Scientific Background

Renal Denervation (RDN)

NOVEL CATHETER-BASED TREATMENT FOR HYPERTENSION

Hypertension and the Symplicity Renal Denervation System

What is hypertension?
Hypertension, or high blood pressure, is a common disorder where blood pressure remains abnormally elevated for a sustained period of time. Although an asymptomatic condition, when left untreated, chronic hypertension can significantly increase the risk of heart attack, stroke, heart failure, kidney disease and death, posing serious health risks to those suffering from the disease.1

What blood pressure level is medically considered hypertension?
Blood pressure measurement is now routine at most medical office visits and, with the availability of inexpensive, reliable and easy-to-use portable digital blood pressure meters, many people also monitor their own blood pressure at home. Nevertheless, since hypertension is usually asymptomatic it remains underdiagnosed, particularly among people not receiving regular preventative medical examinations.

The United States Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, European Society of Cardiology and European Society of Hypertension have established guidelines for blood pressure classification (see Table 1). Blood pressure above 140/90 mmHg is classified as uncontrolled hypertension and blood pressure below 120/80 mmHg is classified as normal.

Table 1. Blood Pressure Classifications^2

<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>90–119</td>
<td>60–79</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Uncontrolled hypertension Stage 1</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥160</td>
<td>≥100</td>
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</tbody>
</table>

Note that target blood pressure for diabetics is <130/80.

How does hypertension affect those who have it?
Hypertension is the single most common contributor to death worldwide, being a root cause of stroke, congestive heart failure and kidney disease. Approximately 62% of cerebrovascular and 49% of ischemic heart disease cases are attributed to suboptimal blood pressure control. After diabetes, hypertension itself is the second most common cause of end-stage renal failure and 80% of chronic kidney disease patients develop hypertension at some point in the course of their disease.3

How many people are affected by hypertension?
Hypertension is a significant and growing global health issue affecting approximately 1.2 billion people worldwide.4 It is the leading attributable cause of death worldwide and is associated with an increased
risk of heart attack, stroke, heart failure, kidney disease and death. The prevalence of high blood pressure increases with age, obesity and sedentary lifestyles.\textsuperscript{5,6} Since all three factors are on the rise worldwide, hypertension treatment represents a huge and growing clinical challenge as well as a major public health cost burden. The estimated annual global healthcare expenditure directly attributable to hypertension is estimated at $500 billion.\textsuperscript{7}

How is hypertension treated?
Patients with mild hypertension are advised to make behavioral and dietary changes such as losing weight, exercising, reducing sodium intake and increasing potassium intake. If these approaches are unsuccessful, drug treatment is usually prescribed.\textsuperscript{8}

While pharmaceutical therapy plays a role in hypertension management, these are not always effective. Approximately 50 percent of patients with hypertension remain uncontrolled, and approximately 15–20 percent of those are resistant.\textsuperscript{9}

How is blood pressure controlled by the body?
Blood pressure is controlled by a complex interaction of electrical, mechanical and hormonal forces in the body. The main electrical component of blood pressure control is the sympathetic nervous system (SNS), which is part of the body’s autonomic nervous system and operates without conscious control. The SNS connects the brain, heart, blood vessels and kidneys, each of which plays an important role in the regulation of the body’s blood pressure.

The brain primarily plays an electrical role, processing inputs and sending signals to the rest of the SNS. The heart plays a largely mechanical role, controlling blood pressure by beating faster and harder to raise blood pressure, or slower and less forcefully to lower it. The blood vessels themselves also play a mechanical role, influencing blood pressure by either dilating to lower blood pressure or constricting to raise blood pressure.

The final and perhaps most central contributors to the regulation of blood pressure are the kidneys, which play electrical, mechanical and hormonal roles. The kidneys affect blood pressure by signaling the need for increased or lowered pressure through the SNS (electrical), by controlling the amount of fluid in the body (mechanical) and by releasing key hormones that influence the activities of the heart and blood vessels (hormonal).\textsuperscript{10}

How do kidneys influence blood pressure control in the body?
Since they are connected to the SNS, kidneys can communicate with other organs via electrical signals to control blood pressure. They receive signals primarily from the brain, which partially triggers the mechanical and hormonal functions of the kidneys. At the same time, they also send signals to the rest of the SNS, which can change the level of activation of all of the organs in the system and correspondingly affect blood pressure.\textsuperscript{11}

From the mechanical perspective, kidneys are responsible for controlling the amount of water and salt in the blood, directly affecting the amount of fluid within the circulatory system. If the kidneys allow the body to retain too much salt and water, as they can among the hypertensive population, the added fluid volume raises blood pressure. This mechanical function can be controlled both in response to electrical stimulus from SNS or automatically by the kidneys themselves.

