Austin Journal of Vascular Medicine

Open Access

Austin Publishing Group

Review Article

Treating Hypertension: Multiple Approaches to a Common Multifactorial Disease?

Chao-Yin Chen[1]* and Stephanie C.Tjen-a-looi[2]

[1]Department of Pharmacology, University of California, US

[2]Department of Physiology, University of California, US

***Corresponding author:** Chao-Yin Chen, Department of Pharmacology, University of California, Davis, US

Received: October 31, 2014; **Accepted:** December 20, 2014; **Published:** December 30, 2014

Abstract

The residual life time risk for developing hypertension in middle-aged and elderly individuals is 90%. While hypertension is well known to have dire cardiovascular consequences, it is estimated that ~50 million Americans (~1 billion individuals worldwide) have uncontrolled hypertension. Factors contribute to the difficulty in preventing and treating hypertension includes noncompliance, high costs, adverse side effects, and the complexity of the origin of hypertension. Recent advance in antihypertensive therapies suggest that the treatment of hypertension may no longer be limited to the simple prescription of pharmaceuticals. In contrast to pharmacological treatments, the key feature in non-pharmacological treatments is that they take advantage of the functional neural network of reflexes that our body uses to set and change blood pressure. This review will focus on the concept that targeting multiple sites along the reflex pathway could provide additional effective approaches for treating hypertension. Because the sympathetic nervous system is a common output of reflex regulation of blood pressure and sympathoexcitation is a hallmark of hypertension, sympathetic denervation was the first non-pharmacological approach being sought out. This approach has evolved to a minimal invasive renal denervation procedure. In contrast to targeting the output side of the reflexes in renal denervation approach, a few more recent developments target the input side of the reflexes including carotid baroreceptor stimulation and carotid chemoreceptor ablation. Finally, non-pharmacological and non-surgical approaches such as exercise and acupuncture may provide additional adjuvant anti-hypertensive strategies by stimulating peripheral somatic afferents. It is conceivable that various combinations of multiple approaches may be tailored to each individual to successfully and adequately treat this multifactorial disease.

Keywords: Hypertension; Beroreflex; Chemoreflex; Renal denervation; Exercise; Acupuncture, Non-pharmacological treatment

Abbreviations

CNS: Central Nervous System; SNS: Sympathetic Nervous System; TPR: Total Peripheral Resistance

Introduction

Uncontrolled hypertension is a well-known major risk factor for stroke, heart failure, and end-stage renal disease [1-3]. The first classification of high blood pressure as a cardiovascular disease dated back to the end of the 19th century [4]. In 1977, the First Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure established the first criterion for hypertension: individuals with diastolic blood pressure over 105 mmHg [5]. Since then, several revisions were made to the definition with emphasis shifting to both systolic and diastolic blood pressure [6]. Table 1 shows the current definition for each stage of hypertension. In the US, the prevalence of hypertension has remained consistent over the past 10 years, at an overall rate of approximately 30% for adults aged ≥ 18 years old [7,8].

Since 1940, many classes of drugs have been developed for pharmacological treatment of hypertension, including diuretics, beta blockers, ACE inhibitors, Angiotensin II receptor blockers, calcium channel blockers, alpha blockers, alpha 2 receptor agonists, central agonists, peripheral adrenergic inhibitors, and blood vessel dilators. The advance in pharmacological treatment has significantly improved the hypertension controlling rates [9]. Although hypertension controlling rates continued to improve in the past decade, there are still about half of hypertensive individuals (~15% or ~50 million of Americans) have uncontrolled hypertension [7,8,10]. It is estimated that 12-15% of hypertensives have resistant hypertension consisting of three patient groups: pseudo resistant hypertension (33%, noncompliance due to factors such as high costs, adverse side effects, and lack of adherence), the need for more than 3 anti-hypertensive medications (33%), and true resistant hypertension (33%) [11]. The difficulty in treating hypertension may reside on the complexity of the origin of hypertension, a complex disease that cannot be ascribed to a single gene mutation or a single environmental factor [12]. Personalized combination of multiple approaches may be needed for optimal treatment of this multifactorial disease. Recently, there are new exciting and promising developments in non-pharmacological anti-hypertensive treatment involving manipulations along the reflex pathways. This review will highlight these approaches.

