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The effects of different cardiovascular devices on carotid and aortic baroreceptors

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THE EFFECTS OF DIFFERENT CARDIOVASCULAR DEVICES ON CAROTID AND AORTIC BARORECEPTORS

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ABSTRACT

The baroreflex is a well-studied physiological mechanism that provides instantaneous nerve impulses to higher brain centers about fluctuations in blood pressure. Located within the aortic arch and carotid sinuses, the baroreceptors are mechanosensitive stretch receptors activated by physical distention. When stretched by elevated blood pressure, the baroreflex is activated and serves to reduce sympathetic nerve activity through increased parasympathetic nerve output, ultimately reducing heart rate, contractility and total vascular peripheral resistance. Therefore, through physical perturbation, the baroreflex can be activated and ensuing physiological changes result. Several medical devices have been developed to treat and manage cardiovascular diseases that are affected by blood pressure dysregulation. A significant portion of devices have their mechanistic application at locations at or near the aortic and carotid baroreceptors, which results in alterations of baroreflex activation. This literature review serves to highlight three clinically important cardiovascular devices and the effects they have on the baroreflex through a summarized review of published work in the scientific community. Intra-aortic balloon pumps, left ventricular assist devices and carotid sinus stimulators are cardiovascular devices that have shown promising development and

clinical impact since each devices' initial application in research trials. Each device has been thoroughly reviewed here and the impact that each device has on blood pressure regulation has been investigated via available published work. Results from a limited number of studies have shown that each device has a definite effect on baroreflex activation and subsequent changes in autonomic nervous system function. Modifications in blood pressure through device use appear to be a potential therapeutic approach to managing pathophysiological states, including hypertension and heart failure. Hypertension and heart failure will be discussed in greater detail, reviewing current approaches to disease management and care. The results from the available publications surrounding device use are specific to certain diseases, however, they are also quite generalizable in the sense that these results have shown an overall true effect on blood pressure modification by the baroreflex. Conclusions established from this literature review are that although promising work has been recognized through studying these cardiovascular devices and their effects on blood pressure regulation, much research and development is still needed in order to gain a better understanding of device use and impact in the clinical setting.

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LIST OF ABBREVIATIONS

ACE..... Angiotensin-converting enzyme

ANS.....Autonomic nervous system

ARB .....Angiotensin receptor blocker

BRO ..... Baroreceptor output

CABG .....Coronary artery bypass graft

CAS.....Carotid angioplasty and stenting

CVLM.....Caudal ventrolateral medulla

DASH.....Dietary approaches to stop hypertension

HF ..... Heart failure

HFpEF..... Heart failure with preserved ejection fraction

IABP ..... Intra-aortic balloon pump

LVAD ..... Left ventricular assist device

MAP.....Mean arterial pressure

NTS.....Nucleus tractus solitarius

PCI .....Percutaneous coronary intervention

RVLM.....Rostral ventrolateral medulla

TPR.....Total peripheral resistance

INTRODUCTION

Cardiovascular hemodynamics are regulated on a moment-to-moment basis with reflex adjustments in mean arterial pressure (MAP) by arterial baroreceptors located in the carotid sinus, which is at the level of the internal and external carotid bifurcation, and aortic arch. **(1)** Other baroreceptor locations also include the brachiocephalic and common carotid arteries, which have a less substantial impact on blood pressure regulation. **(2)** The baroreceptors act as a negative feedback control loop, or "baroreflex," as mechanosensitive receptors that relay information to the central nervous system about acute changes in MAP. The Hering nerve, a branch of cranial nerve –IX, the glossopharyngeal nerve, carries sensory information from the carotid arteries and small vagal branches carry sensory information from the aorta to the nucleus solitarius within the medulla oblongata for continual modifications of cardiac output and total peripheral resistance. **(3)** Control of arterial blood pressure is essential for normal vascular homeostasis and, without precise regulation, may lead to various pathophysiological issues. For example, increased MAP increases the demand for oxygen by the heart and can lead to "ventricular remodeling, vascular injury, end organ damage, and stroke." Conversely, a decreased MAP results in less blood delivery to tissues and organs and thus, fainting and system shock may ensue. **(4)** Due to the location of the carotid baroreceptors above the heart and the effects of hydrostatic pressure while standing, as well as increased sensitivity to pulse pressure, the carotid baroreceptors are vital for modulation of brain pulse pressure and MAP. **(5)**

