NEW CONCEPTS FOR SYMPATHETIC RENAL ARTERY DENERVATION: REVIEW OF EXISTING LITERATURE AND CASE REPORT

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ABSTRACT

Arterial hypertension (HTN) is one of the major risk factors for cardiovascular disease, and also leads to hypertensive heart disease, hypertensive nephropathy, cerebrovascular disease as well as cardiac arrhythmias. Despite receiving antihypertensive drugs, patients often do not reach their individual guideline blood pressure (BP) levels. Interventional sympathetic renal artery denervation (RDN) has been demonstrated to successfully lower blood pressure in patients with systolic blood pressure values ≥160 mmHg while on three or more antihypertensive drugs. The Symplicity™ device (Medtronic, Palo Alto, CA, USA) was shown to be safe, with side effects rarely occuring. Recent data from registries show that this procedure is efficient in about 70% of patients. New upcoming devices aim to significantly reduce procedure time and post-procedural complications through new concepts and strategies for RDN, and may possibly improve its effectiveness. Currently, radiofrequency (RF) is the dominant modality for RDN, but devices using energy delivery via ultrasound (US) have been developed. Intravascular optical coherence tomography (IVOCT) is a novel invasive diagnostic modality, which is able to analyse endothelial integrity at a resolution of approximately 10 μm. Recent IVOCT findings after RDN find evidence for endothelial damage and thrombus formation introduced through RDN, yet the clinical significance is uncertain since similar images are obtained when analysing coronary arteries after stenting. Nevertheless, irrigated RDN devices could reduce the observed issues and deliver more energy to deeper tissue levels similar to that observed in ablation of atrial fibrillation. This article provides an overview of currently available data and devices; furthermore we present a case report on the OneShot™ Renal Denervation System (Covidien, Campbell, CA, USA) and preliminary findings of IVOCT examinations after RDN.

Key Words: Renal denervation, refractory hypertension, intravascular optical coherence tomography.

INTRODUCTION

Today nearly one billion adults worldwide are suffering from arterial hypertension (HTN).[1] As one of the major risk factors for cardiovascular disease, HTN can lead to hypertensive heart disease, hypertensive nephropathy, cerebrovascular disease and cardiac arrhythmias.[2] Treatment strategies for HTN imply lifestyle changes such as smoking cessation, weight reduction, physical exercise and sodium restriction.[3] Combination treatment with drugs such as diuretics, angiotensin receptor antagonists, ACE inhibitors, direct renin inhibitors as well as beta-blockers and calcium antagonists is mandatory.[4]

Holman et al.[5] reported that patients assigned to 'tight controlled' HTN had a relative risk reduction of 32% for diabetes-related death, 44% for stroke, and 37% for microvascular disease compared to those in the 'less tight controlled' group. This relative risk reduction did not persist when blood pressure levels were no longer maintained.

Despite effective antihypertensive drugs, HTN often remains uncontrolled in terms of reaching guideline values, with only 25–35% of patients reaching their individual recommended blood pressure levels.[6] Moreover, around 30% of patients have systolic blood pressure ≥160 mmHg (>140 mmHg for patients

