



Hypertension and the Symplicity® Catheter System™ Scientific Background

What is hypertension?

Hypertension, or high blood pressure, is a condition where the force that blood is exerting on the walls of the arteries of the body is higher than desirable. Although an asymptomatic condition, when left untreated, chronic hypertension can significantly increase the risk of stroke, heart failure, chronic kidney disease and heart attack, posing serious health risks to those suffering from the disease.

What blood pressure level is medically considered hypertension?

Blood pressure (BP) 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 BP at home. Nevertheless, since hypertension is usually asymptomatic it remains under-diagnosed, particularly among people not receiving regular preventative medical examinations.

Normal blood pressure is presently defined as 115/75mmHg (measured in millimeters of mercury) where the first figure represents systolic BP (SBP) and the second diastolic (DBP). For patients receiving treatment for hypertension, the target of treatment is reducing blood pressure below 140/90*mmHg.

	Normal	Hypertensive
Blood Pressure Reading (mmHg)	115/75	Over 140/90*

**Note that the target blood pressure for the diabetic population 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 (ESRF) and some 80% of chronic kidney disease patients develop hypertension at some point in the course of their disease.

How many people are affected by hypertension?

Hypertension and its related conditions, heart failure and chronic kidney disease, represent a significant and growing global health issue. The World Health Organization (WHO) reports that high blood pressure afflicts one billion people worldwide (1 in 3 adults in the developed world). The prevalence of high blood pressure increases with age, obesity and sedentary lifestyles. 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. In the United States alone, 45.3 million doctors' office visits are occasioned by hypertension

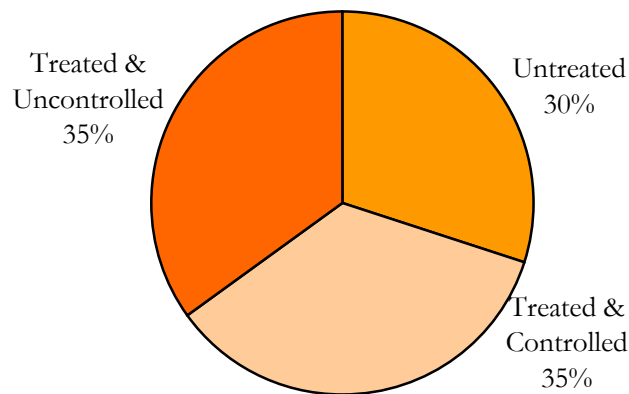


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diagnosis and treatment, at a cost of \$73.4 billion. Of this amount, \$18 billion is spent on anti-hypertension drugs.

How is hypertension treated?

Patients with mild hypertension are advised to make behavioral and dietary changes, such as losing weight, exercising and reducing intake of sodium and increasing intake of potassium. If these approaches are unsuccessful, drug treatment is usually prescribed.



Despite the availability of such drugs only about 35% of hypertensive patients are considered controlled. Another 35% are patients who, despite treatment, are unable to reach that target blood pressure levels for a variety of reasons, including non-compliance (defined as non-adherence and/or non-persistence with a regimen). Within this population of treated and uncontrolled hypertensives, approximately 10% are considered resistant to existing therapy. For these patients, even combinations of different pharmaceuticals and doses have been unsuccessful at allowing them to reach their target blood pressure. The remaining 30% of hypertensives are not being treated for a multitude of reasons, including non-diagnosis and lack of access to medical care.

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), part of body's autonomic nervous system, which operates without conscious control. The sympathetic nervous system connects the brain, the heart, the blood vessels and the kidneys, each of which plays an important role in the regulation of the body's blood pressure.

The brain plays primarily 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 raising pressure or slower and less forcefully lowering it. The blood vessels themselves also play a mechanical role, influencing blood pressure by either dilating (becoming larger in diameter to lower blood pressure) or constricting (becoming smaller in diameter to raise blood pressure).



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The final, and perhaps most central actor in the regulation of blood pressure, is the kidneys, which play an electrical, mechanical and hormonal role. 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).

How do the kidneys influence blood pressure control in the body?