The autonomic nervous system (ANS) sympathetic output affects MAP via increases in venomotor tone, increased arteriolar constriction and increased heart contractility and rate. Parasympathetic vagal stimulation acts in an opposite fashion to sympathetic discharge by decreasing heart contractility, heart rate and venomotor tone, as well as causing arteriolar dilation. The baroreceptors are activated when stretched by distension due to increased blood pressure which relays information to the central nervous system, resulting in increased cardiac vagal stimulation and a coinciding inhibition of sympathetic output to the heart and vasculature. Therefore, the baroreflex acts in response to increased blood pressure by causing excitation of parasympathetic stimulation, and during hypotensive states, discharges firing to vagal centers in the brain while sympathetic discharge from the central nervous system increases. Changes in pulse pressure sensed by the carotid and aortic baroreceptors adjust vagal output to the heart in order to change heart rate swiftly before another beat has completed, whereas sympathetic stimulation of contractility, arteriolar tone and heart rate take 2-3 seconds to begin its effects **(5)**. Figure 1 below depicts the afferent and efferent signaling by the baroreceptors.

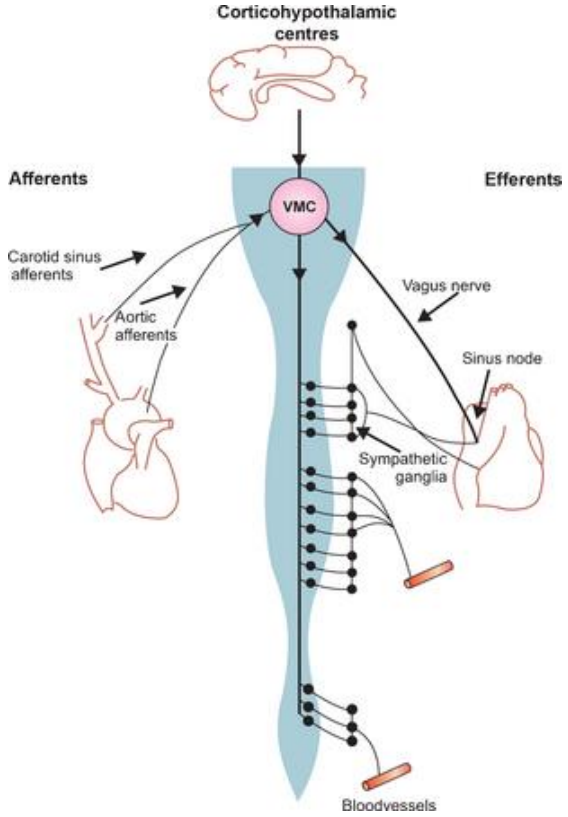

Figure 1. Baroreflex signaling. Depiction of the afferent and efferent nerve signaling involved in the baroreflex mechanism. Input from the aortic and carotid baroreceptors merge within the vasomotor center (VMC), where efferent signals are then produced to generate an autonomic response. Figure taken from **(5)**.

Due to the significance of the arterial baroreceptors within the cardiovascular system and their important physiological role in regulating hemodynamic states, it is of great interest to consider cardiac devices and how they affect the baroreflex. This paper will provide relevant background information on the importance of blood pressure regulation, baroreceptor function, major discoveries and therapies effecting blood pressure regulation, including drug, diet and device treatments. Thereafter, an in-depth discussion of three cardiac devices will be explored and compared, as well as future directions of cardiovascular device therapies.