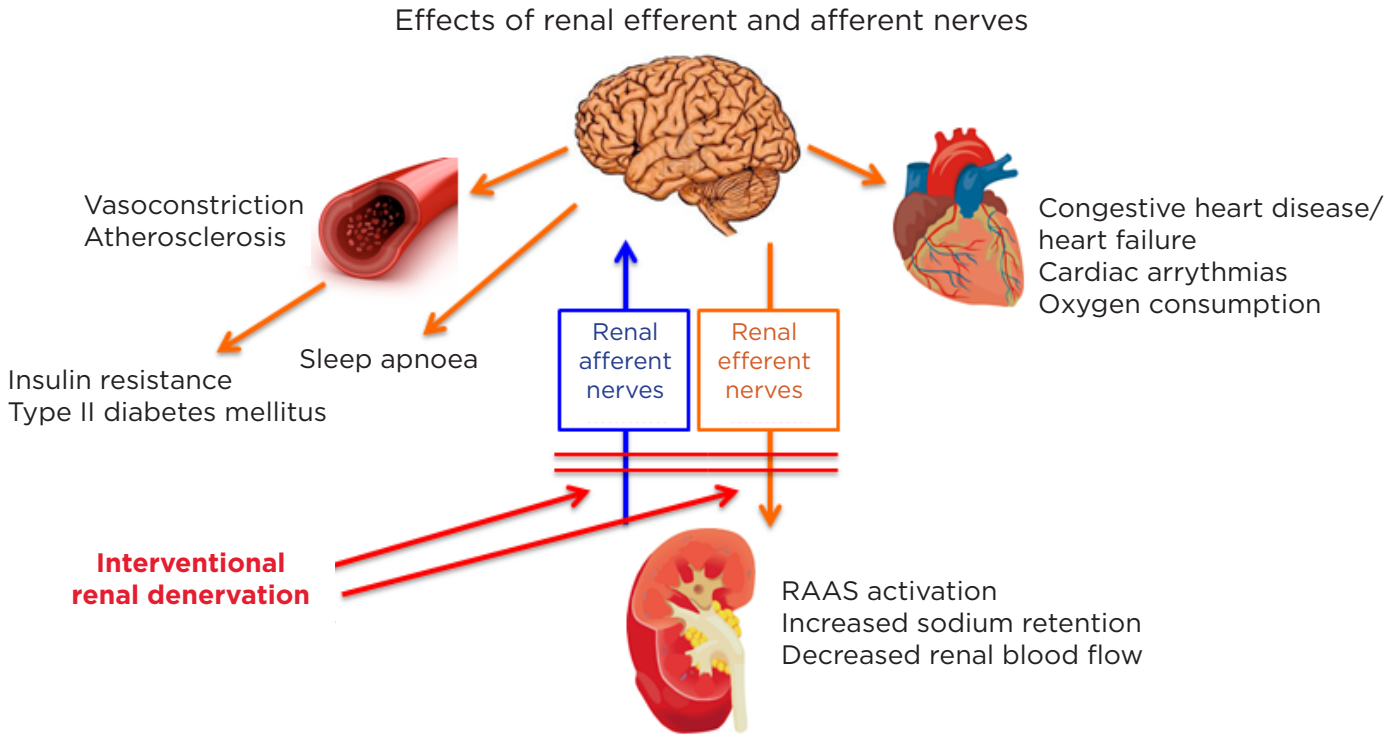

Figure 1: Effects of renal artery efferent and afferent nerves as a target for renal artery denervation (modified from Sobotka et al).[37]

with diabetes) at office-based measurements, despite taking three or more antihypertensive drugs ('refractory HTN').[7,2] Uncontrolled HTN leads to serious adverse cardiovascular events including stroke and cardiovascular mortality.[8] Therefore, there is an urgent need for additional methods to better control blood pressure levels.

High frequency ablation of the renal sympathetic afferent and efferent nerves is gaining momentum as a clinical choice to treat such patients (Figure 1). These nerves are part of a vicious circle where sympathetic drive leads to increased blood pressure, both by the renin angiotensin aldosterone system (RAAS) as well as central stimulation. To date, approximately 10,000 patients have been successfully treated by this method.[9]

Recently published studies have confirmed the safety and efficacy of interventional renal artery denervation (RDN) for the treatment of refractory HTN employing the Symplicity™ ablation catheter.[1,9,10] Several completed and on-going studies examine other potential clinical benefits of RDN using this device for the treatment of cardiac failure, sleep apnoea, diabetes mellitus and cardiac arrhythmia.[2,11] The Symplicity™ device is designed to deliver radiofrequency (RF) energy in a point-by-point application, each point ablation lasting two minutes, at four to six sites along the renal artery. During ablation, general sedation is necessary due to abdominal pain. Bilateral treatment of the arteries takes between 40 and 50 minutes with this system.[12] Our group reported a 30% non-responder (blood pressure reduction of systolic office based measurement ≤10 mmHg) rate after RDN with the Symplicity™ device, when analysed as part of a real-world registry.[13] Several devices have been developed that aim to decrease procedure time and possibly allow for better control with regards to the pattern of ablation (Table 1).