As discussed above, the kidneys play a central electrical, mechanical and hormonal role in the control of blood pressure. Since the kidneys are connected to the sympathetic nervous system (SNS), they can send and receive electrical signals to the other organs related to blood pressure control. They receive signals primarily from the brain, which partially trigger the mechanical and hormonal functions of the kidneys. At the same time, they also send signals to the rest of the SNS, which can boost the level of activation of all of the organs in the system, effectively amplifying electrical signals in the system and corresponding blood pressure effects.

From the mechanical perspective, the 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 kidney itself.

Lastly, the 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) that 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 non-hypertensive 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 kidney. 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 sympathetic nervous system 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, which aim to disrupt the electrical signals involved in the activation of the sympathetic nervous system. Agents aiming 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 hormonal activities of the kidney. 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 the RAAS).



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

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

Renal denervation involves selectively disabling renal nerves within the sympathetic nervous system. 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, but also the electrical activation of the rest of the sympathetic nervous system (SNS). Physiology suggests that blocking sympathetic nerves leading to the kidney will reverse fluid and salt retention, (lowering fluid volume and mechanical load) and reduce inappropriate renin release (stopping the deleterious hormonal RAAS cascade before it starts).

By blocking sympathetic nerves emanating from the kidney, renal denervation may lower the level of activation of the whole sympathetic nervous system. In doing so, renal denervation may also decrease the electrical stimulation of other members of the sympathetic nervous system, such as the heart and blood vessels, having an additional anti-hypertensive effect. In addition, blocking renal nerves has also been shown in various models to have beneficial effects on organs damaged by chronic sympathetic over-activity, since it may lower the level of cytokines and neurohormones that may be harmful to the blood vessels, kidney, and heart.

Furthermore, because renal denervation 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 characterized by increased SNS activity, include left ventricular hypertrophy, chronic renal disease, heart failure, cardio-renal syndrome and sudden cardiac death.

How do we know that renal denervation is safe?

Both kidney transplant experience and direct attempts at denervation of the sympathetic nervous system suggest that targeted renal denervation 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 functions of the kidney maintaining electrolytes, 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 renal denervation 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 sympathetic nervous system. 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



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mortality reduction was repeatedly reported among sympathectomy subjects compared to 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. However, those occasional dramatic successes suggest greater potential effectiveness from a much safer and more targeted procedure aimed specifically at the renal nerves.

What is the Symplicity® Catheter System™?

Based on current knowledge of the role of the renal sympathetic system in hypertension, heart failure and kidney disease Ardian has developed a catheter-based procedure to therapeutically denervate the kidneys. This minimally invasive procedure, using the Symplicity® Catheter System™, disrupts the renal nerves via the renal arteries using radio frequency (RF) energy. The device and procedure produce precise, complete and replicable renal denervation without the risks of invasive surgery or requiring a permanent implant.

The 40-minute outpatient operation is performed by interventionalists, a group of physicians who are technically adept at catheter procedures, within the infrastructure of a standard catheterization lab. The operator introduces a guiding catheter through the femoral artery and threads it up to the target renal artery. The Symplicity device is then inserted into the renal artery through the guide catheter and, using radio frequency energy, ablates the nerves from the inside of the artery, without damaging the renal artery. After ablation, the device is withdrawn and the arterial access site may be closed as with standard interventional techniques. Given the minimally invasive nature of the operation, the procedure is intended to be performed on an outpatient basis, allowing the patient to go home the same day.

What clinical results have been reported using the Symplicity® Catheter System™?

Initial human clinical experience in patients with resistant hypertension suggests that the procedure is safe, straightforward and associated with a substantial and sustained reduction in blood pressure. Investigators presented detailed clinical results from early studies of the device on 50 patients in March 2009 at the American College of Cardiology Meeting. These data showed significant, safe and durable blood pressure reductions of -21/-10, -22/-11, -24/-11 and -27/-17 mmHg at 3, 6, 9, and 12 months respectively with no evidence of vascular abnormality (e.g., stenosis) or impairment in kidney function. A full report and discussion of this data was simultaneously published in *The Lancet*®. If further clinical trials in hypertensive subjects continue to produce durable, clinically meaningful results, additional studies are under consideration for heart failure and chronic kidney disease.