Vessel anatomy and arterial function

Cardiovascular circulation, beginning at the heart, pumps blood through the more-resistant arterial tree, into small, single cell-lined capillaries, and then further into the compliant venous circulation, ultimately returning to the heart to complete the circuit. The structural layers of these types of vessels are altered depending on location and function. The differences in vessel type and vessel wall layers are important throughout the circulatory path of blood flow, and will be discussed in further detail below. **(6) (7) (8)**

Blood vessels are made up of three layers which include: the tunica intima, the innermost layer, the tunica media, the middle layer, and the tunica adventitia, or externa, the outermost layer (Figure 2). The tunica intima surrounds the vessel lumen as a layer of endothelial cells that are adjacent to the basement membrane, separating the tunica intima from the tunica media. Depending on the type of vessel, varying layers of smooth muscle cells compose the tunica media, which act to contract the vessel and adjust vascular tone. Surrounding the tunica media, the tunica adventitia is a combination of connective tissue components that include "loose extracellular matrix, fibroblasts, nerves and small arteries." **(9)** For the purposes of this paper, only the arterial side of the circulatory system will be discussed in further detail.

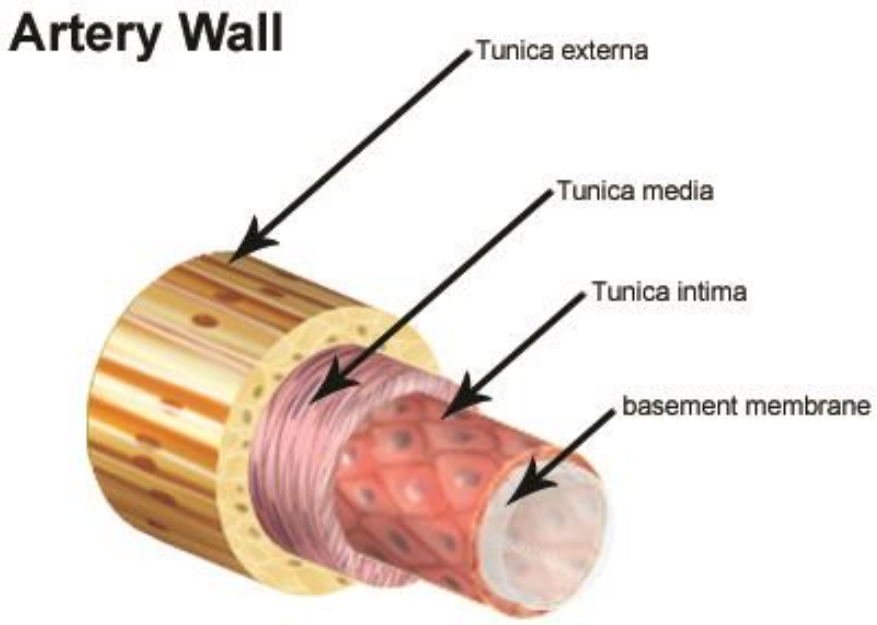

Figure 2. Arterial structure. The layers of arteries. The tunica externa (adventitia) is the outermost layer, the tunica media is the middle layer, and the tunica intima is the innermost layer. Figure taken from **(10)**.

Arteries can be classified as elastic or muscular, large or small, or arterioles, the smallest vessels of the arterial circulation. The location of these vessels depends on their proximity to the heart. Beginning at the aorta, the largest arteries, also known as "Windkessel vessels," have elastic properties for distributing a blood supply to the head, neck and limbs. As blood flow moves further through the arterial tree, vessels gradually decrease in size and shift from blood distributing properties to more resistant features, as well as transition from elastic to muscular vessels, ultimately ending as arterioles that merge with capillary beds. **(2) (11)**

