

# Ultrasound for BP Measurement and Treatment in Subjects with Resistant Hypertension

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**Abstract:** Hypertension already affects one billion people worldwide, leading to heart attacks and strokes. It is estimated there are more than 100 million drug-resistant hypertension patients world over. So the new ultrasound renal denervation (RDN) therapy may offer a massive new market for cath labs to tap into. In view of this, new methods of ultrasonics in measuring blood pressure (BP) as well as lowering BP in patients with resistant hypertension is reviewed including the author's results. In measuring BP ultrasound is shown to be a better technique as it measures BP continuously and can reveal the variations of several parameters viz., blood flow, vascular resistance and BP, which helps physicians for taking preventive steps to monitor cardiovascular diseases. Interestingly, ultrasound of high frequency (1 MHz) and high power levels of (50 to 1500 mWcm<sup>-2</sup>) without medication as well as low intensity (2 mWcm<sup>-2</sup>) and low frequency (800 kHz) in presence of medication were applied to forearm have been investigated. Results revealed that in both cases BP decreased modestly by same magnitude in subjects having hypertension. Typical clinical trials on the first-in-man study of endovascular ultrasound renal denervation (both noninvasive and invasive) carried out by two groups (companies) for the treatment of resistant hypertension is evaluated. Overall results indicated that reduction in office BP was 32 mmHg systolic and 17 mmHg in diastolic is possible by ultrasound application. The study is aimed at not necessary to get rid of medication completely but to make the BP medication – controlled by surround sound technology. Probable mechanism for reducing BP by the application of ultrasound is interpreted by the present author based on the antibiotic studies conducted earlier. Ultrasound is a noninvasive breakthrough technique which has the potential to greatly reduce cost, lower risk and improve access to millions of hypertension patients worldwide who are not adequately controlled by drug therapy.

**Keywords:** ultrasound, measuring BP, controlling BP, resistant hypertension. ultrasound renal denervation)

## 1. Introduction

Blood pressure is the most important parameter and also the main risk factor for cardiovascular disease which are the main cause of death globally. Despite lifestyle interventions and various types of anti-hypertension agents, high blood pressure remains difficult to control in some patients [1]. Device-based treatment approaches for resistant hypertension, such as catheter-based renal sympathetic denervation by radiofrequency ablation and baroreceptor activation therapy, have shown promising results in clinical trials [1,2]. These device-based approaches, however, are invasive and thus their therapeutic applications are limited in primary care. Noninvasive device-based approaches are therefore desirable for the treatment of hypertension. Since ultrasound irradiation is applied for a variety of therapies and ultrasound is a noninvasive technique, stands as forefront runner [3].

Applications of ultrasound in medicine for therapeutic purposes have been an accepted and beneficial use of ultrasonic biological effects for many years. Low power ultrasound of about 1 MHz frequency has been widely applied since the 1950s for physical therapy in conditions such as tendinitis or bursitis. Present author has developed an ultrasonic machine in 1973 using 100% indigenous components for therapeutical use [4,5]. Further, therapeutical ultrasound-current practices and future trends has been reviewed in 2009, focusing on the device should be more portable, more power efficient and available at a low cost [3]. In the 1980s, high pressure-amplitude shockwaves came into use for mechanically resolving kidney stones, and "lithotripsy" rapidly replaced surgery as the most frequent treatment choice. The use of ultrasonic energy for therapy continues to expand, and approved applications now include

uterine fibroid ablation, cataract removal (phacoemulsification), surgical tissue cutting and hemostasis, transdermal drug delivery, and bone fracture healing, among others. Undesirable bioeffects can occur including burns for thermal-based therapies and significant hemorrhage for mechanical-based therapies (e. g. lithotripsy). In all these therapeutic applications for bioeffects of ultrasound, standardization thru power measurement in milliwatt region [6], ultrasound dosimetry, benefits assurance and side-effects risk minimization must be carefully considered in order to insure an optimal benefit to risk ratio for the patient.

Appropriate noninvasive methods and techniques are needed to address the problem of controlling BP. Therefore, this presentation reviews the recent published data. Using ultrasound altogether two BP measuring methods and four BP treatment techniques are presented, viz., (i) measurement of BP continuously with ultrasound and also using ultrasonic scanner for evaluating intrinsic parameters governing BP and (ii) control of BP by four different techniques that use commercially available ultrasound therapy machines and surround sound technology. BP reduction mechanism under the influence of ultrasound is proposed along with future scope of ultrasound medical devices.

## 2. B.P Measurement

In this section conventional method of BP measurement along with two other ultrasonic methods are given, they are: (i) traditional method of measuring BP and (ii) continuous blood pressure measurement with ultrasound.

2 (i). What is BP? : Blood pressure is the force of your blood pushing against the walls of your arteries. Each time your

heart beats, it pumps blood into the arteries. Your blood pressure is highest when your heart beats, pumping the blood. This is called systolic pressure. When your heart is at rest, between beats, your blood pressure falls. This is called diastolic pressure.

About Hypertension: A normal blood pressure is typically at or below 120 systolic and 80 diastolic, expressed as 120/80 mmHg. Hypertension is categorized as a blood pressure reading greater than 140/90 mmHg. Lowering hypertension is important as the risk of cardiovascular death doubles with every 20 point increase in systolic blood pressure. One of the key risk factors for cardiovascular disease is hypertension or “high blood pressure.” Hypertension already affects one billion people worldwide, leading to heart attacks and strokes. Researchers have estimated that raised blood pressure currently kills nine million people every year, according to the World Health Organization (WHO). Known as the “silent killer,” high blood pressure often presents no warning signs or symptoms and many people do not realize they have it. Drug-resistant hypertension is a condition that cannot be controlled through medication. There are more than 100 million people worldwide that are treatment resistant where at least three high blood pressure drugs do not work. The annual global health care expenditure directly related to hypertension is estimated at almost 385 billion Euros every year.

Traditional method of measuring BP: The old inflatable-cuff-around-the-arm (as shown in fig.1) is not only an uncomfortable way of having one's blood pressure measured, but it turns out that it doesn't always provide enough information, either. If a physician wishes to check for vascular diseases such as atherosclerosis,



Figure 1: BP measurement by old inflatable-cuff-around-the-arm

thrombosis or aneurysms, for instance, they're going to want to know how the blood is flowing in areas besides the patient's arm. Because the cuff works by temporarily stopping the blood flow, however, it's not going to work too well on a patient's neck or torso. In the foregoing section the recent discovery is described that ultrasound can be used instead, and that it provides more details.

2.(ii)(a). Continuous blood pressure measurement with ultrasound: Cardiovascular diseases are the main cause of death globally and hypertension is the main risk factor for cardiovascular disease. A long-term blood pressure measurement is crucial to identify hypertension which can lead to cardiovascular disease. Conventional techniques use the automatic arm cuff method which is painful and provides only intermittent results. A new method for continuous measurement has been developed by Weber et al [7] using a

‘doppler ultrasound sensor’ on a superficial artery and a small balloon. A voice coil actuator, as shown in fig.2 is used to change the balloon pressure by means of a control loop. Holding the control variable – the ultrasound signal – constant and low by controlling the balloon pressure permits a continuous measurement. The superficial artery runs closely to the bone. The balloon compresses the artery; the ultrasound sensor measures the remaining blood velocity. The actuator changes the balloon pressure according to the control loop information. The system was tested using a blood pressure simulator with variable pressure curves and abrupt pressure changes. The controller-induced balloon pressure tracks the pressure in the model artery very closely.

