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EDITORIAL

Renal Denervation for Resistant Hypertension: Blinded or Unblinding Recent Trial?

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Renal artery sympathetic denervation, performed via a percutaneous catheter ablation procedure applying radiofrequency energy, has been developed to address renal sympathetic overactivity as a pivotal mechanism in the pathophysiology of hypertension.[1] In 2009, the first-in-man experience with this procedure was published.[2] Several studies followed, including the Symplicity HTN-1 trial (n=45), the randomized Symplicity HTN-2 trial (n=106) and the expanded open-label Symplicity-2 study (n=153).[3-6] However, all the initial evidence suffered from important limitations related to small cohort size, short follow-up and by and large incomplete data.[1] According with a review and meta-analysis of 12 studies, most of them being observational studies without a control group, renal denervation in a total population of 561 patients with resistant hypertension, resulted in a significant reduction in mean blood pressure at 6 months.[7] In the controlled studies (2 randomized controlled trials, n=133; and 1 observational study with a control group, n=50), there was a reduction in mean systolic and diastolic blood pressure at 6 months of –28.9 mm Hg and –11.0 mm Hg, respectively, compared with the control groups ($p < 0.0001$). In the uncontrolled studies (n=396), there was a reduction in mean systolic and diastolic blood pressure at 6 months of –25.0 mm Hg and –10.0 mm Hg, respectively, compared with the pre-procedural values ($p < 0.00001$). One renal artery dissection and 4 femoral pseudoaneurysms were reported as procedural complications.[7]

SYMPLICITY HTN-3 was a prospective, single-blind, randomized, sham-controlled trial[8,9] of the effects of catheter-based renal denervation in 535 patients with severe resistant hypertension and systolic blood pressure ≥160 mmHg, who were receiving an antihypertensive regimen including at least 3 drugs, among which one was a diuretic. As detailed above, prior unblinded trials in similar cohorts indicated a favorable effect of this percutaneous procedure. Initially announced by Medtronic on January 9, 2014[8] and then presented in the 2014 American College of Cardiology Meeting on March 29, 2014, and simultaneously published in the New England Journal of Medicine,[9] the results of this trial were negative for the primary efficacy end point which was the change in office systolic blood pressure at 6 months. The mean change in systolic blood pressure at 6 months was −14.13 mm Hg in the denervation group and −11.74 mm Hg in the sham-procedure group, which is a nonsignificant difference of −2.39 mm Hg (P=0.26). Results were also negative for the secondary end-point, the change in mean

24-hour ambulatory systolic blood pressure (−6.75 in the denervation group and −4.79 mm Hg in the sham-procedure group, a nonsignificant difference of −1.96 mm Hg; P=0.98). Finally, there were no significant differences in safety between the two groups: similar rates of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of >70% at 6 months.[9]

Since the announcement of these results, a heated debate has ensued whether this procedure is here to stay or doomed to oblivion.[10-12] Those who consider these results as unblinding to the "truth", talk about implausible results of prior studies ("too good to be true"), hopeful speculation and foggy hype, intervention bias, and time to close the book on renal denervation. Contrariwise, those who are still fan of the procedure claim otherwise, that the procedure is safe and here to stay, they point to technical inadequacies of the procedure being performed with a catheter providing single point focal ablation compared to other systems capable of circular ablation, perhaps the procedure was performed by less experienced operators; however, they admit that the page on renal denervation should be turned but the book should stay open, and there may be alternative methods to this procedure.

A common ground between these two views appears to converge towards the need for further well-controlled studies, with rigorous design similar to the design of Simplicity HTN-3 trial, perhaps with other technologies and newer generation devices and in more selective patient groups. Better guidance to the performance of the procedure should also be sought, as currently this procedure remains a blind procedure without a specific procedural end-point. The result is only seen clinically during follow-up.

Thus, whether negative or not-positive or neutral, and despite a plethora of speculations why so, the results of SIMPLICITY-HTN-3 trial raised serious questions about the efficacy of renal denervation in resistant hypertension and have significantly curtailed the initial enthusiasm about this procedure and its impact on the treatment of hypertension. Further subanalyses of this trial's data may provide some insight and generate hypotheses whether there may exist any subgroups of patients who might benefit from the application of this procedure. Future clinical trials with newer generation ablation systems in more specific and select patient groups might shed further light on the fate of this procedure.