Primarily, different types of arteries can be distinguished by the components of the tunica media. The tunica media of elastic arteries contains a significant amount of elastic tissue in comparison to smooth muscle fibers, which are arranged as sets of

concentric rings within the layer. During blood flow, the elastic properties of elastic arteries allows for continual distention and recoiling of the artery wall as blood is pumped through the vessels. As for the tunica media of muscular arteries, this layer houses a considerable amount of smooth muscle cells that are organized in a circular fashion. Smooth muscle cells allow for more precise control of muscular arteries via vasoconstriction and vasodilation. **(12)** The changing characteristics of the tunica media between the various vessels plays a significant role in the progression of blood flow throughout the arterial tree. As the heart pumps blood at a high pressure, pulsating waves are generated through the elastic expansion and recoil of larger arteries until reaching medium and small-sized arteries that continue the progression of blood flow via smooth muscle constriction and dilation. The elastic properties of larger vessels serve to dampen the pulse of blood flow, while distributing an adequate volume of blood. As the vessel's tunica media gradually gains more smooth muscle fibers, this functions to continue blood distribution, while more significantly providing increased resistance, resulting in more precisely controlled blood pressure and flow regulation. **(11)**

As the tunica media changes throughout the arterial vasculature, so do the layers of tunica intima and tunica adventitia, although less significantly. While not as distinct as the variations in the tunica media, changes can be observed as the vessel wall thins and the lumen decreases in size. Throughout all of the arterial tree into the arterioles, the tunica intima is still existent, as well as the connective tissue components that make up the tunica adventitia. This is in contrast to the tunica media, which has gradually changing properties until reaching the arterioles, where elastic fibers are nonexistent and

only a single layer of smooth muscle cells are found. As arterioles decrease in size, the three layers of tunics become less distinct, with the smallest arterioles having little lining and one layer of smooth muscle cells. **(13)**

Following the path from the heart, as vessels decrease in size, so do the numbers of elastic fibers, while the amount of smooth muscle cells increases. **(14)** Continuing into smaller vasculature, arteries gradually become arterioles, as the terminal ends of the arterial tree prior to capillary vessels. The bulk of vascular resistance is generated from arterioles, having a significant role in hemodynamic regulation and tissue perfusion. As mentioned previously, arterioles contain only one to two layers of smooth muscle cells, and are considered to be primary "resistance vasculature that provides in excess of 80% of the resistance to blood flow in the body." **(15)**

In order to keep the body hemodynamically stable, the arteries function to supply the peripheral tissues and organs with a sufficient amount of blood, and to perfuse the tissues and organs at a steady rate via intricate capillary beds. The effectiveness of the blood supply is delegated by artery size. Larger, elastic arteries have much less resistance to blood flow and also act to support an adequate blood supply. Tissue perfusion rate is controlled by arteries in order to lessen high pressure oscillations and establish a balanced blood flow. **(16)** As arteries provide high resistance, they do so in order to distribute blood flow appropriately to the capillary bed microcirculation, which contains only endothelial cells and a basement membrane. It is within the capillary beds that the primary exchange of nutrients and waste products occur. Oxygen, carbon

dioxide, proteins, electrolytes, water, circulating hormones and metabolic by-products and substrates are exchanged between the capillary lumen and surrounding tissues. **(11)**

Baroreceptors and the importance of blood pressure regulation

Initial discovery of the baroreceptors in the 1920's began when massaging of the neck produced reflex alterations in blood pressure and heart rate. **(17)** The baroreceptors are considered stretch receptors which contain sensory nerve endings that function to sense changes in pressure within the arterial wall. They are located within large arteries and the walls of the heart, and for the purposes of this paper, only the baroreceptors within vessels will be reviewed in great detail. **(18)** The cell bodies are located with the elastic layers of the vessels themselves, with baroreceptor nerve endings terminating within the tunica adventitia. **(19) (20)** Some literature has also described the baroreceptors to terminate at the medial-adventitial margin in both the aortic and carotid positions. **(21)** The location of the baroreceptors among different vessels originates from the branches of the aorta (Figure 3). The baroreceptors can be found in the following locations of the arterial tree: the aortic arch, brachiocephalic artery and carotid sinuses, as well as in the common carotid arteries, however, these areas do not play a significant role in blood pressure regulation in humans. The aortic arch baroreceptors can be further defined by location as initiating at the beginning of the left subclavian artery and Botallo's duct, while the brachiocephalic artery contains baroreceptors at its origin and its bifurcation into the right common carotid and subclavian arteries. **(2)**