Rare long-term complications like renal artery stenosis have been used to justify further examinations of the consequences of RDN to the vessel wall.[14,15] IVOCT is a novel invasive diagnostic modality, which permits visualisation of the vessel wall with a resolution of about 10-15 µm. This technique allows for an accurate analysis of stent apposition and endothelialisation, endothelial integrity, plaque characterisation and thrombus formation.[16] IVOCT identified small endothelial lesions and thrombus formation following RDN employing the Symplicity™ device as well as the EnLigHTN™ Renal Denervation System (St. Jude Medical Inc., Westford, USA).[17] Preliminary data from our institution confirmed this observation. We were able to visualize small endothelial lesions in two subsequent patients after

Devices (producer)	Characteristics	Modality	CE mark	Major Trials (n) Status
Symplicity™ Renal Denervation System (Medtronic)	Non-occlusive flexible catheter with a single electrode tip	RF, 6Fr	+	Symplicity HTN I (152) completed Symplicity HTN II (106) completed Symplicity HTN III (530) follow-up
OneShot™ Renal Denervation System (Covidien)	Irrigated, helical over the wire balloon catheter	RF, 8Fr	+	RHAS (12) completed RAPID (50) follow-up
Paradise™ Renal Denervation System (ReCor Medical)	Balloon catheter combined with a US-emitting transducer and cooling system	US, 8Fr	+	REDUCE (11) completed REALISE (20) recruiting ACHIEVE (50) recruiting
EnligHTN™ Multi Electrode Renal Denervation System (St. Jude Medical)	Occlusive, over the wire balloon catheter with embedded multi-electrodes	RF, 8Fr	+	EnligHTN I (47) follow-up EnligHTN II (500) recruiting EnligHTN III (30) recruiting
V2 Renal Denervation System™ (Vessix Vascular, Boston Scientific)	Over the wire variable size balloon catheter with embedded bipolar electrodes	RF, 8Fr	+	REDUCE-HTN (150) follow-up
Symplicity Spyral™ Renal Denervation System (Medtronic)	Non-occlusive, multi-electrode helical catheter	RF, 6Fr	-	First Data presented on TCT 2012 by R. Whitbourne, St.Vincent´s Hospital, Melbourne, AUS (9). CE study finished but not yet presented
Celsius® ThermoCool® Renal Denervation Catheter (Cordis)	Irrigated, multi-electrode	RF	-	RENABLATE (30) recruiting

Table 1: Current and upcoming devices for RDN.

RDN with the Symplicity™ device (Figure 2, 3). The clinical significance as well as frequency of such events remains to be determined. IVOCT frequently detects similar lesions after percutaneous coronary intervention (PCI), where no clinical sequelae are observed.[18]

This article aims to give an overview of currently available data as well as upcoming devices and ablation strategies. Additionally, we present a case report of a patient treated with the OneShot™ Renal Denervation System (Covidien, Campbell, CA, USA) and provide preliminary IVOCT findings after RDN.

Current Data on the Symplicity™ RDN Device

RDN has a growing impact as alternate therapy for patients with therapy refractive HTN, defined as office systolic blood pressure ≥160 mmHg (> 140 mmHg for patients with diabetes) despite drug therapy with three or more antihypertensive drugs including at least one diuretic. The Symplicity HTN-2 randomised trial has shown a significant reduction in systolic blood pressure, with ≥10 mmHg shown in 84% of patients who underwent RDN 6 months after the procedure. [10]

Office blood pressure was reduced by -33/-11 mmHg and no adverse events were noted. The 1 year results of the Symplicity HTN-2 trial were recently published: 63% of the initial control group patients crossed over to the interventional therapy and showed a reduction in systolic blood pressure at ≥10 mmHg 6 months after the procedure. Office blood pressure was lowered by -24/-8 mmHg.[1] The first randomised group showed no additional reduction in office blood pressure between 6 and 12 months after the procedure, with the initial effect being maintained. Several studies have been published with similar

