Conference Paper

Renal Denervation Therapy: Indications and Success Factors

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Arterial hypertension is a common and an increasing health care problem. In Germany and other Western countries, prevalence rates are as high as 50%. Of these, 13% of patients suffer from refractory hypertension, where the target blood pressure is not achievable with >3 antihypertensive substances. Renal denervation therapy (RDT) is a relatively new, catheterization-based intervention to treat patients with refractory hypertension. The rationale of RDT is the mechanical destruction with high frequency ablation of renal sympathetic fibers, which can be easily accessed via the renal artery. The first clinical trials evaluating effect and safety of the procedure have been promising, and RDT is being routinely used in specialized centers.

1. Introduction

Arterial hypertension is one of the most important and prevalent risk factors for cardiovascular diseases. In Germany and other Western industrialized countries, a double-digit million number of patients suffer from arterial hypertension. Unfortunately, in the past, perception of arterial hypertension as a major risk factor was poor, as expressed in citations by John Hay: “*The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it*” [1] and Paul D White in 1931: “*The treatment of the hypertension itself is a difficult and almost hopeless task ... we know the hypertension may be an important compensatory mechanism*” (Paul D White. Heart Disease (1st edn.) McMillan, New York (1931)).

This perception was of political relevance: US President Franklin Delano Roosevelt died “unexpectedly” at the end of World War II from a hemorrhagic stroke caused by exorbitantly increased arterial blood pressure as recorded by his personal physician during the Yalta Conference.

Since then, the attitude towards arterial hypertension has changed. Today, we know that the blood pressure significantly

correlates with the incidence of cardiovascular events; reduction of only 20 and 10 mmHg in systolic and diastolic blood pressure, respectively, results in an almost 50% decrease of death caused by cardiovascular events, independent of the patient's age [2].

Today, cut-off values for a detailed definition of hypertension are available. Gold standard is the 24-hour blood pressure measurement, which should not exceed 125–130/80 mmHg. Most clinical trials use the office blood pressure, where the threshold is set at 140/90 mmHg. Cut-off values for day, night, and home measurement have also been defined [3].

Using these cut-offs, the prevalence of arterial hypertension in Western Industrialized Nations is alarming, with rates of over 50% in Germany [4]. These rates are increasing and have been prognosticated to increase even further due to factors like increasing age, BMI, and prevalence of metabolic syndrome. In the Western countries, the prevalence of arterial hypertension is likely to increase by around 25% until 2025. The most dramatic development is expected in newly industrialized countries like China and India, where hypertension might increase by around 80% during this time [5].

FIGURE 1: Role of sympathetic activation in blood pressure regulation.

For the treatment of arterial hypertension, a wide variety of pharmaceutical substances is available. Unfortunately, the majority of patients require at least two or three of these drugs to achieve normotension [6–8]. Considering this, it is hardly surprising that in clinical practice, controlled hypertension is achieved in only 45% of patients, and in 42%, hypertension is uncontrolled (target blood pressure not achievable with <3 substances) and refractory in 13% (target blood pressure not achievable with >3 substances) [9].

Renal denervation therapy addresses this last group of patients with refractory arterial hypertension.

This paper gives an overview of the new procedure and discusses its indications, limitations, and success factors.

2. Methods and Results

2.1. Renal Denervation Therapy (RDT). The rationale of RDT is a mechanical weakening or destruction of renal sympathetic activity. Afferent and efferent sympathetic fibers enter the kidneys on the level of the renal arteries, and this provides us with an invasive access for catheterization-based procedures.

Sympathetic vasoactive mediators directly regulate vasoconstriction of vascular smooth muscle cells. Additionally, there is an indirect activation of the renin-angiotensin system (RAS), regulating fluid balance and blood pressure (Figure 1) [10]. Sympathetic activation, therefore, plays a major role in the pathogenesis of arterial hypertension, and patients with hypertension exhibit increased catecholamine levels in the renal veins compared to patients without hypertension. Renal

sympathetic activation is also the cause of secondary health issues, including hypertrophy of cardiac myocytes resulting in heart failure and myocardial ischemia, insulin resistance, and insomnia (Figure 1).

The easy access to the sympathetic fibers gives us the opportunity to use our knowledge from high frequency ablation procedures for a transversal thermal damaging of these fibers.

So far, data on this new procedure are sparse. Still, the results of the few studies available are impressive. In the Simplicity-HTN1 trial the office blood pressure of 45 patients with refractory hypertension, using a median of 4.4 pharmaceuticals and a median blood pressure of 177/101 mmHg, was markedly reduced over time and to an extent that would not be achievable with medication [11]. When defining nonresponders as patients with a reduction in systolic office blood pressure below 10 mmHg, there were 6 nonresponders in Simplicity-1 (13%). When using 24-hour blood pressure instead of the office blood pressure, results were slightly less impressive but still remarkable with a median reduction of 11 mmHg, which, considering the effect of blood pressure reduction on cardiovascular events, is a true benefit for the patient.