It is important to note that there are two classifications of baroreceptors: high-pressure and low-pressure. The arterial baroreceptors are considered high-pressure baroreceptors, whereas the cardiopulmonary receptors are considered low-pressure. As the focus of this literature review is on the high-pressure arterial baroreceptors, only a brief summary of the low-pressure cardiopulmonary baroreceptors will be discussed here. These receptors are found within the chambers of the heart, large systemic veins and in pulmonary circulation. **(18)** Imbedded within the walls of the heart, both the atrial and ventricular cardiopulmonary receptors provide reflex changes, but it is the ventricular receptors that prove to be most vital as pressures inside of the heart chambers decrease. The main characteristic of cardiopulmonary receptors is that they serve as sensors of changes in fluid volume. The receptor nerve fibers synapse within the vagus nerve, therefore as fluid volume increases and the receptors are stretched, parasympathetic activity is generated, ultimately causing alterations in cardiovascular and renal function. **(22)** As the cardiopulmonary receptors fire at a "low basal discharge rate," they act as a negative feedback mechanism that is inhibitory to TPR via increased parasympathetic discharge. **(23)** Conversely, as fluid volume decreases and the stretch of the receptors is lessened, parasympathetic activity decreases to the heart and vessels. **(24)**

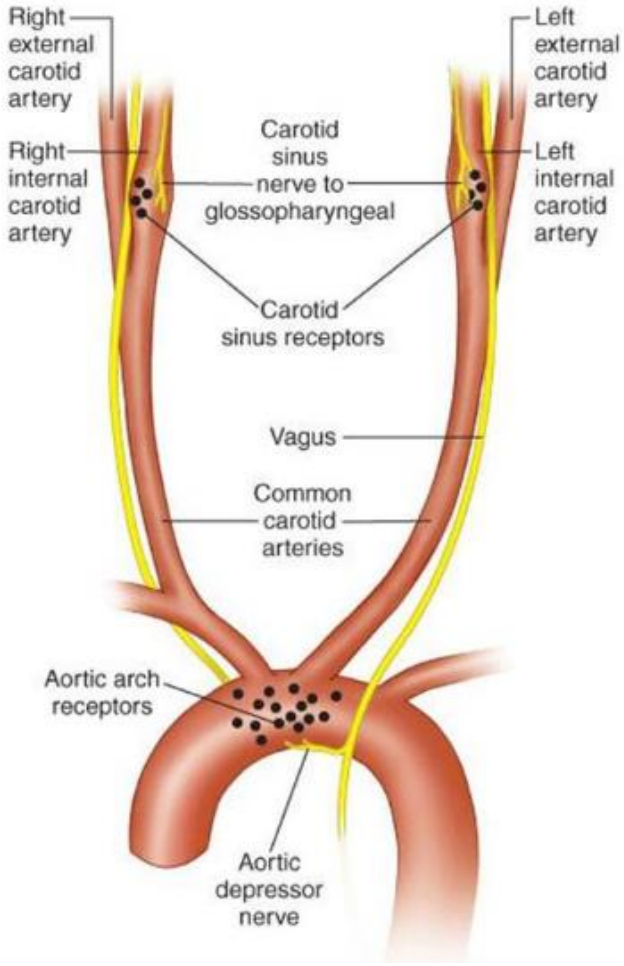

Figure 3. Baroreceptor location. Location of baroreceptors within the carotid sinus and aortic arch. The carotid baroreceptors are innervated by the carotid sinus nerve, which is a branch of the glossopharyngeal nerve, and the aortic baroreceptors are innervated by the aortic depressor nerve, which is a branch of the vagus nerve. Figure taken from **(25)**.