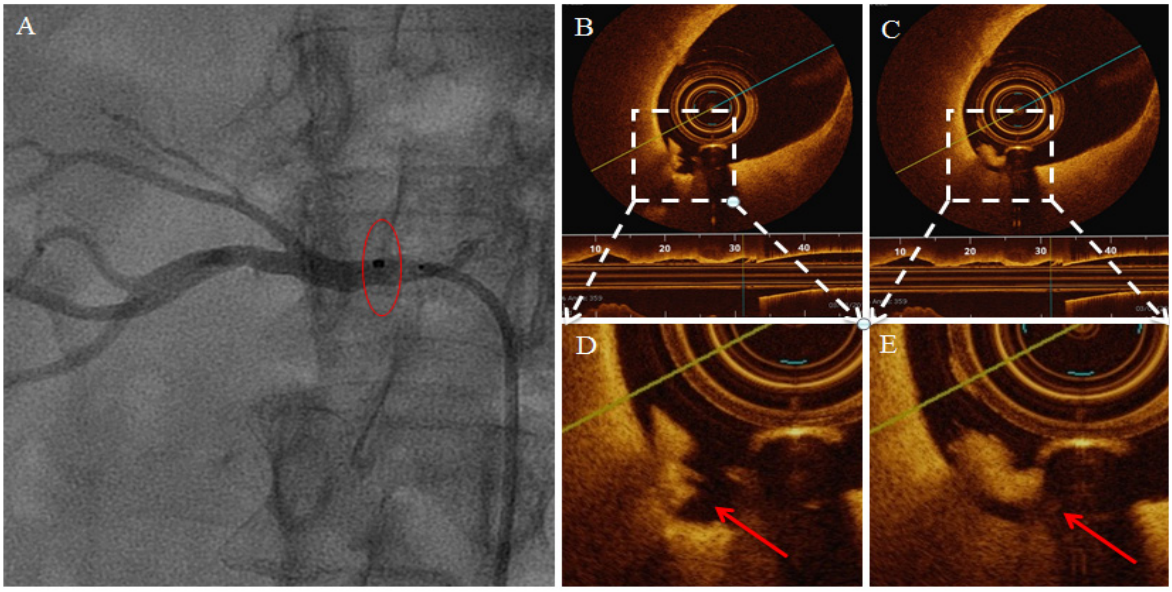

Figure 2. Intravascular optical coherence tomography (IVOCT) findings after RDN with the Symplicity™ RDN System. I

A: Angiography of the right renal artery with the Symplicity™ RDN catheter. Red circle marks the region analysed with IVOCT and presented in B,C,D,E. No endothelial lesions are visible via angiography.
B/C: IVOCT-analysis after RDN employing the Symplicity™ RDN system. D/E magnified region in white box. The red arrows mark local endothelial damage with thrombus formation. No other lesion was observed in this vessel after six ablation points.

results in the investigated patient cohort.[19-22] In our institution, we followed patients who underwent RDN in a registry called ALSTER BP to determine if the described findings can be reproduced in a real world setting.[13] The results underline the safety profile of interventional RDN procedures.

Since it is generally known that RDN influences sympathetic tone, several studies have been performed to investigate a possible influence, not only on the blood pressure, but also on other diseases modulated by sympathetic drive including heart failure, metabolic syndrome or atrial fibrillation, suggesting that there might be more targets for this therapy. RDN has been found to improve glucose tolerance in diabetic patients, reduce cardiac hypertrophy in the context of diastolic heart failure and improve control of sleep apnea.[19,22-26]

New Strategies for RDN

In order to improve actual RDN systems, several new devices have been developed (Table I). The goal of these systems is the reduction in procedural duration, by performing a single-shot energy application (RF or US) to the vessel wall while increasing effectiveness.[2] The shorter duration of RDN procedure will potentially lower the amount of contrast dye used. Furthermore, these devices aim

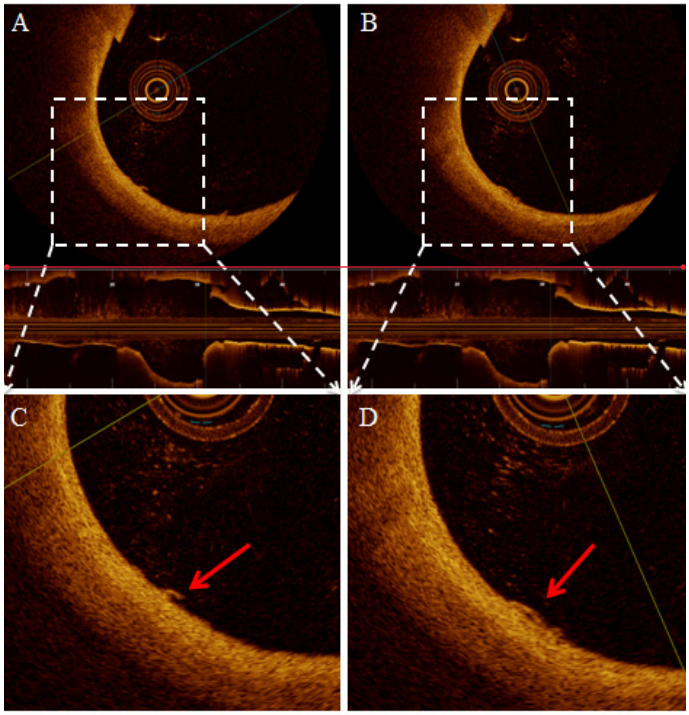

Figure 3: Intravascular optical coherence tomography (IVOCT) findings after RDN by Symplicity™ RDN System. II

A/B: IVOCT-analysis after RDN employing the Symplicity™ RDN system. C/D: Magnification region in white box. The red arrows mark local endothelial damage. This was the only lesion observed after six ablation points in this vessel.