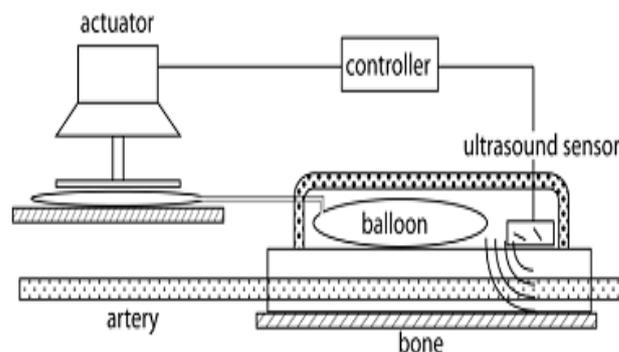


Figure 2: Drawing of the device

2.(ii)(b) Blood pressure simulator: Measurements were executed on a blood pressure simulator, as shown in Fig.3. A linear motor drives a piston and provides pressure oscillations in a windkessel superimposed with a mean pressure generated by a water column. Pressure balloon and ultrasound sensor are located over the model artery in a tissue model. The control loop consists of ultrasound sensor, controller, actuator and pressure balloon. The mock circulation is an open system; a roller pump refills the water column constantly. The signal-to-noise ratio of the ultrasound signal should be enhanced to reach a higher reliability of the measurement principle. This can be done by suitable filter techniques or by improving the geometry of the ultrasound sensor and the processing of the signal by the ultrasound electronic. During the continuous blood pressure measurement the patient will be able to move.

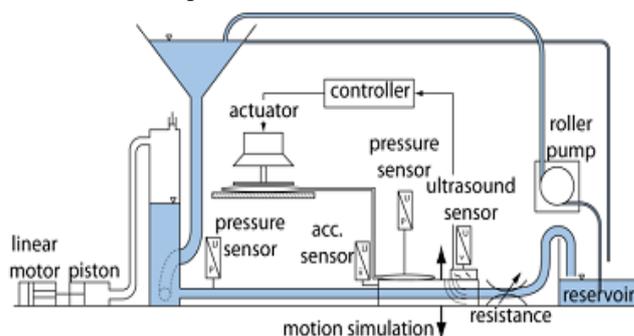


Figure 3: Schematic of blood pressure simulator.

2.(iii). Measuring BP with ultrasound scanner: Recently, researchers at Eindhoven University of Technology, together with the Italian company Esaote, have developed a new technique to measure blood pressure [8]. Using an ultrasound scanner, which is commonly used for pregnancy ultrasound scans, the new technique enables patient-friendly local blood pressure measurements. Scientists have for years

been looking for a non-invasive method to measure the blood pressure pulses at highly localized points in the body. The usual method is to insert a catheter with a pressure sensor. But that's an invasive procedure, and not suitable for preventive diagnostics. There's also the traditional method using an inflatable arm cuff, as discussed in previous section 2(i). But that doesn't allow any conclusions to be drawn about -- for example -- the blood pressure in the carotid artery. In this method, the cuff is inflated until the blood flow in the arm is stopped, allowing the systolic and diastolic (maximum and minimum) values in the arm to be measured. That means you won't find anyone willing to have the blood pressure in their neck measured using an inflatable cuff.

Using the new technique, 'Atherosclerosis', blood pressure can be non-invasively measured at any point in the body. The new technique uses ultrasound to make patient-friendly blood pressure measurements at many points in the body. All that is needed is to apply a small amount of gel so that the ultrasound scanner makes good contact with the skin. The key to the new technique is above all the sophisticated signal processing. Experiments were conducted using plastic tubes, worked their way up to carotid arteries from pigs, and are now performing trials on human subjects. The researchers are able to achieve good visualization of the blood flow and the blood vessel wall motion, from which the blood pressure can be derived, by means of a mathematical model. They can also see the variations in blood pressure and flow in time as a result of the beating of the heart. The simultaneous knowledge of pressure and flow also provides information about 'downstream' parts of the vascular system. It is based on key factor viz., blood flow  $\times$  vascular resistance = BP. The new technique will allow physicians to carry out preventive investigations of the cardiovascular system, for example, and to monitor the development of diseases such as atherosclerosis, thrombosis or aneurysms (dangerous dilations of a blood vessel). By plugging that data into a mathematical model, the blood pressure at that exact location can be derived.

This will provide much more information about the vascular system than the traditional measurement method using an inflatable cuff on the arm. As a result, physicians will be able in the future to quickly gain an overall impression of the condition of the heart and blood vessels. The technique is currently being tested on volunteers, in advance of clinical tests with patients. The results are promising. It is still expected to take several years before the technique can be used in clinical practice, for example in family doctors' surgeries. By performing a simple scan, the physician can detect vascular disease in an early stage and decide for a preventive treatment. The technology also allows users to observe variations in blood pressure and flow, in time with the beating of the heart, which will provide information on what's going on "downstream" from that location. This is in line with the current trend in healthcare with an increasing focus on the prevention of cardiovascular disease. Thus, this new method for measuring blood pressure is part of a new direction for the researchers.

### 3. Ultrasound treatment methods for BP control

Growing awareness of the harmful effects of radiation exposure is driving the uptake of ultrasound systems, which are radiation free, less expensive, and more versatile than bigger modalities such as magnetic resonance. The numerous benefits that ultrasound procedures provide have encouraged many small hospitals and primary care centers world-over to adopt the technology. Ultrasound also has therapeutic applications, which can be highly beneficial when used with dosage precautions: Therapeutic ultrasound is a treatment modality commonly used in physical therapy. It is used to provide deep heating to soft tissues in the body. These include muscles, tendons, joints and ligaments. However, towards controlling BP by ultrasound is a novel area of research. Using commercially available therapy machines BP control has been attempted for both the conditions with and without using medicines. Later, an innovative and newly developed ultrasound renal denervation technology a noninvasive as well as invasive application of ultrasound are investigated. Typical results obtained in BP reduction are promising and are presented below.

3(i). Influence of ultrasound therapy without medication on patient's BP control: Change in blood pressure due to ultrasound therapy has been investigated [9,10] among people with normal blood pressure and with hypertension. Research on influence of applied dose of ultrasounds and time of application has been studied by measuring BP before and after application of ultrasound.

An innovative method of noninvasive application of ultrasound has been proposed by the present author in 2006 [9] to reduce BP. Ultrasound of low frequency (720 kHz) and high intensity ( $2.4 \text{ Wcm}^{-2}$ ) without medication as well as low intensity ( $0.2 \text{ Wcm}^{-2}$ ) at the same frequency in presence of medication applied to forearm for 25 min.. Results obtained on 21 subjects revealed that in both cases BP decreased modestly by same magnitude in subjects having hypertension upto 11 mmHg systolic and 5 mmHg in diastolic.

