# Considering a New Approach to Treatment of Uncontrolled Hypertension With the ROX Coupler Device

A discussion with Dr. Krishna Rocha-Singh and Prof. Dr. Felix Mahfoud on what makes the ROX Coupler device different from other hypertension interventions, how to implant the device, clinical study results, and anticipated results from ongoing studies.

**WITH KRISHNA ROCHA-SINGH, MD, AND FELIX MAHFOUD, MD**

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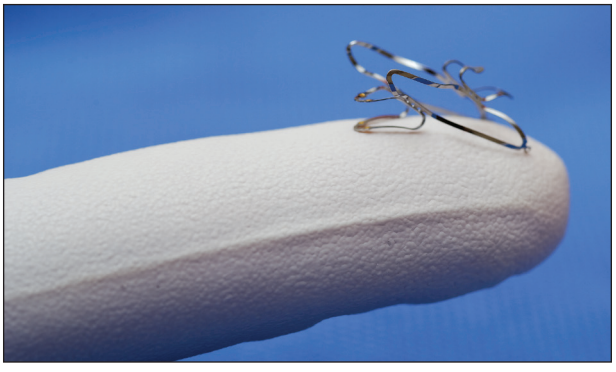
## What is the biggest risk of uncontrolled hypertension? Why is it important to consider new approaches?

Clinicians frequently encounter patients with uncontrolled hypertension. Retrospective cohort studies have established that patients with resistant and uncontrolled hypertension have a 25% increased risk of progression to end-stage renal disease or cerebrovascular accident over a 5-year period when compared to patients with nonresistant hypertension.[1] Additionally, not only is the risk of progression to end-stage renal disease and cerebrovascular accident increased, the incidence of ischemic heart events and mortality is markedly increased.[1]

The incidence of truly resistant hypertension is difficult to assess but is felt to represent a subpopulation of approximately 15% to 20% of all hypertensive patients. Although this cohort of patients is relatively small, it drives both morbidity and mortality in the overall hypertensive population.[1] Additionally, despite the use of multiple antihypertensive medications of differing classes, the incremental benefit in blood pressure control with the addition of each medication diminishes. It is uncertain whether this poor response in blood pressure control reflects the underlying pathophysiology or medication noncompliance of this population. Regardless, there is an increasing recognition that therapeutic inertia, both in the identification of these patients and their subsequent care and follow-up, leaves patients at a high risk, and thus there is a need to explore additional nonpharmacologic therapies that may improve their blood pressure control and ultimately may reduce cardiovascular events.

## What is the ROX Coupler device (ROX Medical), and how is it designed to reduce blood pressure in patients with uncontrolled hypertension?

The ROX Coupler device is an implantable nitinol device that creates a conduit between the external iliac artery and vein. The device is implanted percutaneously



in the cath lab. The randomized controlled, prospective ROX CONTROL HTN-1 trial and an ongoing European postmarketing registry (NCT01885390) have shown a high rate of procedural success by accomplished interventionalists.[2] When fully deployed, the ROX Coupler creates a calibrated 4-mm conduit between the central arterial and venous circuit. The ROX Coupler has received European CE Mark approval and is not available for commercial use in the United States.*

In appropriately selected patients with resistant hypertension, the formation of the arteriovenous (AV) conduit results in an immediate and sustained drop in blood pressure, which has been maintained through 6- and 12-month follow-up.[2,3] The ROX CONTROL HTN-1 trial demonstrated a mean 6-month blood pressure reduction of 25 mm Hg, which persisted through 12 months of follow-up.[2,3] Importantly, in ROX CONTROL HTN-1, hard cardiovascular events (including hypertensive crisis and transient ischemic attack) were observed in the control group through 6-month follow-up. As such, given the observed mean blood pressure reduction of 25 mm Hg through 1 year, it is reasonable to extrapolate that in appropriately selected patients with resistant hypertension, the use of the ROX Coupler could translate into a reduction of cardiovascular endpoints when followed over the long term.