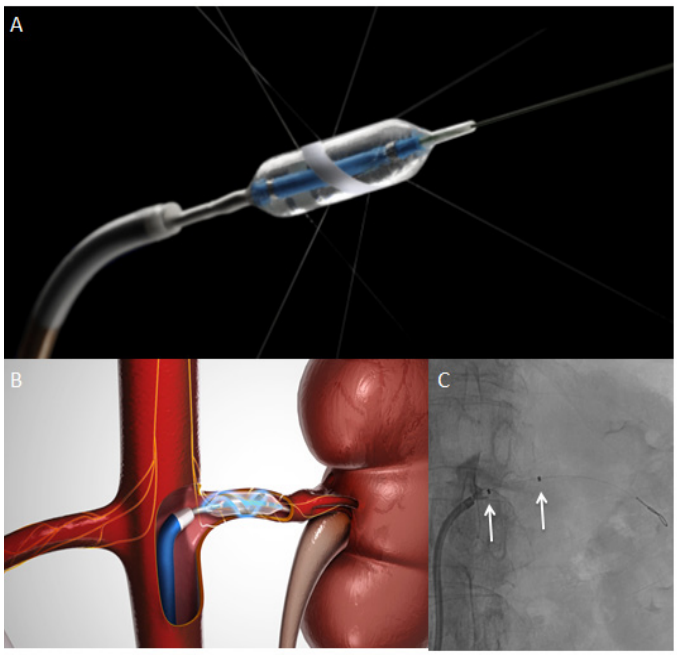

Figure 4: The Covidien OneShotTM RDN device. A: The OneShot™ RF balloon catheter with a spiral RF electrode and irrigation holes. A low pressure irrigation runs continuously during balloon inflation, providing cooling of the non-treated region of the artery during ablation. B: Left renal artery cutaway showing inflated balloon with spiral electrode (silver with blue halo). C: Left renal artery selective angiogram showing inflated balloon with two radiopaque markers (white arrows) for visualisation.

to improve the responder rate by a more defined ablation pattern.

Symplicity Spyral™ Renal Denervation System

The Symplicity Spyral™ (Medtronic, Palo Alto, CA, USA) device is not yet commercially available. It will feature a radio-frequency-emitting, four-electrode, non-occlusive spiral catheter to significantly reduce procedure time. First data with the device were presented at the TCT 2012 congress but measurements are not yet published. The CE mark is expected shortly and studies are on-going.[27]

EnligHTN™ Multi Electrode Renal Denervation System

The EnligHTN™ multi-electrode Renal Denervation System offers a 'cage' with four embedded electrodes to deliver RF energy to the target vessel wall. Preliminary data of the first-in-human, multicentre, EnligHTN I study (ClinicalTrials.gov Identifier: NCT01438229) showed safety and efficacy in a small cohort of patients (n=47) with resistant HTN with a surprisingly early effect. The 6 month follow-up showed a rapid and sustained reduction of HTN, with 76 % of participants presenting with ≥10 mmHg reduction in systolic blood pressure and 33% reaching <140 mmHg measurements in office blood pressure.[28] Currently, further clinical trials are recruiting patients (EnligHTN II, ClinicalTrials.gov Identifier: NCT01705080 and EnligHTN III, ClinicalTrials.gov Identifier: NCT01836146). A recently published trial showed evidence for local tissue damage with oedema and thrombus formation after RDN measured by IVOCT. The comparison of the EnligHTN™ vs. the Symplicity™ devices showed no significant difference in the amount of oedema or vessel spasm. Nevertheless, one incidence of arterial dissection with the Symplicity™ catheter and two cases of endothelial and intimal disruptions were observed after RDN by the EnligHTN™ device. Furthermore, a trend towards a greater amount of thrombus formation and a significantly greater thrombus load per renal artery was observed after RDN with the EnligHTN™ system compared with the Simplicity system, in a small patient cohort.[17]

V2 Renal Denervation System™ (Vessix Vascular, Boston Scientific)

