, one prolongation of hospital stay because of paresthesias, and a vasovagal reaction in seven patients during intervention. RDN did not affect renal function (cystatin C estimated glomerular filtration rate [eGFR]) in patients with preserved renal function at 3- and 6-month follow-up [5].

RDN can produce a lot of beneficial consequences as well as blood pressure reduction. In fact other important studies demonstrate on these different effects [6]. Central hemodynamics was improved thanks to RDN and 110 patients who underwent bilateral RDN had their arterial stiffness reduced [7]. In addiction of this RDN dropped left ventricular mass and improved diastolic function in patients with resistant hypertension, only one month after its treatment, as confirmed by transthoracic echocardiography [8]. That study underlined the deep connection between the use of RDN and myocardial hypertrophy reduction. As far as concern heart rate (HR) a recently published study which involved 136 patients, proved that HR was reduced by 2.6 ± 0.8 bmp after 3 months, and by 2.1 ± 1.1 bpm after 6 months [9].

A fundamental study represents the next step towards new scientific research: the Symplicity HTN-3. It is a multicenter, prospective, single blind, randomized, placebo-controlled trial currently ongoing in the USA [10]. More than 500 patients will take part in this trial; they will be randomized in a single blinded 2:1 treatment design in 90 centers in the USA [11].

A recent official statement of Medtronic's January 9, 2014 revealed that the early data from the study Symplicity HTN-3, the primary endpoint efficacy has not been achieved, and the method has been confirmed safe. Only a recent work, which consists of a method different from Symplicity, shows that, in patients with resistant hypertension, using the EnligHTN multi-electrode catheter there is a rapid and significant office blood pressure reduction that was sustained through 6 months [12].

In conclusion, currently denervation is presented as a valid method. This method cannot be considered as an alternative to medical treatment, but a method that with an increasingly complementary. Based on limited data from the scientific literature, now it becomes essential to define the patient on which the method will be effective. It is not possible to come to other conclusions because of the limited available data, and the lack of data on long-term (There are no studies in order to consider any additional benefit in terms of reduction of cardiovascular events and mortality). Moreover, the few data comes mainly from studies with methodical symplicity, which would suggest in terms of scientific value, the need for more practice tests and other data from experimental work.

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