## What is different about this approach compared to other interventions for hypertension?

The ROX Coupler device creates an AV conduit between a high-pressure arterial circuit and high capacitance venous bed. The immediate reduction in blood pressure observed at the time of the procedure has been validated through 1-year follow-up. Additionally, compared to devices for renal denervation (eg, Paradise renal denervation system, ReCor Medical; Symplicity Spyral multielectrode catheter, Medtronic) that use radiofrequency energy or focused ultrasound to modulate the sympathetic nervous system, the ROX AV Coupler is an implanted endovascular device that directly and immediately impacts the underlying pathophysiology of resistant hypertension, arterial noncompliance, or stiffness. This important concept of worsening arterial compliance is an age-related process, resulting in a wide pulse pressure and increased pulse wave velocity, and is the pathophysiologic basis of isolated systolic hypertension (also referred to as structural or mechanical hypertension). These patients are typically very sensitive to vasodilator therapy and diuretics, which frequently results in orthostatic hypotension. These patients are also unlikely to respond to renal denervation[4] and therefore define a specific hypertension phenotype, distinct from adrenergically mediated hypertension.

Finally, patients who received the ROX Coupler device in the ROX CONTROL HTN-1 trial had a very high response rate, approaching 100%, through 1-year follow-up. Importantly, if clinical necessity requires this device effect to be reversed, the anastomosis created by the ROX Coupler device can be closed by the implantation of a nitinol stent graft.

## What clinical studies have been conducted with the ROX therapy in hypertensive patients?

Lobo et al published the 6-month results of the randomized prospective trial of 83 patients with resistant hypertension using the ROX Coupler device.[2] This sentinel study, along with the 1-year follow-up of the active treatment group,[3] established a sustained drop in mean office blood pressure of 25.1 mm Hg through 12-month follow-up. Importantly, this reduction in office blood pressure was associated with a concomitant drop in the 24-hour ambulatory systolic blood pressure of 12.6 mm Hg. This proof-of-concept trial formed the foundation for the trial design of the ROX CONTROL HTN-2 trial, which is currently enrolling in the United States.

## Venous stenosis appears to be the most important adverse event associated with this therapy. Can you describe how a venous stenosis is diagnosed and treated and what the prognosis is for patients with venous stenosis?

At present, the pathophysiology of a venous stenosis centers around two hypotheses:

1. The high arterial jet that traverses the ROX Coupler creates turbulence in the contralateral venous wall that may incite a hyperplastic response.
2. A second more recent hypothesis suggests that preexisting arterial compression of the vein due to tortuosity and/or poor arterial compliance may create a milieu that increases turbulence, resulting in a venous wall injury and a hyperplastic tissue response.

Regardless of the pathophysiology involved, follow-up studies from the European registry cohort suggest that deployment of the ROX Coupler placed exclusively to the right AV iliac tree may reduce the incidence of venous stenosis compared to deployment in the left external artery and vein, presumably due to avoiding upstream May-Thurner anatomy.[5] As such, use of the ROX Coupler will be confined strictly to the right side in the ROX CONTROL HTN-2 trial.

The typical presentation of venous stenosis is lower extremity edema associated with a rebound in hypertension. The venous stenosis is readily treated with balloon angioplasty and concomitant implantation of a venous-specific nitinol stent. To date, limited follow-up through 3 years of a patient cohort treated for venous stenosis suggests a very high patency rate for patients treated with a

venous stent. Long-term follow-up and close postmarket surveillance studies are planned as part of the United States investigational device exemption trial and will provide additional information regarding the incidence and follow-up of venous stenosis.

### What are the most critical questions that remain unanswered with the ROX therapy?

The durability of the blood pressure effect beyond 1 year after implantation of the ROX Coupler requires full elucidation, along with better definition of the time course of venous stenosis and secondary benefits of blood pressure reduction of cardiovascular endpoints, particularly regression in left ventricular hypertrophy, progression of renal dysfunction, or the incidence of potential pulmonary hypertension.

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### What is the current status of device interventions for hypertension in Europe? Has there been renewed interest after the EuroPCR and the European Society of Hypertension meetings?

Consideration of device-based therapies for the treatment of hypertension has been showing signs of a resurgence. The field struggled in the aftermath of the disappointing results of the SYMPLICITY III trial for renal denervation, but more recent, positive results and a focus on conducting well-controlled randomized clinical trials has renewed interest in device-based solutions for patients whose blood pressure is not well controlled on hypertension medications.

Importantly, at the 2018 EuroPCR meeting, one of the six primary tracks for the scientific program was entitled "Interventions for Hypertension." This is a significant change from even just a few years ago, and this year's scientific sessions at EuroPCR, the European Society of Hypertension, and the European Society of Cardiology included numerous presentations and discussions of novel device-based treatments for hypertension.

### Are there any pivotal randomized controlled trials (RCTs) being conducted? If so, what technologies are being evaluated?