This RDN system uses a variable sized balloon catheter with embedded RF bipolar electrodes, the balloon allows RF applications in different vessel sizes. This system is able to totally occlude blood flow, minimising heat loss into the bloodstream, thereby increasing effectiveness of the procedure. First clinical data were presented at the TCT 2012 congress (REDUCE-HTN Pilot Study Cohort, ClinicalTrials.gov Identifier: NCT01541865).[29]

Paradise™ Renal Denervation System

The Paradise™ RDN system (ReCor Medical, Ronkonkoma, NY, USA) uses a balloon catheter with a cylindrical transducer that emits US energy circumferentially to the selected vessels. Since US passes through the surrounding fluids, no direct tissue contact is required to focus energy to a specified depth and induce high temperatures within the target vessel surrounding soft tissue. This allows for a liquid-cooling system around the transducer to cool down the arterial wall, reducing damage to non-target tissues. The first-in-man, single-arm, open-label REDUCE study (n=11 patients) showed an effective and sustained decrease in blood pressure. The 3 month follow-up measurements were comparable to RF RDN (which had reduction in office blood pressure of –36/–17 mmHg). The REALISE trial (ClinicalTrials.gov Identifier: NCT01529372) is a safety and efficacy,

single-arm, open-label, prospective study to be conducted on 20 eligible patients with a 12 month follow-up period. Completion will be approximately July 2014. The ACHIEVE study (ClinicalTrials.gov Identifier: NCT01789918) is a further single-arm, open-label, prospective, post-market, study (n=50 patients) with a twelve month follow-up period which is currently recruiting participants. In conclusion, the existing preliminary results indicate that US RDN is a safe and effective treatment for refractory HTN. Nevertheless, these results have to be proven in larger trials and registries.

Covidien OneShot™ Renal Denervation System

The first irrigated ablation system for RDN was presented initially by Maya Medical in 2012 with the release of the OneShot™ Renal Denervation System, now part of Covidien. This over the wire balloon-based irrigated catheter applies low-level RF energy with a single application per artery to perform rapid and effective RDN (Figure 4).

The irrigated RF balloon catheter features a helical configured mono-polar silver electrode on the non-compliant balloon. This ensures the desired spiral RF application with one single ablation. During the ablation procedure, saline continuously flows out of special irrigation holes in the balloon, which 'dilates' the balloon with a nominal pressure of one bar. These holes are designed to avoid injury of the non-target area and reduces overheating as well as clotting formation during RF delivery process.[12] The RF generator (RFG) provides the RF energy, while the intergraded pump system warrants saline irrigation during the whole procedure. A 7/8 Fr compatible system in combination with a conventional guidewire is used to deliver the balloon to the renal artery. Radiopaque markers at the distal and proximal balloon ends warrant exact positioning under fluoroscopy. Currently 5, 6 as well as 7 mm diameter and 20 mm length balloon sizes are available for renal arteries between 4 and 7mm diameters. For RDN, the balloon is inflated with normal saline automatically delivered by the RFG. The inflated balloon stabilises electrode contact within the renal artery and warrants wall contact during the ablation process. For RDN, a single, 2 minute, 25W RF energy delivery is performed in each artery, reducing the process duration to 4 minutes ablation time.[12]

Preclinical animal studies presented a good efficacy and safety profile at 6 months of follow-up, without any evidence of significant angiographic stenosis or intimal hyperplasia.[12] The RHAS (Renal Hypertension Ablation System) trial (n=8 patients) showed promising results for humans concerning feasibility and efficacy. A mean change of -31 mmHg on systolic blood pressure after 30 days and -34 mmHg at 6 months follow-up was presented.[30] Change in systolic blood pressure at 1 month was similar to the data of the Symplicity™ HTN trials.[12] The RAPID trial (ClinicalTrials.gov Identifier: NCT01520506) is a prospective multicentre safety and efficacy 50-patient study and has enrolled participants in Europe and New Zealand. The study is in follow-up and data presentation is pending.