Research investigations in the same direction were continued in Poland [10] among 29 patients (aged from 30 to 83) qualified to ultrasound therapy by a physician. Each patient was treated with a one series of 10 ultrasound sessions. The ultrasound device used at that time was US 10 with applicator of  $5 \text{ cm}^2$  surface and 1 MHz frequency. The dose was  $0.05\text{-}1.5 \text{ Wcm}^{-2}$  of continuous ultrasound wave applied dynamically. Time of each session was 3-9 minutes. Blood pressure was measured before and after therapeutic sessions by keeping the control group were 10 patients without ultrasound influence.

Statistical analysis of results revealed that application of ultrasound decreased B.P for both among people with normal B.P and patients having hypertension. Decrease of systolic blood pressure was observed after an application of medium dose of ultrasound ( $0.5\text{-}1.5 \text{ Wcm}^{-2}$ ) and medium time (4-9 min). Investigators did not observe any changing of blood pressure statistically in control patient's group. It

has been concluded that ultrasound therapy was found to have a decreasing influence on blood pressure. Ultrasound intensity and time of application may have an influence on blood pressure.

3 (ii) Effect of low-frequency and very low intensity ultrasound in presence of anti-hypertension agents on BP control: Ultrasound irradiation is applied for a variety of therapies. The therapeutic effects of ultrasound depend on both frequency and intensity. High-frequency (>1 MHz) and high-intensity pulsed ultrasounds have analgesic effects when applied to focal sites in the human body. High-frequency and low-intensity pulsed ultrasound (1.5 MHz and 30 mWcm<sup>-2</sup> with a 20% duty cycle 1:4 enhances fresh fracture and nonunion healing. The effects of lower frequency (< 1 MHz) and very low-intensity ultrasound (< 10 mWcm<sup>-2</sup>) on the human body, however, have not yet been evaluated.

Nonogaki et al [11] examined the effects of low-frequency and low-intensity ultrasound (800 kHz, 2 mWcm<sup>-2</sup>) applied to the forearm on blood pressure (BP), pulse rate, pulse pressure, cardiac output (CO), total peripheral vascular resistance (TPR), and cardiac index (CI) in 42 Japanese subjects (14 men and 28 women; mean age±SE, 58±1 years) with hypertension (systolic BP>140) using the GP-303 PS-501 ultrasound device (Parama-Tech Inc., Japan). The subjects were treated with anti-hypertension agents, including candesartan cilexetil, a selective angiotensin-1 subtype angiotensin II receptor antagonist; amlodipine, a long-acting calcium channel blocker; and/or beta-adrenoceptor blockers. The weight and height of each of the subjects were recorded, and baseline BP and pulse rate were measured with the subject in a seated position.

The ultrasound device comprises of a main unit and application pads which operates at 800 kHz fixed frequency. The main unit generates an electric signal to drive the ultrasound wave oscillator in the pads. Silicon rubber pads, which have two cells with oscillators of 250(φ)×4 mm(t), are attached to the skin and used to apply the ultrasound to the forearm. When the cable of the pads is connected to the output connector of the responding main unit, a series of sinusoidal wave currents makes the oscillators generate an ultrasound wave of 2 mWcm<sup>-2</sup> intensity from the surface of the pads. The intensity of the ultrasound at 800 kHz was adjusted to 2 mWcm<sup>-2</sup> for evaluating the results.

Subjects underwent ultrasound irradiation applied to the forearm for 30 min at 800 kHz and 2 mWcm<sup>-2</sup> with 100% duty, or placebo irradiation. After treatment for 30 min, BP and pulse rate were again measured using a BP monitoring system. All of the participants provided written informed consent to participate in this study, which was approved by the ethics committees of the Nonogaki Diabetes Clinic. The clinical studies were conducted in accordance with the

institutional guidelines for clinical research at Tohoku University Hospital. Comparisons among more than two groups were performed using analysis of variance with Bonferroni's correction for multiple comparisons. A P value of less than 0.05 was considered statistically significant. BP obtained for control group base line and 30 min, further ultrasound treatment base line and 30 min respectively for systolic BP are 153±2 152±3 155±2 141±2 and for diastolic BP 91±3 92±2 91±2 86±2.

In summary, these findings suggest that low-frequency (800 kHz) and very low-intensity (2 mWcm<sup>-2</sup>) ultrasound irradiation to the forearm has potential usefulness as a therapeutic application for hypertension.

3(iii). Treatment of resistant hypertension by noninvasive ultrasound renal denervation (RDN) therapy: Renal denervation is a specialized ablation procedure is of recent origin. It has demonstrated a reduction in blood pressure for patients with hypertension, or high blood pressure, that is resistant to medical therapy. Initially radiofrequency (RF) is applied for RDN therapy. It is a novel catheter-based, percutaneous procedure using RF energy to ablate nerves within the renal arteries. This procedure might help to significantly lower blood pressure (BP) in patients with resistant hypertension, defined as BP > 140/90 mm Hg (> 130/80 mm Hg for those with diabetes) despite use of 3 optimally dosed antihypertensive agents, ideally including 1 diuretic agent. [12]. The current evidence on safety and efficacy of this procedure revealed that in patients with systolic BP ≥ 160 mm Hg (≥ 150 mm Hg for patients with type 2 diabetes) despite use of 3 antihypertensive agents, bilateral renal denervation was associated with significantly lower BP (-22/11 to -34/13 mm Hg) at 6 months with a low periprocedural complication rate. Thus, ultrasound RDN has demonstrated a reduction in blood pressure for patients with hypertension, or high blood pressure, that is resistant to medical therapy.

Hence devices which are currently in development for the treatment of hypertension have been compiled recently [13]. Different therapy types >12 are reported, viz., Chemical denervation, RF ablation, Cardiac stimulation, Radiation therapy, Implantable BP sensor, Ultrasound ablation, Carotid body modulation, Cryo-ablation, Baro-receptor activation, Microwave energy, Vagal nerve blocking, Shock waves, and Stent-like implant. Since ultrasonic is a noninvasive technique, many companies are now making proto-types/commercial devices based on therapeutic technology and are presented in table-1. Focused ultrasound phenomena has been elaborated in the foregoing since, focused ultrasound treatments can be performed on an outpatient basis, require no incisions, and can result in minimal discomfort and few complications, allowing for rapid recovery.

**Table 1:** Hypertension devices in development based on ultrasound ablation technique

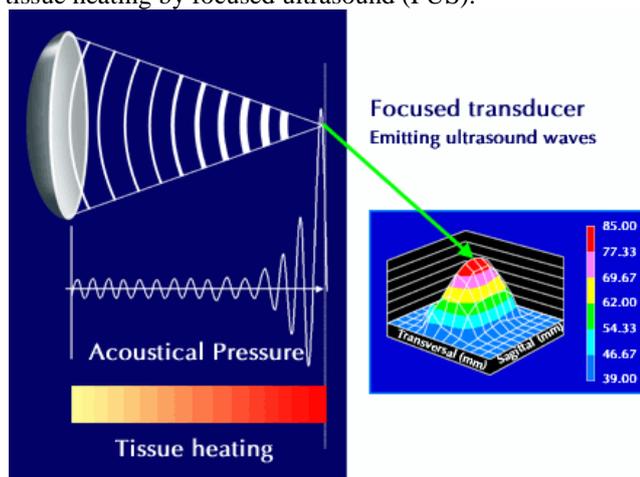
Company	Product	Description	Status International	Status in USA
1. Kona Medical	Surround Sound System	External focused ultrasound-guided, non-invasive, Doppler-based tracking system for optimized treatment delivered in 3 minutes per side; treatments do not require a cath lab or fluoroscopy	International feasibility trial underway	Preclinicals underway
2. ReCor	Paradise	6 Fr over-the-wire ultrasound device; 2nd-gen version is designed	CE Mark	