Determinants of arterial pressure

A full appreciation of current advance in anti-hypertensive treatments rests on a basic understanding of how resting arterial

Citation: Chao-Yin Chen and Tjen-a-looi SC. Treating Hypertension: Multiple Approaches to a Common Multifactorial Disease?. Austin J Vasc Med. 2014; 1(2): 1008.

Table 1: Current hypertension definition.

Category	SBP (mmHg)		DBP (mmHg)
Normotensive	< 120	and	< 80
Pre-hypertension	120 – 139	or	80 – 89
Stage 1 hypertension	140 – 159	or	90 to 99
Stage 2 hypertension	≥ 160	or	≥ 100

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

pressure is regulated. The Guyton's ground breaking systems approach to arterial pressure control provided the first comprehensive view on arterial pressure regulation [13]. The center of this computational model is the kidney function (pressure-volume regulation) in determining long-term arterial pressure. In his "hierarchy of pressure control systems" [14], Guyton proposed that the nervous controls (e.g. cardiovascular reflexes) serve to buffer the arterial pressure on a short-term basis rather than to provide long-term control. This concept was supported by observations that mean arterial pressure returned to near normal within two weeks in baroreceptor denervated animals [15] and that baroreceptors discharge resets rapidly (within 48 hours) when arterial pressure was acutely raised [16]. It was concluded that the long-term control of arterial pressure is vested almost entirely in the long-term control of body fluid volumes and an alteration in the pressure–natriures is relationship underlies arterial hypertension. Since then, reports from other investigators supported these observations [17-20]. The effectiveness of low salt diets and diuretic medications in treating hypertension further strengthens this hypothesis.

However, more recent studies raised the possibilities that, under certain conditions, renal-blood volume pressure control may not be the sole contributor of arterial hypertension and baroreceptor reflexes may contribute to long-term control of mean arterial pressure. For example, Osborn and Hornfeldt [21] showed that combination of baroreceptor denervation and high salt intake resulted in hypertension in rats while either treatment alone had no significant effects on mean arterial pressure. Tsyrli and colleagues [22] demonstrated that two-kidney one-clip did not result in hypertension in 34 of 68 control rats in contrast to baroreceptor denervated rats that invariably developed significant elevated blood pressure following two-kidney one-clip. Furthermore, Thrasher [23] developed a chronic baroreceptor unloading animal model by ligating the common carotid artery proximal to a single innervated sinus (with the opposite sinus and aortic baroreceptors denervated). Although the initial increase in mean arterial pressure was not sustained, arterial pressure declined to a level that was modestly higher than control that persisted at the end of the 5-week recording period. This is in contrast to unilateral carotid sinus carotid denervation and sinoaortic denervation in which arterial pressure declined back to control level within two weeks of denervation. Finally, in a recent refined computational analysis [24], Beard and colleagues suggest that long-term control of arterial pressure is primarily through the baroreflex arc and the renin-angiotensin system. Thus, in the view of the multifactorial origin of hypertension and elevated sympathetic nerve activity in almost all form of hypertension, it is conceivable that manipulations along the cardiovascular reflex arc may provide additional options for lowering arterial pressure in hypertension.

As illustrated in figure 1, there are three well-known afferent

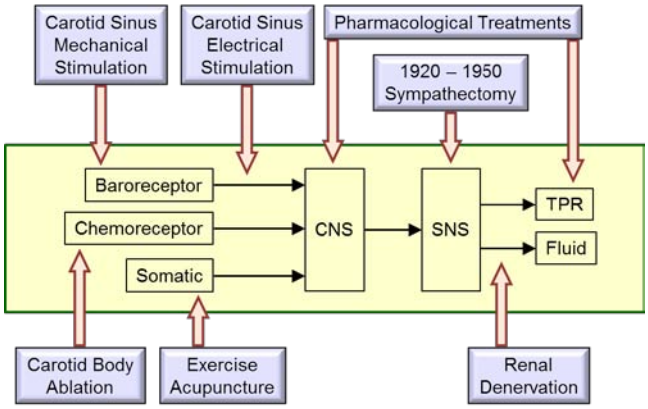

Figure 1: Neuronal pathways in blood pressure regulation and anti-hypertensive treatment sites. Three well-known reflexes (baro, chemo, and somatic) regulate blood pressure. These reflex pathways send afferent signals to the central nervous system (CNS) to regulate the sympathetic nervous system (SNS) out flow to change blood pressure by adjusting total peripheral resistance (TPR) and blood volume (Fluid). On the reflex output side, pharmacological treatments, sympathectomy, and selective renal sympathetic denervation lower blood pressure by reducing vascular resistance and/or fluid retention. On the reflex input side, carotid sinus stimulation (both electrical and mechanical) activates baroreceptor/afferent to trigger reflex reduction in SNS activity to lower blood pressure. Carotid body ablation reduces chemoreflex mediated sympathoexcitation. In addition, activation of somatic input may increase blood pressure during stimulation but trigger a prolonged reduction in blood pressure after stimulation.