Perhaps, until more data become available, the Swiss Expert Consensus[13] might be a pertinent guide for the use of this procedure: ● confirmation of truly resistant hypertension, ● exclusion of secondary forms of hypertension, ● a multidisciplinary decision confirming the eligibility, ● facilities that guarantee procedural safety and ● a long-term follow-up of the patients, if possible in cooperation with a hypertension specialist. The authors of this consensus indicate that these steps are essential until long-term data on safety and efficacy are available. All these, of course, should be explained to the patient and his/her family, together with the recent results of the SIMPLICITY HTN-3 trial, within the context of participatory medicine before obtaining a written informed consent for the procedure. Indeed, according with the Copenhagen experience, 10% of those referred for renal denervation had secondary forms of hypertension and together with other exclusions uncovered, only 51% were finally eligible for the procedure.[14]

Thus, until more data become available from further subanalyses of the SIMPLICITY HTN-3 trial or other appropriate trials, patients undergoing this procedure should be rigorously scrutinized and carefully selected, and perhaps better enrolled in investigation protocols. However, encouraging are the results of safety of the procedure from both the SIMPLICITY HTN-3 trial and the 3-year report of the SIMPLICITY HTN-1 trial.[8,15] Finally, some other novel areas of potential benefit of renal denervation might still be worth exploring, such as in patients with atrial fibrillation and patients with heart failure.[16,17]

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REVIEW

Transvenous Temporary Cardiac Pacing

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Abstract

Transvenous temporary cardiac pacing is a rather old but still contemporary life-saving technique, with a unique value in the treatment of critically ill patients suffering from rhythm disturbances and associated hemodynamic compromise. Physicians involved in the management of such patients should always keep in mind the indications and contraindications of transvenous temporary cardiac pacing, and should be at least familiar with the insertion technique and the post-insertion care.

Key Words: temporary cardiac pacing; bradycardia**;** overdrive pacing

List of Abbreviations

AMI = acute myocardial infarction; AV = atrio-ventricular; BBB = bundle branch block; CHB = complete heart block; ECG = electrocardiogram; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LPFB = left posterior fascicular block; RA = right atrium; RBBB = right branch bundle block; RV = right ventricle; SVT = supraventricular tachycardia; SuVT = sustained ventricular tachycardia; TCP = temporary cardiac pacing; TdP = torsade de pointes

Introduction

Temporary cardiac pacing is a life-saving procedure used as a means of electrical stimulation of the heart through the use of pacing leads, in order to treat dysrhythmias, until they are resolved or until a long-term therapy is adopted.[1-5] Temporary pacing is effected via transvenous, transcutaneous, or epicardial approaches. Transcutaneous pacing is delivered via cutaneous adhesive pads placed in an anteroposterior position, has the advantage of being immediately available for emergency cases of asystole but it requires high energy to capture the heart, causing significant discomfort to the wake patient, and is reserved for those who are comatose or as a bridge until transvenous endocardial pacing is rendered feasible.[1,5,6] Epicardial wires are routinely placed during cardiac surgery to provide backup pacing in the event of perioperative bradyarrhythmias, but also to diagnose and overdrive certain tachyarrhythmias (e.g. atrial flutter).[7] However, the most common and reliable approach to temporary pacing is provided with transvenous insertion of temporary pacing wire.[1-5]

Transvenous temporary cardiac pacing (TCP) was first described by Furman et al in 1958 in dogs and in 1959 in human beings,[8,9] initially for the correction of complete heart block, but the indications have subsequently expanded to comprise a variety of bradyarrhythmias but also a list of tachyarrhythmias, including the diagnosis and overdrive suppression of supraventricular and ventricular tachycardias.[1,3,4] In its most common use of supporting the patient with bradycardia, temporary pacing typically serves as a bridge to a more definitive solution to a low heart rate, such as permanent pacemaker implantation, or resolution of a transient or reversible cause, e.g. bradycardic effect of drugs, electrolyte disturbance, inferior-wall myocardial infarction, etc.

Indications

Transvenous temporary cardiac pacing is most commonly used to treat symptomatic bradycardia due to sinus node dysfunction or atrioventricular (AV) block. In