		to reduce energy delivery to 30 seconds by maximizing cooling of the endothelium and efficiently treating the nerves circumferentially	approval gained	
3. ReCor	Radiance	Latest Paradise system is an ultrasound balloon catheter with cooling; it features a new generator and the 5 Fr, rapid exchange Radiance catheter; can be introduced via radial artery	CE Mark approval gained	
4. Cardiosonic	TIVUS	Non-focused, high-intensity, non-occlusive, high-frequency, directional ultrasound catheter and control system for remote tissue ablation for the treatment of hypertension; 3rd-gen version features a multi-directional catheter	International clinical study underway	U.S. pivotal study planned
5. Enigma Medical	Enigma Device	Non-invasive pre-aortic ganglion ablation for the treatment of hypertension		Intellectual property developed
6. Sound Interventions	Sound-360	Cylindrical ultrasound transducer mounted on the tip of the intravascular catheter for delivering circumferential bilateral renal artery sonications; allows for selective renal nerve denervation	First-in-man study underway	Preclinicals underway
7. VytronUS	Vytron US RDN	Ultrasound-based system in which collimated energy is directed to a renal vessel to create necrotic regions in the tissue in order to alleviate hypertension		Intellectual property developed

Focused ultrasound: Focused ultrasound is an early-stage, non-invasive therapeutic technology with the potential to transform the treatment of many medical disorders by using ultrasonic energy to target tissue deep in the body without incisions or radiation. Focused ultrasound is the marriage of two innovative technologies:

- **focused ultrasound**—which provides the energy to treat tissue deep in the body precisely and noninvasively, and
- **magnetic resonance or ultrasound imaging**—which is used to identify and target the tissue to be treated, guide and control the treatment in real time, and confirm the effectiveness of the treatment.

The fundamental principle is analogous to using a magnifying glass to focus beams of sunlight on a single point to burn a hole in a leaf. Much like a magnifying glass focusing multiple beams of light on a single point, focused ultrasound concentrates beams of ultrasound energy on a target in the body without harming healthy surrounding tissue. Fig.4 shows variation of acoustical pressure and tissue heating by focused ultrasound (FUS).



**Figure 4:** Variation of acoustical pressure and tissue heating by focused ultrasound (FUS).

With focused ultrasound, an acoustic lens is used to concentrate multiple intersecting beams of ultrasound on a target deep in the body with extreme precision and accuracy. Depending on the design of the lens and the ultrasound parameters, the target can be as small as 1x1.5mm or as

large as 10x16mm in diameter. Fig.5 shows typical sonication sizes achievable.



**Figure 5:** A graphic representation of the numerous sonication sizes that can be achieved using focused ultrasound (FUS)..

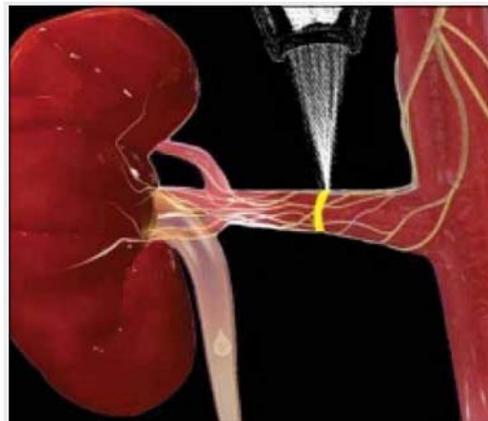
Where each of the individual beams passes through the tissue, there is no effect. But, at the focal point, the convergence of the multiple beams of focused ultrasound energy results in many important biological effects, creating the possibility of treating a variety of medical disorders. .

High-Intensity Focused Ultrasound (HIFU, or sometimes FUS for Focused UltraSound) is a highly precise medical procedure that applies high-intensity focused ultrasound energy to locally heat and destroy diseased or damaged tissue through ablation. HIFU is a hyperthermia therapy, a class of clinical therapies that use temperature to treat diseases. HIFU is also one modality of therapeutic ultrasound, involving minimally invasive or non-invasive methods to direct acoustic energy into the body. Clinical HIFU procedures are typically performed in conjunction with an imaging procedure to enable treatment planning and targeting before applying a therapeutic or ablative levels of ultrasound energy. When diagnostic sonography is used, the technique is sometimes called Ultrasound-guided Focused Ultrasound (USgFUS or USgHIFU).

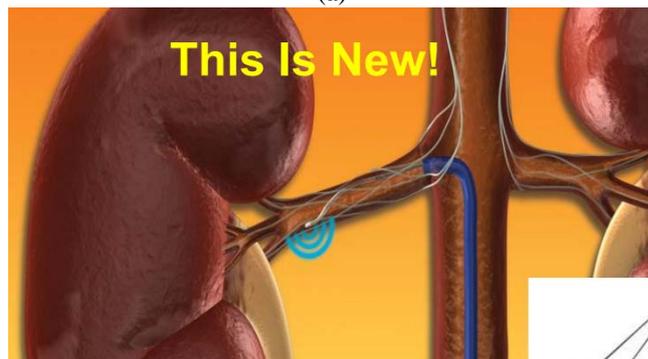
Can ultrasound reduce BP?: Kona medical spent \$50m to find out whether ultrasound reduce BP and finally it has developed an ultrasound-based approach to address severe high blood pressure (hypertension) through ablation of the renal nerves. This ultrasound-based platform which enables non-invasive imaging, targeting, tracking, and treatment of soft tissue structures throughout the body without radiation and without the cost or complexity of MR and other

technologies. *Surround Sound* [14] system utilizes ultrasound imaging to guide the external delivery of focused ultrasound energy to specific target tissue, while automatically tracking movement and enabling continuous therapy delivery.

Development of noninvasive ultrasound device by Kona: Renal nerve ablation, and by extension, regional and system-wide suppression of the sympathetic nervous system, has the potential to radically alter the treatment of hypertension and prevent associated mortality. In today's medical world, a procedural solution for hypertension, which would decrease costs, pharmaceutical burden for patients, and essentially enforce compliance, would be of enormous worldwide benefit. Almost all current renal denervation devices require the intravascular manipulation of catheters to deliver energy, pharmaceuticals, etc. Specific therapies deliver pharmaceuticals through the arterial wall via micropuncture to reach the adventitia (eg, Mercator Bullfrog catheter [MercatorMedSystems, Inc., San Leandro, CA]). There are several limitations to these invasive approaches: (1) the expense and logistics of using a cath lab; (2) the requirement that all treatments be completed during a single procedure because multiple invasive procedures are not practical; (3) current devices only allow fluoroscopic visualization, not visualization of the target area, and therefore, the extent and thoroughness of the procedure cannot be fully assessed; and (4) only patients with highly resistant hypertension are considered for these invasive procedures. Addressing these limitations Kona Medical (Campbell, CA) has developed ultrasound technology. The system delivers energy from outside the patient to the renal nerves. Ultimately, the procedure will be a "no puncture," noninvasive technique, compatible with technologies that will allow for temperature and lesion mapping. A noninvasive procedure will allow titration of the therapy—that is, the application of patient-specific dose fractions while monitoring therapeutic effect in between fractions. The concept of "outside-in" energy delivery to the renal nerves without instrumentation of the vessel is shown in fig.6(a). The basis of the technology is focused ultrasound, not high intensity (HIFU) as one might see and expect in the treatment of tumors, but low-intensity focused ultrasound (LIFU). The biologic underpinnings of this treatment are described in past literature for treating nerves using ultrasound. Nerves are particularly sensitive to mechanical vibration and heat. They are more sensitive to these energy modalities than the surrounding structures such as the artery; it is this differential effect that allows treatment of the nerves without damage to the blood vessel. The heat effect on nerves is well known, and the safety and efficacy of this approach is the likely basis of the simplicity radiofrequency treatment.