Conducting very high-quality randomized controlled clinical trials is critically important to evaluating new therapies in hypertension, and there are multiple important new trials underway in hypertension. Medtronic recently announced positive results for the SPYRAL HTN-ON MED and SPYRAL HTN-OFF MED RCTs, and ReCor Medical recently presented results for the RADIANCE-HTN SOLO study. Both companies initiated pivotal RCTs with FDA approval.

Another potentially interesting therapy is a stent-like implant that is placed in the carotid sinus. A randomized trial for this technology has recently been initiated, and the first-in-man results look quite promising.

The ROX CONTROL HTN-2 study builds on the learnings of other recent RCTs in hypertension and is designed to evaluate the safety and efficacy of the ROX Coupler

device. If the trial is successful, the results will serve to support both United States regulatory approval and market adoption of the therapy in other geographies in appropriate patients.

### What interests you most about the ROX therapy?

The ROX Coupler has the potential to be more effective in certain patient populations that are difficult to treat with hypertension medications and/or device therapies such as renal denervation. For example, older patients with stiff arteries and patients with isolated systolic hypertension are very interesting target populations for the ROX Coupler.

The ROX Coupler has a unique dual mechanism of action that targets both mechanical and neurohormonal causes of hypertension. In contrast to other device therapies for hypertension, the ROX Coupler is designed to cause an immediate and significant reduction of central aortic and peripheral blood pressure through mechanisms that impact all patients, including those who have defective aortic elastic properties.

Recent data on failure of medications in hypertension identifies underlying inelastic aorta and mechanical causes of hypertension as predictors of drug futility. Similarly, noncompliance of the aorta may be one of the predictors of nonresponders in renal denervation. Two retrospective studies of renal denervation have identified higher nonresponder rates among patients with evidence of inelastic aorta.[1,2]

### How would you describe the ROX procedure to your interventional colleagues?

The ROX procedure is a straightforward catheter-based procedure that is analogous to many other procedures that we undertake in the cath lab. The ROX procedure typically requires less than an hour to perform, and procedural complications are similar to those commonly observed with other peripheral interventions. The training and learning curve required to implant the device is uncomplicated.

Importantly, the blood pressure–lowering effect of the ROX Coupler typically is immediate and verifiable. It is not uncommon to see blood pressure reductions of more than 20 mm Hg within the first 10 heartbeats after the Coupler is in place. For the interventionalist, this provides instantaneous confirmation that the Coupler is in place and is functioning as intended.

### What were the most interesting findings from you and your colleagues' recently published case study on ROX therapy?

At our center in Homburg, we have conducted a number of pressure-volume loop measurements on patients undergoing the ROX procedure. The results of the first patient were published in a case study in the *European Heart Journal*.[3] As is typically the case for a patient undergoing the ROX procedure, this patient observed a blood pressure reduction of 39/21 mm Hg as soon as the device was implanted. Interestingly, the pressure-volume loop demonstrated an increase in cardiac output, stroke volume, and ejection fraction, as well as a reduction in end-diastolic pressure. These findings suggest that reduction in ventricular work in hypertension allows an improvement in left ventricular mechanical function.

The acute data on cardiac function and hemodynamics collected from this and other similar cases are encouraging. Additional data on the mid- and longer-term impact of the ROX Coupler will be informative and will be evaluated in the ROX CONTROL HTN-2 clinical trial.

### What do you anticipate will be the most important lessons learned from the ROX CONTROL HTN-2 study?

We have learned from other device therapies for hypertension that conducting well-designed, randomized trials is very important to understanding the treatment effect. ROX CONTROL HTN-2 is designed to provide evidence that will be needed to support regulatory approval in the United States and clinical guidelines and reimbursement decisions in all countries.

In the ROX CONTROL HTN-2 study, we are collecting data on the blood pressure–lowering effects of the Coupler versus control at 6 months. The study will also assess safety of the ROX therapy in the context of clinical events observed in this very difficult-to-treat population. Recall that patients with uncontrolled hypertension are at very high risk for comorbidities such as stroke, cardiovascular disease, and kidney disease. The study is not powered to show a difference in these clinical outcomes, but earlier studies of the ROX device have provided interesting signals that blood pressure–lowering effects of the Coupler resulted in fewer hospitalizations versus control patients. Importantly, right heart function and effects on the pulmonary circulation are also being investigated.

This is an important study that will potentially support the adoption of a very interesting new tool for the treatment of patients with uncontrolled hypertension. ■

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