As seen in Figure 3, the aortic arch baroreceptors are innervated by an afferent branch of the vagus nerve, known as the aortic depressor nerve. Additionally, the carotid baroreceptors are innervated by an afferent branch of the glossopharyngeal nerve, the carotid sinus nerve. **(25)** Baroreceptors located within the carotid sinus, which is contained within the internal carotid arteries, have been shown to be the major contributor to MAP regulation, compared to the receptors found in the aortic arch,

therefore, their innervation and signaling to higher centers in the brain will be discussed here in greater detail. **(26)** As the carotid baroreceptors sense an increase in pressure within the vessel, an electrical signal is sent via sinus nerve afferent fibers, and further by the glossopharyngeal nerve, to medullary centers in the brain. **(27)** The axon signal reaches its synaptic location in the brain at the nucleus tractus solitarius (NTS), which resides in the medulla oblongata. The NTS is an assembly of nuclei that receives sensory input and projects to regions that provide motor output via autonomic regulation to maintain body homeostasis. Its structure resembles the letter "V," and depending on the location of neurons, it relays varying signals from different organ systems. These different NTS areas "serve gustatory, cardiovascular/respiratory, and gastrointestinal functions." **(28)** Continuing from then NTS, neuronal projections synapse with the caudal ventrolateral medulla (CVLM), which is a part of the ventrolateral medulla. The CVLM is located caudal to the rostral ventrolateral medulla (RVLM), and contains inhibitory interneurons which regulate RVLM signal output. The RVLM serves to generate sympathetic output to peripheral locations within the body. Therefore, as MAP begins to increase, baroreceptor signaling occurs, and the end result is an inhibition of sympathetic activity to different organ targets and precise cardiovascular control. **(27)** Figure 4 below depicts these synaptic pathways.