(a)



(b)

**Figure 6:** (a) (Left) The concept of "outside-in" energy delivery to the renal nerves without instrumentation of the vessel. 6(b) (Right) Left renal artery cutaway showing inflated balloon with catheter based RDN system, an invasive one described in section 3(iv).

For the purpose of comparison with noninvasive focused ultrasound, an invasive system is given in fig 6(b) along with fig 6(a). Fig 6(b) shows left renal artery cutaway showing inflated balloon with catheter based RDN system and is described in detail in section 3(iv).

Initial clinical application addresses high blood pressure (hypertension) through ablation of the renal nerves. Renal nerves are located proximal to the renal arteries, which provide blood flow to the kidneys. Renal nerves are part of the sympathetic nervous system and play a significant role in determining blood pressure. Clinical data have shown that ablation of renal nerves can result in profound and lasting reduction in hypertension in patients whose blood pressure is not adequately controlled by medication.

The first –in – man study of endovascular ultrasound renal denervation on resistant hypertension studies: In contrast to catheter-based renal denervation systems, which rely on internal delivery of energy through the wall of the renal artery to ablate renal nerves, the system delivers the energy from outside the body to create an ablative field around the vessel which ablates the nerves without impacting the artery. Kona's fully-integrated, portable, standalone system can be used in virtually any exam room in a hospital, office or clinic, and does not require a catheterization lab. Tests conducted using Kona surround sound system – clinical tests have been performed in four stages viz., WAVE I to IV. Of which first two by catheter based renal denervation system and the later two by noninvasive ultrasound application.

The WAVE I and WAVE II clinical studies were conducted to evaluate safety and efficacy using FUS on 24 WAVE I and 18 WAVE II patients in Australia, Canada, and the Czech Republic that were followed for at least 6 months and 3 months, respectively. The studies safely produced clinically significant drops in both systolic and diastolic blood pressure. These studies used a targeting catheter inside the renal artery. From a development standpoint and to address the targeting and tracking challenges out of the equation the therapy delivered safely and effectively through the window behind the patient. WAVE I and II accomplished this.

Data from WAVE II demonstrated that resistant hypertension on 69 patients treated with the Surround Sound RDN system experienced a 19.4 mmHg drop in systolic blood pressure and 6.5 mmHg drop in diastolic blood pressure at three months (n = 17). For WAVE I, patients experienced blood pressure reductions of 22 / 9 mmHg at three months and 29 / 12 mmHg at six months (n = 24). There were no device related serious adverse events in WAVE I or WAVE II indicating an excellent safety profile. WAVE II utilizes a dosing pattern that reduces therapy delivery time from 13 minutes per patient side to less than three minutes when compared with WAVE I. Data from the WAVE I and WAVE II studies continue to indicate the effectiveness of external ultrasound as a method of renal denervation.

It is known that the nerves could be treated from outside, and potentially this was a better way to treat the nerves given their variable location. However, radiation wasn't the way to do this because nerves are difficult to ablate with ionizing energy, requiring high doses of radiation with precise targeting. The only other really penetrative energy is ultrasound. As a surgeon, one can look at renal arteries many times through the patient's back. With a view to evaluate if renal sympathetic denervation (RSD) could be accomplished with externally applied focused ultrasound, Kona developed a novel applicator. Fig.7 (a) is a noninvasive treatment system based on doppler signals from the renal artery and Fig.7 (b) shows ultrasound is delivered from outside the body through the patient's back. It incorporates an anatomically customized phased-array ultrasound transducer to generate and focus therapeutic energy to the depth of the renal artery, and an ultrasound imaging transducer to facilitate locating, targeting and tracking the renal artery for treatment. After locating the renal artery in an appropriate acoustic window using duplex ultrasound, single-sided therapy was directed in a single plane perpendicular to the renal artery in multiple rows. Energy dosing between 50-60 watts at 4 centimeter depth was targeted at seventeen 10x1.5 millimeter regions. The results demonstrate the feasibility of targeted external ultrasound for renal sympathetic denervation.

Fig.7(a).shows the Kona noninvasive system and is depicted in a custom chair; another version of the system as in fig.7(b) is compatible with a standard fluoroscopy or MRI table. Both ultrasound (through elastography and the evolution of temperature mapping and MRI) allow further imaging and analysis of the treatment area. Studies showed that a heat/vibratory cloud at one plane along the artery is

highly effective at long-term inhibition of renal nerves with no visible effect on any portion of the artery at any time point.



(a)



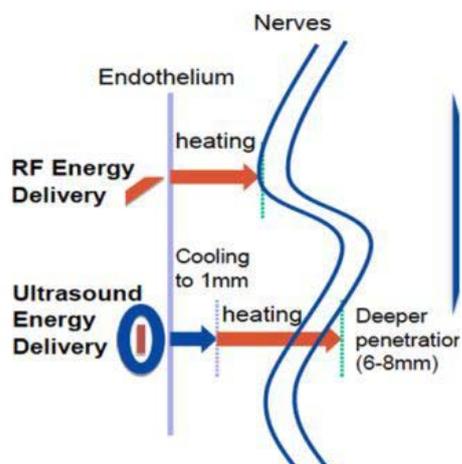
(b)

**Figure 7:** (a) (Left) Kona medical noninvasive treatment system based on doppler signals from the renal artery 7(b)(Right) Noninvasive application of ultrasound from outside the body through the patient's back to zap high BP

Figuring that researchers had target the renal artery doppler signal (not necessarily the nerves), and this is how one could do it noninvasively. Treating patients using doppler guidance and ultrasound imaging for targeting and tracking of the blood vessels paves the way the path to noninvasive ultrasound to be staged in WAVE III trial. Ultimately, FUS may be a better way to treat the nerves – you can retreat, and it is safer on blood vessels than catheter-based radiofrequency. From an anatomical standpoint, the nerves are located diffusely around the blood vessels, and there are likely technological challenges in the delivery of radiofrequency from inside the vessel. Surround Sound can deliver energy and treat a very large volume of tissue quickly. How large and how quickly will be the subject of the pre-clinical and clinical studies for years to come. WAVE III, which will use non-invasive ultrasound imaging to guide Surround Sound's external ablation. The great promise of this technology is the opportunity to treat hypertension patients outside the cath lab, without the use of catheters, invasive instruments or radiation.