Cordis Celsius® Thermocool® Renal Denervation System

Ablation for cardiac arrhythmias has developed into two directions, namely 3D mapping systems for precise analysis of arrhythmia patterns, as well

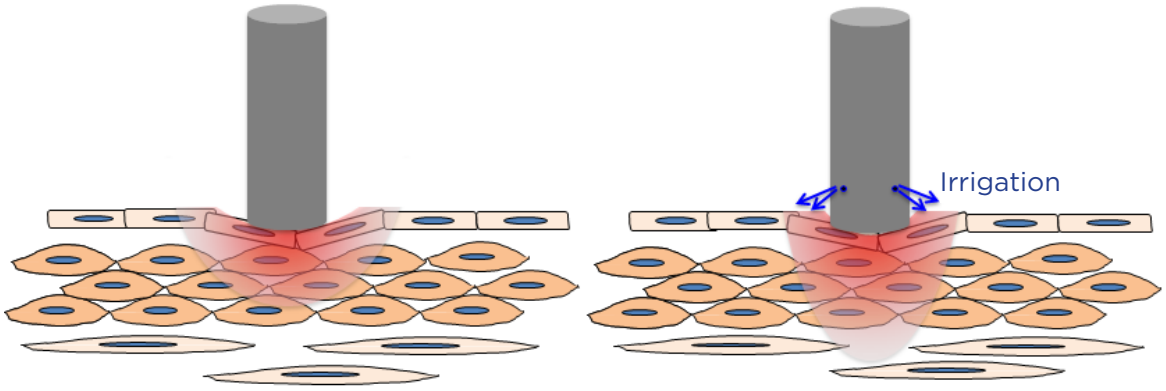

Figure 5: Irrigated RF ablation as investigated in pulmonary vein isolation: Irrigation limits the 'backheating' of the ablation electrode, enabling maximum energy to be delivered deeper into the tissue.

as irrigation technology to maximise lesions depths while reducing char formation. A similar approach is taken with the development of Cordis in conjunction with Biosense Webster, two subsidiaries of Johnson &Johnson. The first-in-man data are expected to be presented during 2013.

Irrigated RF Ablation

Irrigated RF ablation has the potential to limit endothelial damage while increasing lesion depth, possibly allowing for a more consistent sympathetic denervation. Figure 5 shows the potential benefits of this technique as irrigation next to the surface of the electrode limits the 'backheating' of the ablation electrode and results in maximum energy delivery to occur deeper in the tissue. As sympathetic innervation is anatomically located in the adventitia of the renal artery this technique may be particularly suitable for RDN. The design of the OneShot™ provides irrigation holes that deliver saline during the course of the procedure. In ablation for atrial fibrillation, irrigated cooling maintains a lower electrode-tissue temperature, thus reducing the occurrence of char and limiting damage to the endothelium.[31] Another device allowing for irrigated renal denervation is currently being investigated (Cordis RDN device).

CASE REPORT

Renal Denervation by the Covidien OneShot™ Renal Denervation System

The patient was a 49-year-old non-smoking, non-diabetes male with refractory HTN (>160 mmHg office systolic blood pressure) and repetitive hypertensive crisis (>200 mmHg) despite multiple drug therapy (candesartan 32 mg daily, metoprolol 95 mg twice daily, hydrochlorothiazide 25 mg daily, moxonidine 0.2 mg daily) and intolerance of calcium channel blockers. Secondary causes for HTN were excluded. Further diagnoses were coronary artery disease with status post-anterior myocardial infarction (08/2005) and PCI/Stenting of left anterior descending artery as well as hyperlipidaemia. The patient reported repetitive systolic blood pressure >180 mmHg systolic and suffered from headache and reduced capacity during these episodes. The patient gave written informed consent for RDN with the OneShot™ Renal Denervation System. RDN was performed under sedation with midazolam, propofol and fentanyl. Prior to ablation, 7500I.E. of heparin was administered to achieve an ACT of > 200 sec. An 8Fr guide catheter was used to introduce the device into the renal arteries. The diameter of both

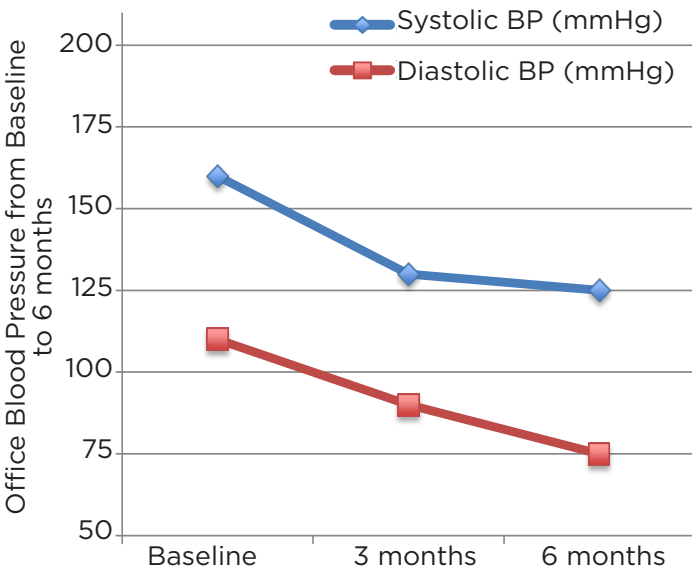

Figure 6: Follow-up after RDN via the OneShot™ RDN device. Office-based measurements of systolic and diastolic blood pressure at baseline, 3 and 6 months after RDN.