Finally, kidneys produce hormones including renin, cytokines and other neurohormones. Renin is a hormone that starts a cascade of events called the renin-angiotensin-aldosterone-system (RAAS), which causes vasoconstriction (contraction of the blood vessels), elevated heart rate and salt and water retention. This cascade, which can be triggered by electrical means or automatically by the kidneys, operates normally in nonhypertensive patients but can become hyperactive among
hypertensive patients. The kidney also produces cytokines and other neurohormones in response to elevated sympathetic activation. These hormones, though also active in blood pressure regulation, can be toxic to the tissues of the body, particularly those of the blood vessels, heart and kidneys. As such, they may be responsible for much of the damage caused by chronic high blood pressure.

How do pharmaceutical agents target the activities of the kidneys to lower blood pressure?

Since the 1940s, pharmaceutical companies have developed many drugs to counteract the effects of hyperactivity of the SNS and subsequent RAAS activation in hopes of reducing blood pressure. These medicines target the electrical, mechanical and hormonal functions of the kidneys. Pharmaceutical therapies targeting the electrical system include centrally acting sympatholytic drugs that aim to disrupt the electrical signals involved in the activation of the SNS. Agents designed to lower the mechanical load in the circulatory system, such as diuretics, counter sodium and water retention to lower fluid volume. Lastly, and perhaps most abundantly, several agents target the kidneys’ hormonal activities. The medicines include beta blockers (to reduce renin release and heart rate), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and aldosterone blockers (to counteract RAAS).12

Despite increasing understanding of the biochemical mechanisms involved, current pharmacologic strategies have significant limitations, including unsatisfactory efficacy, often unpleasant side effects and patient noncompliance (defined as nonadherence or nonpersistence). Drug failures, noncompliance and adverse events make a compelling case for additional or alternative therapies.

What is renal denervation (RDN) and why might it be effective at lowering blood pressure in cases where pharmaceutical therapies have failed?

RDN addresses uncontrolled hypertension by reducing the SNS drive, which is central to blood pressure regulation. It is a minimally invasive procedure that modulates the output of the sympathetic nerves located outside the renal artery walls and represents a breakthrough approach and first-of-its-kind device-based treatment for resistant hypertension.

Specifically, RDN involves selectively disabling renal nerves within the SNS. Denervation, which affects both the electrical signals going into the kidneys and those emanating from them, has the potential to impact the mechanical and hormonal activities of the kidneys themselves, as well as the electrical activation of the rest of the SNS. Physiology suggests that blocking sympathetic nerves leading to the kidneys will reverse fluid and salt retention and reduce inappropriate renin release (stopping the harmful hormonal RAAS cascade before it starts).

By blocking sympathetic nerves emanating from the kidneys, RDN may lower the level of activation of the whole SNS. In doing so, RDN may also decrease the electrical stimulation of other members of the SNS, such as the heart and blood vessels, thereby providing an additional antihypertensive effect. Blocking renal nerves has also been shown in various models to have beneficial effects on organs damaged by chronic sympathetic overactivity, since it may lower the level of cytokines and neurohormones that may be harmful to the blood vessels, kidneys and heart.

Furthermore, because RDN reduces the hyperactive impulses generated by the SNS, it is likely to be valuable in the treatment of several additional clinical conditions related to hypertension. These conditions, which are characterised by increased SNS activity, include left ventricular hypertrophy, chronic renal disease, heart failure, insulin resistance, cardiorenal syndrome and sudden cardiac death.13

Independent epidemiological research has shown that each incremental 20/10 mmHg increase of blood pressure above normal levels directly correlates to a doubling of cardiovascular mortality over a 10-year period. Reducing systolic blood pressure by as little as 5 mmHg can reduce the risk of stroke by nearly 30 percent.

The Symplicity Renal Denervation System from Medtronic, a leader in the development of RDN therapy, represents a breakthrough approach for the treatment of resistant hypertension.

How do we know that RDN is safe?