inputs (baroreceptor, chemoreceptor, and somatic sensory afferents) projecting to the Central Nervous System (CNS) that play significant rolls on blood pressure regulation by altering the Sympathetic Nervous System (SNS) outflow. On the reflex output side, earlier non-pharmacological approach involved invasive surgical sympathectomy that resulted in unacceptable side effects. Recent advance in technology in selectively denervate renal sympathetic nerves with minimal surgical procedure showed promising results. On the reflex input side, a couple of approaches have been developed to activate baroreceptor to reduce blood pressure, including electrical and mechanical stimulation, also showed promising results. In addition, ablation of chemoreceptor in carotid body may benefit hypertensive individuals with enhanced chemoreflex. Finally, as proof-of-concept, activation of somatic afferent may provide addition adjunct therapeutic anti-hypertensive treatment options.

Sympathectomy/ Renal denervation

In the early 20th century, various surgical sympathectomies were introduced as extreme measures for treating malignant hypertension [25-30], including bilateral lumbar sympathetic neurectomy, subdiaphragmatic splanchnicectomy, thoracolumbar splanchnicectomy and sympathectomy, section of anterior nerve roots, and total sympathectomy. The original concept was to remove sympathetic-mediated vasoconstriction to a large portion of the vasculature as well as to improve renal functions. The splanchnic nerves were believed to be a great target because they control a large portion of the visceral blood supply. However, this surgical approach was short lived for various reasons: invasive nature of the surgery, high mortality rates, unacceptable side effects, and the significant advance in anti-hypertensive drug therapy [9,31].

Recently, an endovascular catheter technology made it possible

to selectively denervate renal nerves using radiofrequency delivered via the renal artery lumen (Medtronic Symplicity™ Renal Denervation System).The original concept for this treatment was to reduce renal sympathetic efferent activity and thus reduce renin release, sodium reabsorption, and renal vascular resistance. As a proof of principle, results from the first clinical trial of this minimally invasive procedure showed promising outcome in lowering arterial pressure without obvious side effects in some patients with stage 2 resistant hypertension [32]. Although the number of patients completing the 24-month follow-up measurement was low, the arterial pressure 2 years after the procedure was 32 mmHg (systolic) and 14 mmHg (diastolic) lower than before the procedure [33]. These data were confirmed in a subsequent report with a larger sample size that also demonstrated a persistent lower arterial pressure after three years [34].

Similar results were achieved in a randomized controlled trial [35]. At 6-month follow up, there was a 32 mmHg and 12 mmHg (systolic and diastolic, respectively) decrease in arterial pressure in renal denervated group while the control group had no change in arterial pressure. The reduction in arterial pressure was sustained 3 years after the denervation procedure [36,37]. Interestingly, although the average arterial pressure was not changed in control group, 35% of control patients had greater than 10 mmHg decrease in systolic blood pressure. Furthermore, even though the overall average arterial pressure was dramatically decreased after the procedure, a small subset of patients (10%) were not responsive to renal denervation [35].

Encouraged by the success of previous two renal denervation clinical trials, a third single-blind, randomized, sham-controlled trial was conducted [38]. However, this blinded trial failed to demonstrate a significant difference in systolic blood pressure between renal denervation and sham control at 6-month follow-up point. Factors contributing to the discrepancy are not entirely clear. Several possibilities have been proposed including lower statistical power from smaller sample sizes in the first two trials, the Hawthorne effect, placebo effect of the procedure per se, patients' medication adherence, population differences, and the degree of denervation achieved in each patient [38-40].