renal arteries was measured angiographically to 6.5-7.00 mm; therefore the 7 mm OneShot balloon was used to perform RDN with a single 2 minute ablation at each side. An angiography demonstrated no evidence of dissection or spasm of the renal arteries. Post-interventional creatinine levels remained stable. The patient was discharged from the hospital the next day in good condition. Dual antiplatelet therapy was administered with aspirin in combination with clopidogrel for 4 weeks according to our own protocol. The other medication remained unchanged. Mean office blood pressure 24 hours post-procedure was 149/105 mmHg. At 3 and 6 month follow-up visits, the patient was in good clinical condition, on the same medical regimen as at baseline and presented an effective reduction in blood pressure levels (Figure 6).

IVOCT Analysis After RDN

To date, no histological examinations of ablated human renal arteries have been published. Therefore, despite limited animal studies, nothing is known about the consequences of high energy application to the tender endothelial layer and the pathophysiological processes within the vessel wall after RDN.[32] Intravascular optical coherence tomography (IVOCT) is an invasive modality with the ability to provide detailed images at an axial resolution of 10-15 µm, enabling real-time visualisation of blood vessel wall microstructure in

vivo. This method enables accurate evaluation of tissue coverage after intracoronary stenting and has become an exploratory tool for different issues in the field of interventional cardiology.[16] For example, IVOCT is currently used for pre and post-procedural guidance in percutaneous coronary interventions, visualising stent apposition and endothelialisation as well as thrombus formation, characterisation of atherosclerotic plaques and artery wall dissection.[33-35] Recent findings of IVOCT analysis after RDN showed local endothelial damage with oedema and thrombus formation at the ablation spots.[36] IVOCT is able to visualise these vascular lesions.[17] We performed IVOCT analysis after RDN with the Symplicity™ system. Small endothelial damage sites (in one case with thrombus formation) were identified within the ablation area of the renal artery, suggesting that they were caused by RDN (Figure 4, 5). Based on published data from recent trials and registries, RDN is shown to be safe, with up to 3 year follow-up data available for patients participating in the Symplicity HTN-1 trial.[9] Nevertheless, the number of patients is still too low to evaluate the frequency of rare events.[14,15] Yet, no recommendation has been published regarding antiplatelet therapy following RDN with the Symplicity™ system. At our institution, we suggest the use of dual antiplatelet therapy for 4 weeks, to reduce the risk of thrombus formation after RDN.

Templin et al.[17] found evidence for an even higher formation of endothelial damage by the use of the EnligHTN™ Renal Denervation System compared to the Symplicity™ system. These findings suggest that the increase in electrodes may increase the risk for kidney infarction and renal artery stenosis through plaque formation induced by endothelial damage after RDN. The OneShot™ System aims to reduce these risks by the use of an irrigated balloon. We performed IVOCT analysis in two subsequent patients after RDN by this system and did not observe any endothelial damage within the examined renal arteries. We postulate that irrigated and fluid-cooled RDN devices may reduce the observed issues. Yet, these preliminary findings need to be proven in larger trials or registries to draw definitive conclusions.

CONCLUSION

Despite effective drug therapy, only 25–35% of HTN patients are reaching their individual recommended blood pressure levels, leading to end-organ damage and serious adverse cardiovascular events.[6] RDN is an effective technique for the treatment of refractory HTN; published data with the Symplicity™ device confirm efficacy, allowing for the introduction of this treatment into routine practice. This may limit HTN-associated end-organ damage. Several new devices are currently being studied in clinical trials, with the aim of reducing procedure time, while enhancing effectiveness and safety. These and any individual advantages and disadvantages have to be proven within the next years by executing larger clinical trials and registries. By performing IVOCT-analyses after RDN, it is now possible to understand the effects of the procedure concerning endothelial damage, thrombus and plaque formation as well as formation of renal artery stenosis.

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