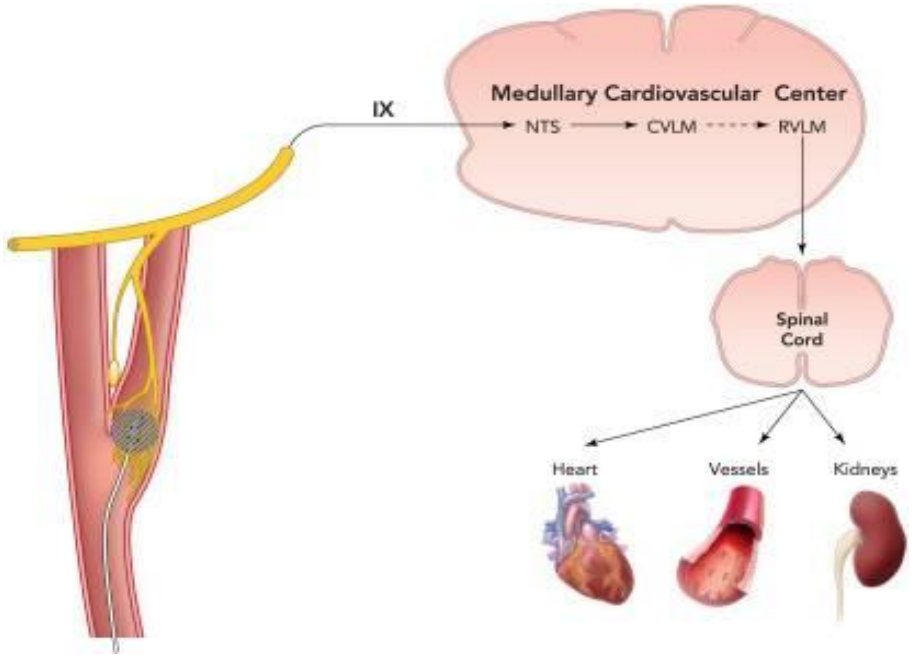

Figure 4. Carotid baroreceptor signaling. Diagram displaying carotid baroreceptor signaling to the medullary cardiovascular center within the brain and key efferent signaling targets in the periphery. As the baroreceptors are stimulated (as shown here via electrical stimulation), sensory information is sent via the glossopharyngeal nerve to the NTS within the medullary cardiovascular center. From the NTS, the information is relayed to the CVLM, which acts in an inhibitory fashion (shown as dashed lines above) to the RVLM, inhibiting sympathetic outflow of efferent signaling to peripheral organs. Figure taken from **(27)**.

Acute blood pressure regulation is clearly a very sensitive dynamic that is modulated very closely in a negative feedback manner by the baroreceptors. In the short term, as MAP varies, the response of the baroreceptors happens quickly to alter downstream sympathetic and parasympathetic output. As MAP increases, baroreceptors firing leads to increased parasympathetic activity and decreased sympathetic activity, with subsequent effects on the cardiovascular system, including reduced heart contractility, heart rate, venous return and total peripheral resistance (TPR). As MAP decreases, baroreceptors have a decreased pressure sensed, which dampens firing and

enhances sympathetic discharge and decreases parasympathetic discharge, resulting in increased heart contractility, heart rate, venous return and TPR. It is important to note that the sympathetic and parasympathetic responses facilitated by baroreceptor activity do not happen in identical time frames. As parasympathetic activity is activated, it does so in an almost instantaneous fashion, on the order of milliseconds. In contrast, sympathetic discharge is delayed, taking two to three seconds to activate and longer for maximal results to be reached. **(26)**

Several other physiological mechanisms contribute to the baroreceptor function and maintaining normal blood pressure levels. One such example impacting the baroreflex occurs during breathing; a physiological process termed "respiratory gate" affects heart rate by opposing methods during respiration. Inspiration reduces baroreceptor vagal motor neuron stimulation, whereas expiration increases it. This example and others, such as environmental, humoral and behavioral elements, influence the baroreceptor regulation of MAP. **(26)** Other systems also have a significant bearing on blood pressure modulation. These systems include: the renin-angiotensin-aldosterone system to maintain vascular tone and volume homeostasis, the adrenergic receptor system to alter heart contraction, vascular tone and heart rate, heart and brain natriuretic peptides and the kinin-kallikrein system to maintain renal salt management and vascular tone. Additionally, the blood vessels generate numerous elements that act locally to cause vasoconstriction and vasodilation as they are released into the bloodstream. **(29)** Long-term blood pressure regulation within the body is predominately assumed by the kidneys. The renal system acts to keep a steady balance of fluid volume over time to ensure that

the intake and output of water and electrolytes, mainly sodium, are stable. As water and sodium balance are regulated, MAP is continually adjusted over time to provide the kidneys with adequate perfusion to perform their fluid balance duties. **(30)**

Blood pressure regulation is vital to maintain body homeostasis, as with any changes from normal, pathophysiological states can develop. MAP is closely related to cardiac output and TPR, therefore an alteration in either direction has a wide effect on other cardiovascular mechanisms. With sustained higher levels of blood pressure, or hypertension, "end-organ damage" can result. **(31)** Hypertension is a significant risk factor for "stroke, myocardial infarction, congestive heart failure, and end-stage renal disease," demonstrating the importance of baroreceptor function in acute blood pressure changes that with dysfunction over time, can result in many diseases affecting a vast range of patient populations. **(29)** As hypertension is a significant risk factor for disease, low blood pressure, or hypotension, is also problematic. Hypotension can lead to decreased nutrient and oxygen delivery, depriving tissues and depleting organ's abilities to maintain adequate operating conditions, potentially leading to fainting, an insufficient blood supply to organs, or system shock. **(31) (32)**