In the view that the origin of hypertension is complex and involves many genetic and environmental factors, it is perhaps not surprising that not every patient responded to renal denervation treatment, even in the first two clinical trials. Given that the procedure appeared to be safe with no unanticipated side effects (as demonstrated in all three clinical trials), the failure of the third clinical trial in lowering arterial pressure does not necessarily rule out renal denervation as a potential anti-hypertensive treatment. Rather, it presents an opportunity to tease out a sub-population of patients with resistant hypertension that might best benefit from renal denervation. One challenge is to identify individuals who are responsive to this procedure. Another challenge is to sort out the interaction between pharmacological treatment and renal denervation (e.g. the possibility that some pharmacological treatments may become more effective after renal denervation in certain patients).

Baroreceptor stimulation

Electrical stimulation: In early 1964, Bilgutay and Lillehei introduced an implantable electronic device "Baropacer" for lowering arterial pressure in hypertensive dogs [41]. The idea was to supplement baroreceptor activity with low background electrical stimulation to offset the baroreceptor resetting in hypertension. Subsequently, electrical stimulation device was implanted to a carefully selected group of patients in a few institutions. These studies showed positive and promising results in lowering arterial pressure with the longest follow-up point of 3 years [42]. However, this anti-hypertensive approach subsided after 1980 because of uncertainty in optimal stimulation parameters and placement that yielded inconsistent results, significant side effects due to current spread to outside of baroreceptive regions, and better pharmacological treatment options [42].

In 2004, Lohmeier and colleagues, as a proof of principle, demonstrated that activation of the carotid baroreflex produced sustained reduction in mean arterial pressure over a 7-day period in normotensive dogs using a refined stimulation system developed by CVRx, Inc (Rheos Baroreflex Hypertension Therapy System) [43]. The results also suggested that there is minimal, if any, current spread outside of baroreceptive areas – no extraneous muscle stimulation or appreciable effects on respiration, appetite, or level of activity. The sustained decrease in arterial pressure was also observed in angiotensin II- and obesity-induced hypertensive dog models [44,45].

Using the Rheos system, the first clinical trial conducted between 2004 and 2007 showed promising results [46]. Systolic blood pressure reduced by 21 mmHg in those 37 patients (out of 45 enrolled) completed 3-month follow-up. Only 17 of the 45 enrolled patients completed the 2-year follow-up and the decrease in systolic arterial pressure was sustained (33 mmHg reduction). Building on these positive results, a multicenter, double-blind, randomized, placebo-controlled clinical trial was conducted between 2007 and 2009 [47,48]. Patients were randomly assigned to either have the device immediately (group A, 68%) or delayed till the 6-month follow-up point (group B, 32%). As expected, group A displayed significant reduction in systolic blood pressure (26 mmHg) at 6-month follow-up and was sustained at 12-month follow-up (35 mmHg reduction). Surprisingly, the control group (group B) also had a significantly reduction in systolic blood pressure (17 mmHg) at 6-month follow-up. The study did not meet the short-term efficacy endpoint because both groups have ~50% responders. Because of the short fall in acute efficacy, the long-term efficacy at 12-month follow-up may not be valid. The study also did not meet the endpoint of short-term safety of 82% event free rate. However, the study did demonstrate positive outcome for the endpoints of sustained efficacy, baroreflex activation therapy safety, and device safety. Currently, another randomized, controlled trial is underway in the US with a second generation device (Barostimneo™) with a target follow-up period of three years. So far, the second generation system appears to be as effective as the first generation system for electrical activation of the baroreflex [49].

While studies from first generation system clearly suggest that over the long-term, baroreflex activation therapy can safely reduce arterial pressure in patients with resistant hypertension, the reduction in arterial pressure in control group at 6-month follow-up is an interesting, albeit unexpected, finding. Several possible explanations have been proposed including the timing of blood pressure measurement in reference to medication, changes in medication, and issues with baseline arterial pressure measurement [47]. Alternatively,

it could be the case that placement of the insulative backer housing the carotid sinus stimulation leads changed geometry of the carotid sinus and mechanically activated the baroreceptors [50]. It also could be the case that the insulative backer that was wrapped around the carotid sinus limited the movement of the vessel it came in contact with, resulting in a greater distension in other part of the carotid sinus in each pressure pulse and enhancing baroreceptor activities.

Mechanical stimulation: Severe cardiovascular depression has long been observed in some patients undergoing carotid endarterectomy or stenting, presumably due to increased mechanical stretch of baroreceptors located in the carotid sinus. Mlekusch and colleagues [51] reported that about 7% of patients developed severe hypotension and/or bradycardia after Elective carotid artery stenting. In a long-term study, Chung and colleagues [52] showed that, compared to the arterial pressure before carotid artery stenting, the arterial pressure was significantly decreased at both 1-month and 1-year follow-up. These data suggest that mechanical stimulation of baroreceptors could be an effective mean of anti-hypertension treatment.