Importantly, Simplicity-1 also showed that RDT has no impact on the patient's renal function.

Simplicity HTN-2 was a multicentre, prospective, randomized trial enrolling 106 patients with systolic blood pressure >160 mmHg despite taking ≥3 antihypertensive drugs. The results in this trial were similarly promising with a reduction in systolic blood pressure of up to 30 mmHg. After

FIGURE 2: Effect of RDT on systolic and diastolic 24-hour blood pressure over time in the first series of Charité patients (unpublished data).

a 6-months followup, over 80% of patients who were randomized into the RDT group had systolic blood pressure values below 160 mmHg, with 40% of patients below 140 mmHg [12]. Limitations of both simplicity studies are the small patient numbers and the use of office blood pressure.

At the Charité Berlin, already over 100 patients were treated with RDT. Unlike in Simplicity, 24-hour blood pressure was used to measure the effect. As expected, the measured effect is, with a blood pressure reduction around 6 mmHg, smaller than in the Simplicity trials (Figure 2).

When performed by an experienced investigator, RDT causes very few complications. Sievert et al. reported 4 complications in 153 procedures, including one dissection of the renal artery and three pseudoaneurysms after venipuncture (Sievert, European Society of Cardiology 2010).

The indication for RDT was defined by an expert consensus in 2011 [13]. Patients eligible for RDT should have a systolic blood pressure >160 mmHg (150 mmHg in patients with diabetes mellitus) and ≥ 3 antihypertensive drugs. The GFR should not be below 45 mL/min.

The expert consensus also defined that the procedure should be performed in an interdisciplinary cooperation of hypertensiologists, nephrologists and possibly neurologists forming a Hypertension Excellence Centre. It is of utmost importance to concentrate patients in centers where many procedures per year can be performed.

Preconditions include the rule-out of secondary hypertension and pseudorefractory hypertension (white coat hypertension), securing of a credible long-term medication adherence, and optimization of conservative therapeutic strategies. Additionally, all patients require vascular imaging diagnostics like renal angiography, CT or MRI prior to RDT to study the anatomic conditions and exclude renal artery stenosis.

FIGURE 3: So-called notches in the renal artery after successful RDT. These notches disappear over time.

It is very important to recognize that the procedure can be very painful; patients require effective analgesia and sedation. Furthermore, radiation exposure and, even more importantly, contrast media exposure, which is injected directly into the renal artery, need to be kept at a minimum (<30 mL of contrast media/artery). Interventional standards include starting the procedure in the distal section of the renal artery, avoiding recrossing and tenting and avoiding side branches (Figure 3). Ablation should not be performed in significant stenoses, calcifications and in fibromuscular dysplasia. Centers performing RDT need to know and deal appropriately with complications like renal artery spasms, which can persist for hours and days in certain patients.

3. Discussion

Patients with a GFR below 45 mL/min should currently not undergo RDT except for in the setting of clinical trials. Still, especially some patients with a GFR below this cut-off often require treatment of refractory hypertension the most. If strict minimization of contrast media exposure and minimalistic interventions is applied, the procedure could also be performed in this patient group.

There is no age restriction for RDT; patients in the 7th or 8th decennium profit from RDT, and most patients may leave the hospital on the same day.

A very important factor in trials regarding RDT is the method of assessing the blood pressure. The office blood pressure, which was assessed in both Simplicity studies, is especially sensitive towards sympathetic activation. This is most likely the reason why the office blood pressure is reduced much more significantly after RDT than the 24-hour blood pressure, and the results using the office blood pressure cannot be directly compared to studies using the 24-hour blood pressure. Continuous 24-hour blood pressure measurement includes the blood pressure during nighttime with low sympathetic activity and leads to underestimate the daytime values. Currently, there are no data available correlating office blood pressure and 24-hour blood pressure. Still, blood pressure reduction varies markedly between patients, and even if the median reduction is below 6 mmHg, many patients profit from the procedure.

Long-term data on the effectiveness of sympathetic denervation are available from the 50 s and 60 s, when surgical

denervation was a method to treat refractory hypertension, but with a mortality rate of around 30%. Long-term data regarding RDT are so far limited, but 3-year data of Simplicity I show that the arterial blood pressure in treated patients is still low and in some patients even declining at this stage.

4. Conclusion

Renal denervation therapy (RDT) is an invasive procedure but, when performed by an experienced operator, has a very low rate of complications. With adequate analgesia and sedation, RDT is well accepted by the patients. First results of clinical trials have shown that RDT is an effective measure against refractory arterial hypertension, but long-term data are still lacking.

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