Ultrasound RDN is shown to be an efficient in lowering blood pressure in resistant hypertension: Circumferential ultrasound heating is potentially a more uniform and effective method for performing RDN than radiofrequency systems [15]. Fig.8 illustrates radiofrequency vis-à-vis

ultrasound energy delivery renal denervation. It is evident that ultrasound is beneficial and has edge over radiofrequency in BP reducing application.



**Figure 8:** Radiofrequency vs Ultrasound Energy Delivery Renal Denervation

Surround sound utilizes ultrasound, delivered from outside the body, to treat nerves leading to and from the kidney. When hypertension is not adequately treated by lifestyle modifications and medication, these nerves may be overactive, contributing to high blood pressure. People with high blood pressure are more likely to suffer stroke, heart failure, coronary artery disease and other debilitating conditions. WAVE IV will evaluate the safety and efficacy of Surround Sound in people with resistant hypertension, and will include a treatment arm for those who have failed alternate forms of RDN. Initiation of clinical trials WAVE IV is an important milestone and it will be the first randomized, sham-controlled renal denervation trial, which helps in the development and commercialization of surround sound. This non-invasive surround sound hypertension therapy system trial will treat 132 subjects at sites in Europe, New Zealand, Australia, and South America.

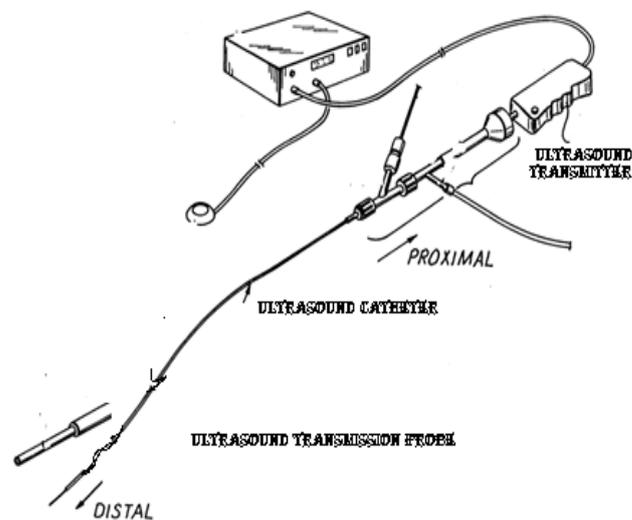
Studies conducted in New Zealand using ultrasound for BP reduction: It is seen that ultrasound therapy, without the need for any incisions through the skin, is the latest development in the rapidly changing field of non-drug treatment for blood pressure [16]. In New Zealand, more than 25 per cent of adults have high blood pressure and in up to 10 per cent of them the condition is resistant to drug treatment. High blood pressure increases a person's risk of heart attack, stroke and kidney failure. New Zealand patients with drug-resistant high blood pressure are among a small group internationally to be treated with a promising new technique that involves ultrasound.

The angiography service at the private Mercy Hospital in Auckland is one of several centers involved in international trials. Trials were conducted using ultrasound machine supplied by M/s Kona Medical, for the therapy. The treatment is a form of renal de-nervation, which interferes with nerves in the outer walls of arteries supplying the kidneys by damaging them with heat. Around 14 bursts of ultrasound energy, each lasting 15 seconds, are aimed at each of the two renal arteries. 42 patients were treated in two trials using ultrasound system for drug-resistant high blood

pressure. The effectiveness of the ultrasound system is found to be that 73% had a clinically significant drop in blood pressure at three months, and 81% at six months. The aim of this study is not necessarily to get rid of medication completely but to make the blood pressure medication-controlled. Many patients are able to reduce their medication

3(iv) Invasive ultrasound renal denervation therapy for treatment of resistant hypertension: The core of the therapeutic intravascular ultrasound technology is a miniaturized ultrasonic transducer, located at the tip of a flexible catheter, and capable of emitting ultrasonic waves which creates controllable levels of heat for selective tissue ablation.

Ultrasonic catheter for ablating obstructions within tubular anatomical structures like small tortuous blood vessels, such as the coronaries arteries is shown in fig.9. Ultrasound transmitting catheters have been utilized to successfully ablate various types of obstructions from blood vessels of humans and animals. Particular success has been observed in ablation of atherosclerotic plaque or thromboembolic obstructions from peripheral blood vessels such as the femoral arteries. Successful applications of ultrasonic energy to smaller blood vessels, such as the coronary arteries, necessitates an ultrasound catheter for removing obstructions from tubular anatomic structures such as blood vessels, comprises of an elongate flexible catheter body having an ultrasound transmission member or wire extending longitudinally.

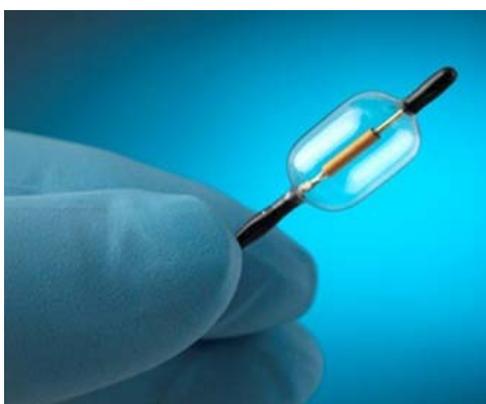


**Figure 9:** Perspective view of therapeutic intravascular ultrasound ablative catheter over the wire for radial ultrasonic energy emission

A distal head is formed on the distal end of the ultrasound transmission wire and is affixed to the catheter body. At the distal end of the catheter is an ultrasound transducer contained within an inflatable balloon that once activated will deliver uniform circumferential ultrasound energy to cause denervation. The distal portion of the ultrasound transmission wire is of reduced diameter to provide enhanced flexibility and/or amplification of the ultrasonic energy through the distal portion of the ultrasound transmission wire. A proximal end connector could be

provided with a sonic connector to effectively couple the catheter to the ultrasound transducer. The use of ultrasound transmitting catheters which are sufficiently small and flexible to permit transluminal advancement of such catheter through the tortuous vasculature of the aortic arch and coronary tree. Accordingly, the safety and efficacy of removing obstructions from coronary arteries by way of ultrasound is largely dependent upon the size and flexibility of the ultrasound transmitting catheter(s) employed.

ReCor Medical, Inc, pioneered in developing ultrasound renal denervation. The clinical trials conducted were named (i) as REDUCE, and (ii) as the 'Paradise' catheter system. Paradise Gen 2 is a commercial ultrasound device [17] based on RDN system for control of hypertension, has received clearance for its from European authorities. The original system was approved for sale a year ago and the new one improves it with an over-the-wire 6Fr device size and faster denervation. All other known similar systems use low power radiofrequency waves to reduce sympathetic nervous system hyperactivity by denervating nerves in the renal artery walls. The system uses a balloon to position the transducer centrally, as shown in fig.10, in within the lumen to deliver consistent denervation and cooling evenly to the artery walls.