Toorop and colleagues rationalized that a device in the form of open C shaped cylinder could change geometric shape of the carotid sinus and increase the strain of the carotid sinus wall while preserving the arterial pulsatility [53]. As proof of concept, they presented preliminary data from a pilot study demonstrating significant reduction in patients with hypertension [54]. Using fluid structure interaction stimulation methodology, Weisberg and colleagues showed that deployment endovascular devices in the carotid sinus slightly increased circumferential and longitudinal wall stretch (2.5 – 7.5%) but greatly increased (~50%) von Mises arterial stress at the sinus wall baroreceptor region (~50%) [55]. Currently, Vascular Dynamics, Inc. is conducting a "first-in-man" clinical trial to test its MobiusHD™ device for treatment of drug resistant hypertension (Controlling and Lowering Blood Pressure With The MOBIUSHD™, CALM-FIM).

One advantage of mechanical stimulation of baroreceptors is that it avoids any potential pressor effect from stimulating chemoreceptors in the carotid body [56,57]. Although previous studies suggest that mechanical activation of baroreceptor may have great potential for treating hypertension, an obvious question is the impact of baroreceptor resetting in the long-term efficacy of such device. Earlier studies showed that, in sustained hypertension, baroreceptors reset to a higher operating pressure by shifting the pressure threshold for firing action potentials in the towards the prevailing mean arterial pressure, suggesting that baroreflex serves to maintain rather than suppress the hypertension [58]. However, more recent studies suggest that baroreceptor resetting is "incomplete" [59]. In addition, baroreceptors associated with unmyelinated C-fibers do not appear to display acute or rapid resetting and have been proposed to provide input related to longer-term maintenance of mean arterial pressure [60,61]. In the view that most of the baroreceptor afferents are unmyelinated C-fibers [62] that are required for sustained reduction in arterial pressure [63], these data raised the potential for sustained anti-hypertensive treatment by activating additional unmyelinated C-fibers with such mechanical device.

Chemoreceptor ablation

The chemoreceptors are located in carotid body and are different from baroreceptors in two major ways: 1) activation of chemoreceptors increases arterial pressure (in contrast to decrease in arterial pressure by baroreceptors), and 2) prolonged activation of chemoreceptors with hypoxic stimulation resulted in facilitation of chemoreceptor reflex (in contrast to baroreceptor resetting) [63]. It has been shown that chemoreceptor reflex is enhanced in hypertensive [65] and borderline [66] hypertensive humans as well as in obstructive sleep apnea patients with hypertension [67]. These data raised the possibility of treating hypertension with chemoreceptor ablation in these patients.

To isolate chemoreceptor function from baroreceptor function, inhalation of 100% oxygen has been used to functionally deactivate chemoreceptors and leave carotid baroreceptors intact. As a proof of principle, Paton and colleagues [68] showed that inhaling 100% oxygen decreased arterial pressure in SHRs but not their normotensive control rats. However, the results from human studies are somewhat mixed. Although breathing 100% oxygen consistently decreased muscle sympathetic nerve activity in hypertensive humans, the arterial pressure responses were variable, presumably due to other uncontrolled chemo-stimulators such as carbon dioxide level [69,70].

While breathing 100% oxygen selectively deactivate oxygen sensing aspect of chemoreceptors, the clinical application maybe limited. Carotid sinus denervation or carotid body ablation (leaving aortic baroreceptor reflex intact) is one potential alternative. Carotid sinus denervation reduced arterial pressure by ~20 mmHg in SHRs and showed no signs of recovery throughout the 3-week experimental period, suggesting the potential for this procedure [68,71]. Bilateral carotid sinus nerve resection also has been shown to attenuate the development of hypertension in SHRs [71] and diet-induced obesity-hypertension [72]. In humans, while surgical removal of the carotid body for treating pulmonary-related diseases and carotid body tumors has been performed since the 1940s, its effects on long-term outcome of arterial pressure was not documented. Recently, de Francis and colleagues [73] demonstrated a significant reduction in arterial pressure after surgical removal of carotid body tumor (at 10-day follow-up point), especially in patients with hypertension. Together, these studies suggest a potential for chemoreceptor ablation in the treatment of hypertension. The efficacy and safety of this approach in lowering arterial pressure in hypertensive humans remain to be determined. It appears that this procedure maybe more effective in hypertensive patients with increased chemoreceptor reflex, such as those with obstructive sleep apnea.