Both kidney transplant experience and direct attempts at SNS denervation suggest that targeted RDN allows both normal kidney function and normal blood pressure control. Research on kidney transplant
patients, in whom denervation occurs as part of the operation, shows that severing renal nerves surgically does not affect normal kidney functionality with regard to electrolyte maintenance, volume control or blood pressure control.

In addition, thousands of surgical attempts at therapeutic human denervation have been reported since the 1930s to treat hypertension, end-stage renal disease and left ventricular hypertrophy. One of the first attempts to influence hypertension through RDN was reported in 1935. In 1953 several additional reports were published related to thoracolumbar splanchnicectomy, a procedure intended to disable nerves in the abdomen, including those connecting the kidneys to the SNS. Consistent among many of these early surgical attempts is the documentation of a significant, lasting reduction in blood pressure in many patients and occasional dramatic improvements in certain manifestations of hypertension, including retinopathy, papilledema and heart failure. In fact, significant mortality reduction was repeatedly reported among sympathectomy subjects compared with controls receiving no treatment.

Many of the physiologic findings, including resolution of heart failure and reduction of heart size, can indeed be attributed to the success of the surgical procedure in treating hypertension. Unfortunately, morbidity and collateral damage in these sympathectomies was considerable, owing largely to the extensive and invasive nature of the procedure itself, which could not selectively remove the renal contribution. Moreover, it is unlikely that these surgical procedures were able to consistently block neural communication from the kidney to the SNS. However, those occasional dramatic successes, in retrospect, suggest greater potential effectiveness from a much safer and more targeted procedure aimed specifically at the renal nerves.

What is the Symplicity Renal Denervation System?

The Symplicity Renal Denervation System accomplishes RDN, a minimally invasive procedure that disables sympathetic nerves located in the renal artery walls. The system consists of a generator and a flexible catheter. The catheter is introduced through the femoral artery in the upper thigh and is threaded through the renal artery near each kidney. Once in place, the top of the catheter delivers low-power radio frequency (RF) energy according to a proprietary algorithm, or pattern, to affect the surrounding sympathetic nerves. The procedure does not involve a permanent implant.

The Symplicity Renal Denervation System has received CE (Conformité Européenne) Mark and Australia’s Therapeutic Goods Administration (TGA) listing, but is not yet approved for use in the United States by the Food and Drug Administration (FDA) nor is it approved for use in Canada or Japan.

What clinical results have been reported using the Symplicity Renal Denervation System?

Clinical research shows that RDN therapy with the Symplicity Renal Denervation System can provide significant and sustained reduction in blood pressure levels for patients with uncontrolled blood pressure despite multiple antihypertensive medications. This research includes Symplicity HTN-1\textsuperscript{14} and Symplicity HTN-2.\textsuperscript{15}

- Symplicity HTN-1 was a series of pilot studies involving 153 patients at 19 centres in Australia, Europe and the USA. In these studies, patients achieved a mean blood pressure reduction of -25/-11 mmHg at six months and the reduction was sustained through 24 months. There was no evidence of vascular injury or stenosis at the treatment sites at six months, confirmed by imaging (CTA/MRA), and renal function was sustained (eGFR and creatinine). These data were published in the April 2009 issue of \textit{The Lancet}.

- Symplicity HTN-2 was a randomised, controlled clinical trial of 106 patients in Europe, Australia and New Zealand. Patients randomised to RDN therapy achieved a mean blood pressure reduction of 32/12 mmHg at six months, whereas patients in the control group randomised to receive antihypertensive medications alone had blood pressures that did not vary from baseline (1/0 mmHg). The investigators noted no serious procedure- or device-related events and the overall occurrence of adverse events did not differ between groups. These data were published in the November 2010 issue of \textit{The Lancet}.

- Symplicity HTN-3: On July 11, the FDA approved the protocol for this study, which is a single-blind, randomised, controlled trial designed to evaluate the safety and effectiveness of RDN with the Symplicity Renal Denervation System in patients with resistant hypertension. Patient enrollment in this study will begin soon across 60 US medical centres. The study will enroll approximately 500
patients who will be randomised to receive either RDN and treatment with antihypertensive medications, or treatment with antihypertensive medications alone. The primary endpoints of the study are the change in blood pressure from baseline to six months following randomisation and the incidence of major adverse events one month following randomisation.

Future RDN clinical investigations may focus on heart failure, insulin resistance, chronic kidney disease and other diseases characterised by hyperactive SNS drive. Medtronic will continue to guide leading studies on RDN therapy.