**Figure 10:** (a) (Left) Paradise renal denervation catheter, 6-french catheter over the wire delivery low pressure balloon. 10(b)(Right) Ultrasound transducer within an inflatable low-pressure balloon

**Ultrasound energy delivery:** The PARADISE technology (Percutaneous Renal Denervation System) includes a 6 French catheter with a cylindrical transducer that emits ultrasound energy circumferentially, allowing for a more efficient renal denervation procedure. Ultrasound energy consists of high-frequency sound waves (i.e., rapid mechanical oscillations), which are emitted circumferentially by the cylindrical transducer. These sound waves pass through the surrounding fluids and generate frictional heating in soft tissues resulting in a temperature increase and nerve damage at depth. Pre-clinical data revealed that it this approach "did not affect the arterial wall". The ultrasound transducer lies within a low-pressure balloon which allows for self-centering of the transducer and

gentle contact with the artery wall for uniform, circumferential denervation. This means nerves below the surface of the artery wall are damaged in 360 degrees with a single emission. The balloon also enables cooled fluid to circulate during the energy delivery process, thereby cooling the endothelial wall and protecting it from any excessive heating that could be caused by other energy sources or designs. Fig.11 shows two models of ultrasonic generators to drive the transducer.



**Figure 11:** (a) Ultrasonic generator to drive the transducer. (b). Paradise renal denervation generator.

Paradise catheter system: Ultrasound ablation paradise technology system uses a balloon catheter with a cylindrical transducer that emits ultrasonic energy circumferentially to the selected vessels. Since ultrasound 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 nontarget tissues. It has an automated generator designed with the aim of allowing complete circumferential denervation using a 6-Fr compatible catheter. At the distal end of the catheter is an ultrasound transducer within an inflatable low-pressure balloon (as shown in fig.9b). The balloon is inserted over a 0.014" angioplasty wire through a 6 Fr guiding catheter engaged in the renal artery. Once activated, the ultrasonic sound waves are emitted in a circumferential manner from the central core of the balloon and require a 30 second treatment in each renal artery. The

Paradise renal denervation control unit automatically controls the balloon inflation, fluid flow, energy delivery as well as real time safety checks.

Sapoval presented six-month results from the REDUCE trial, the first-in-man study of endovascular ultrasound renal denervation with the Paradise system (ReCor Medical) for the treatment of resistant hypertension. It consists of an intravascular, catheter-based approach that, as with radiofrequency, is achieved by inducing thermal necrosis.

Fifteen consecutive patients with resistant hypertension as defined by the European Society of Hypertension/European Society of Cardiology guidelines were enrolled in the REDUCE study in South Africa. All patients were on a minimum of three anti-hypertensive medications including a diuretic at baseline (average five medications). The mean age of patients was 52 years (32–80 years), and 60% were men. Enrolment was completed in May 2012.

It has been observed that, at baseline, the average systolic and diastolic blood pressure measurements were, respectively,  $182 \pm 22$  mmHg and  $111 \pm 15$  mmHg in the office,  $170 \pm 21$  mmHg and  $101 \pm 14$  mmHg at home, and  $173 \pm 19$  mmHg and  $102 \pm 16$  mmHg in ambulatory.

Bilateral denervation was performed by delivering an average of 5.5 ultrasound emissions in each patient. The average heating time was 4.3 minutes per patient; up to three 50-second emissions per artery; up to 5 minutes total heating time at an average of 23 minutes between the first and the last emissions performed under local anesthesia. There was no need for general anaesthesia, only sedatives and analgesics.

Data obtained on 11 patients who completed six months of follow-up shown that, the reduction seen in office blood pressure was 32 mmHg systolic and 17 mmHg diastolic. The ambulatory blood pressure reduction was 13 mmHg systolic and 8 mmHg diastolic. Further studies conducted and started in 2012 by enrolling 20 patients at two sites in France, and will enroll 50 patients at nine European sites.

The first –in-man study, the REDUCE trial [18], was a single-arm, open-label trial that enrolled 15 patients and showed an average sustained reduction of 30 mmHg systolic blood pressure at 1-year follow-up. Two patients experienced stenosis requiring stent intervention. There were no complications at the puncture site; however abdominal or lower back pain was seen in 63% of the patients following intervention which resolved within a few days. Study of the Paradise system evaluating the safety and effectiveness in a 100 patients expected to complete enrollment by mid-2014 [18].

In conclusion, ultrasound renal denervation, has been efficient in lowering blood seen in the Paradise system preserves the artery and prevents subsequent pressure in patients with resistant hypertension". Investigators noted that that high flow rate cooling featured complications.

#### 4. Probable Mechanism of BP Reduction by Ultrasound

Ultrasound exhibits different phenomena when applied noninvasively and invasively. Also during non-invasive ultrasound application in presence and absence of medication mechanism differs. Detailed implications of various factors that govern BP reduction by ultrasound renal denervation technology are given below.

4.i(a). When ultrasound applied non-invasively without medication: The ultrasound therapy is one of physical methods to treat disorders of movement organ. The ultrasound wave, while passing through layers of tissues gives away acoustic energy. Each tissue of the body has got different structure and different ability to absorb the ultrasound energy. A biological influence of ultrasounds on the body depends on an amount of energy absorbed by the tissues. The influence is resultant of thermal and non-thermal effects of ultrasound, which includes cavitation and acoustic streaming. Beside local reaction of tissues treated with ultrasound, there is also a general reaction of a whole body [10]. Depends on parameters of ultrasound wave alone with ultrasound intensity of  $1.5 \text{ mWcm}^{-2}$  may have an influence on cardiovascular system, especially blood pressure, both on people with normal blood pressure and hypertension.

4.i(b). Non-invasive ultrasound application with medication: The mechanisms by which ultrasound irradiation applied to forearm for 30 min, decreased CO (cardiac output, l/min) and pulse rate remain unclear. Ultrasound irradiation might suppress central sympathetic outflow and/or sympathetic neural activity via novel afferent neural pathways from the forearm to the cardiovascular system. Sympathetic nervous system hyperactivity contributes to the initiation and progression of hypertension [11], and device-based approaches such as catheter-based renal sympathetic denervation and baroreceptor activation to treat resistant hypertension suppress sympathetic neural hyperactivity [11]. In addition, substances released by ultrasound irradiation may affect BP and pulse rate. Furthermore, ultrasound irradiation might acutely increase systemic blood flow and/or drug delivery system function, thereby enhancing the effects of anti-hypertension agents. Even at mild ultrasonic intensity of  $2 \text{ mWcm}^{-2}$  applied noninvasively in combination with medicines have profound effect on BP reduction [11].

This observation is in line with the finding by the author's group in 1996 [19, 20] that ultrasound has synergistic effect in enhancement of antibiotic activity. Break through observation was made by the author's group that bacterial viability is noticed much below the MIC (minimum inhibitory concentration) levels. In fact, whatever antibiotic effect was observed with high intensity ultrasound of  $1 \text{ Wcm}^{-2}$  an identical effect has been found by using mild ultrasound intensity ( $20 \text{ mWcm}^{-2}$ ) with low dosage of medication. It means a synergistic effect was observed and bacterial viability was reduced an order of magnitude where medicine concentration and ultrasonic levels which by themselves didn't reduce viability, were combined. However, the mechanisms by which ultrasound irradiation applied to the forearm acutely improves hypertension warrant further examination in future studies.