Somatic nerve stimulation

Lifestyle modifications, including physical activity, has a long history of success in lowering blood pressure and is recommended as the first line of anti-hypertensive treatment [74]. This section will focus on a couple of approaches that activate somatic sensory afferents to modulate central pathways that influence sympathetic and parasympathetic outflows ultimately to regulate cardiovascular reflex responses.

Exercise: The observation of blood pressure lowering effect of exercise can be traced back as early as 1971 where Groom reported a consistent decrease in blood pressure in runners immediately after

running [75]. It is well acknowledged now that a single bout of mild-to-moderate exercise can lead to a postexercise decrease in blood pressure for up to 13 hours in hypertensive individuals, named postexercise hypotension [76-78]. Postexercise hypotension is mediated, in part, by substance P-induced changes in inhibitory synaptic transmission at the second-order baroreceptive neurons located in the nucleus tractussolitarius [79]. Specifically, during exercise, muscle afferent releases substance P to activate the NTS inhibitory interneurons to reset baroreflex to a higher blood pressure level (a.k.a. exercise pressor response) [80]. Activation of substance P receptors during exercise triggers the receptor to undergo internalization, which dampens the inhibitory interneurons and resets baroreflex to a lower blood pressure level after exercise (postexercise hypotension) [79]. Similarly, direct muscle stimulation or stimulation of group III muscle afferent fibers induced an increase in arterial pressure during stimulation and a decrease in arterial pressure after cessation of the stimulation, an effect that lasted for 6-12 hours in hypertensive rats [81-83]. In the view that some hypertensive patients may have limited exercise capability, these studies raised the possibility of using muscle stimulation as an alternative strategy for the beneficial effect of exercise in lowering blood pressure.

Acupuncture: Using acupuncture as an anti-hypertensive therapy has recently been explored. Many clinical studies have been conducted to evaluate the effects of this medical modality. However, randomized, blind, and controlled clinical trials showed mixed results [84-87]. Several factors related to the treatment protocols make it difficult to sort out the differences between studies, including treatment frequency and duration, selection of acupuncture points, acupuncture technique employed (twirling, tonifying, or reducting), and the use of anti-hypertensive medications. Mechanistically, recent animal and human studies suggest that electro-acupuncture at acupuncture points overlaying median and/or deep peroneal nerves (P5-6 and S36-37) can effectively reduce sympathoexcitatory reflex responses [88-90]. The effects of electro-acupuncture are mediated by stimulation of thinly non-myelinated Aδ and unmyelinated C-fibers (group IV fibers) [91-93] in the somatic afferents that, in turn, activate various supraspinal cardiovascular regions in the hypothalamus, midbrain and brainstem [94-96]. Interestingly, both exercise and electro-acupuncture alter brainstem inhibitory signal transmission and the effects on blood pressure are both blocked by opioid receptor antagonism [97,98], suggesting common neuronal pathways maybe involved. Thus, electro-acupuncture may provide additional adjunct anti-hypertensive therapy. However, more research is needed in this area.

Conclusion

Hypertension, a silent killer, is the single-most common reason for doctor visits [99] and disease attributable to hypertension is the number 1 cause of mortality in the world [100]. Hypertension is a multifactorial disease that cannot be attributed to a single factor or genetic mutation, making it difficult, if possible, to develop a "one size fits all" treatment strategy. Multiple approaches tailed for each individual may be necessary for optimal efficacy with minimal unwanted side effects. Recent advance in non-pharmacological approaches are relatively safe and some are reversible, making them excellent candidates as complementary and/or adjuvant anti-hypertensive therapies. These non-pharmacological treatments not only have the potential for treating resistant hypertension, they also can benefit patients responsive to pharmacological treatment by reducing pill burden and/or drug-related side effects.

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Austin J Vasc Med - Volume 1 Issue 2 - 2014
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Citation: Chao-Yin Chen and Tjen-a-looi SC. Treating Hypertension: Multiple Approaches to a Common Multifactorial Disease?. Austin J Vasc Med. 2014; 1(2): 1008.