4.(ii) By invasive ultrasound method: This method can be termed as ultrasound renal denervation technology. Ultrasound energy consists of sound waves that pass through the fluids and generate frictional heating in soft tissue. No direct contact is required, and energy can be emitted circumferentially. Further, with this device, cooling the arterial wall minimizes damage to non-target tissues; the self-centered transducer enables controlled and uniform energy delivery; and circumferential heating allows for more rapid treatment, therefore reducing procedure times. The 'sounds intervention catheter' is an 8 Fr standard sheath and ultrasound energy is delivered circumferentially up to 2 applications in each artery not lasting longer than 2 min per patient[17].

Renovascular hypertension is high blood pressure due to narrowing of the arteries that carry blood to the kidneys. This condition is also called RAS (renal artery stenosis). RAS is a narrowing or blockage of the arteries that supply blood to the kidneys. The most common cause of RAS is a blockage in the arteries due to high cholesterol. This problem occurs when a sticky, fatty substance called plaque builds up on the inner lining of the arteries. When the arteries that carry blood to your kidneys become narrow, less blood flows to the kidneys. The kidneys mistakenly respond as if your blood pressure is low. As a result, they release hormones that tell the body to hold on to more salt and water. This causes your blood pressure to rise irrespective of medication used, BP would not be controlled and high BP persists [17].

Ultrasound is a unique approach is in stark contrast to RF, which is limited in its depth of penetration to just a few millimeters (refer fig.8), due to inconsistent arterial wall contact, as well as its inability to heat circumferentially in any given location. In addition, RF technologies generate unnecessary heating at the level of the arterial wall. It has been concluded that renal nerves are actually much further at depth than previously thought, and run circumferentially around the renal arteries, which underscores the 'Paradise ultrasound' advantage. The benefit of Paradise catheter system developed by ReCor's ultrasound approach is three-fold. Firstly, it is designed to penetrate much deeper into the tissue, up to 8 millimeters; secondly, it delivers heat circumferentially, to target all of the renal nerves in one location; thirdly, it does this while simultaneously cooling the artery wall's surface to protect the vessel.

Ultrasound Vs Radiofrequency RDN technology: RDN is a novel catheter-based, percutaneous procedure using radiofrequency energy to ablate nerves within the renal arteries. This procedure helps to significantly lower blood pressure (BP) in patients with resistant hypertension. On the other hand radiofrequency RDN has the ability to disrupt the nerves in adventitia (outer layer of the artery wall) by applying heat directly to the endothelium. Whereas ultrasound energy consists of high-frequency sound waves that pass through fluids and generate frictional heating in soft tissues, without requiring any direct contact to the tissue. The energy is delivered volumetrically to a specific target limiting extensive heating of intervening or adjacent tissues, allowing ultrasound energy to be delivered within the blood vessel from a distance, without any direct contact.

Ultrasound renal denervation is a technique that does not "touch" the intima of the artery and applies energy at 360 allowing for less manipulation and good catheter stability, as shown in fig.12. Furthermore, ultrasound RDN destroys the renal nerves without damaging the arteries. The blood absorbs very little ultrasound energy and acts as coolant for the arteries, reducing endothelial (intimal/ inner layer) damage and offering deeper penetration into the arterial tissue. Leading companies currently pursuing ultrasound based renal denervation are given before in table-1 with another 50 or so in various stages of development.

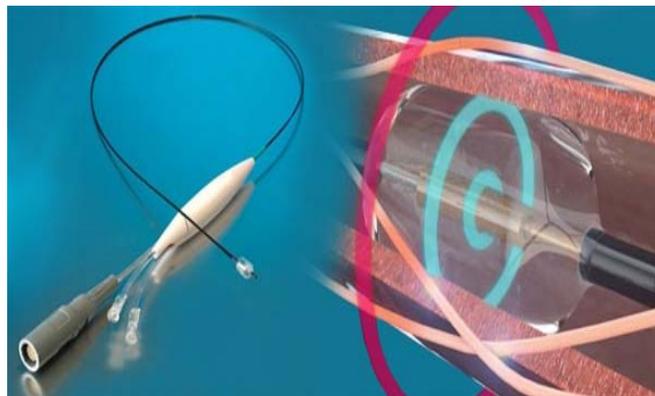


Figure 12: Ultrasound renal denervation technique.

## 5. Summary and Future

In line with the current trend in healthcare with an increasing focus on the prevention of cardiovascular disease new methods of BP measurement and control is a must. Ultrasound is an emerging technique in this therapy area and this presentation reviews and gives an insight into the latest research conducted after 2010. Altogether two BP measuring methods and four treatment techniques using both noninvasive and invasive ultrasound have been presented. Conventional BP measurement gives instantaneous or intermittent values whereas the continuous BP measurement using ultrasound is described which permits the patient to follow his daily activities. Also a user friendly BP measurement with ultrasonic scanner is elucidated which allow physician to carry out investigations of the cardiovascular system to prevent certain diseases. For the first time in 2006 the present author has initiated work on noninvasive ultrasound application for BP reduction [9] which has opened a new window for clinical applications. In all the four different ultrasonic methods presented BP is shown to be reduced at least by 10 mmHg including patients who are drug resistant. For patients who completed six months follow-up by using surround ultrasound system [14] the reduction seen in-office BP was 32 mmHg systolic and 17 mmHg diastolic. The fourth generation catheter which is currently under development will be a multi-directional catheter that gives real time feed back of the denervation effect which can be used for trans-radial access. Ultrasound-based, non-invasive RDN has the potential to greatly reduce cost, lower risk, and improve access to millions of hypertension patients worldwide who are not adequately controlled by drug therapy. So, physicians have now an innovative option for dispensing safe, home-based, inexpensive ultrasonic therapy for patients. Coupled with the early potential effects of renal denervation on improved

glucose control, sleep apnea, and treatment of heart failure syndromes and renal dysfunction (all consequences of sustained hypersympathetic activity), we are truly on the verge of a brave new frontier, by the use of ultrasound, that holds the promise of substantially improving the lives of our patients. Overall commercialization success of noninvasive ultrasound would be tied to that of with invasive competitors. In case of invasive ultrasound RDN treatment physicians in general will follow patient preferences (e.g. minimally invasive surgery). If the procedure is easy for physicians to learn, this will also drive adoption, and so this is one of the system requirements. From the patient standpoint, the requirement for the treatment is that noninvasive ultrasound by Kona takes only a few minutes to set up and a few minutes to administer, which will be great marketing points. The method is predicted to be inherently safer than a catheter (which applies heat through the wall of the artery) and this will also help on the marketing side. Finally, in the commercial angle, handheld-ultrasound market grew by 42% in 2007 to \$565 million. However, Klien the leading ultrasound industry expert expects the global market to exceed \$1.2 billion in five years.

This presentation has highlighted the potential of a novel ultrasound based RDN technology. Several clinical trials conducted worldwide demonstrates the implementability of this new technology for controlling BP in drug resistant subjects. Aspirations for ultrasonic therapy applications are there which all medical professionals would welcome clinically proven revolutionary new technology part of BP reduction regimen. In truth there are many therapeutical ultrasound systems available, but, few are optimized. There are now several multi-disciplinary groups involved in medical ultrasound project, and this is undoubtedly the way forward. The future of ultrasound is therefore rosy, both from the point of view of greater interest in the fundamental principles of its action, and in the development of programmes in applied research and technology.

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