Baroreflex failure also demonstrates the major role the baroreceptors play in the cardiovascular system. This phenomenon typically occurs as result of a physical trauma or radiation to the carotid sinus or glossopharyngeal nerves, leading to symptoms of continuous high blood pressure, headache and increased heart rate. Encephalopathy and cerebral hemorrhage can transpire as systolic blood pressure rises over 250 mmHg in acute baroreflex failure. Chronically, baroreflex failure can produce "volatile

hypertension," which appears usually days to weeks after initial failure. **(17)** Volatile hypertension is categorized by sudden changes in sympathetic activation that lead to increases in blood pressure. The baseline blood pressure may be within the normal range or elevated, but sudden surges in blood pressure, with associated increased heart rate, may occur for minutes to hours during a single episode. **(33)** Moreover, volatile hypertension continues to be aggravated by the body's response to increase sympathetic activity even further. **(34)** Due to a heightened sensitivity of sympathetic discharge, physical and mental triggers can yield rushes of volatile hypertension and increased heart rate. These triggers may include "exercise, cold and sexual arousal," or stressful mental states. Other symptoms of amplified sympathetic action are listed in Table 1. Additionally, opposing effects of hypotension may be produced in between highly active hypertensive states. Hypotension, asystole and decreased heart rate can sometimes be seen, particularly during the hours of sleep. Further symptoms of hypotension due to baroreflex failure are summarized in Table 1. **(17)** It should also be noted that baroreflex failure does not necessarily have to occur at the level of receptors themselves; damage to the synaptic pathway signaling to or from the NTS can also demonstrate symptoms of baroreflex failure. **(35)** Table 1 below lists the side effects associated with baroreflex failure.

ACUTE PHASE FOLLOWING BARORECEPTOR DENERVATION (DAYS-WEEKS)	
Severe sustained elevation of blood pressure (systolic pressure typically >250 mmHg)	
Tachycardia	
Elevation of plasma catecholamines	
Headache	
Complications of hypertension	Encephalopathy
	Cerebral haemorrhage
CHRONIC PHASE (WEEKS-YEARS)	
Common	
Volatile hypertension and tachycardia	
Paroxysm of	Palpitations
	Headache
	Diaphoresis
	Light headedness
	Anxiety
	Emotional instability
	Increased intraocular pressure
Rare	
Hypotension (during sleep)	
Bradycardia, asystole	
Fatigue	
(Orthostatic) dizziness	
Syncope	

Table 1. Symptoms and signs of baroreflex failure. Table taken from **(17)**.

THERAPEUTIC METHODS & BLOOD PRESSURE; A MULTITUDE OF OPTIONS

Blood pressure abnormalities can lead to a plethora of pathophysiological states, with hypertension being the leading risk factor for disease. Sabbahi et. al. have described that approximately "one in every three Americans has one or more types of cardiovascular disease, and nearly the same percentage have hypertension." They go on to state that 17.3% of these individuals are unaware of their underlying condition, and that roughly 50% of patients receiving any form of therapeutic treatment are able to keep their blood pressure under control. Additionally, their statements regarding the healthcare costs surrounding hypertension was that it totaled roughly $46.4 billion in 2011, with anticipated costs to rise close to "six-fold by 2030." **(36)**

It is of no surprise then, that significant efforts in research and development have resulted in therapies to treat and manage disorders in blood pressure dysregulation. Given that hypertension has been described as the leading risk factor for disease, several possible treatment options will be considered in this review. First, this review will explore prescribed diet and exercise regimens directed at improving blood pressure regulation. Thereafter, drug therapies focused on hypertension will be discussed, and lastly, device therapies will be described.

Diet and exercise

Hypertension can be defined as blood pressure within the arteries that reaches or exceeds 140mmHg for systolic blood pressure and 90mmHg for diastolic blood pressure. Throughout a majority of patient populations, a positive correlation can be seen amongst

"systolic blood pressure and risk of cardiovascular mortality, cardiovascular events and strokes." **(37)** Globally, given its impact on morbidity and mortality, hypertension is high on the list of preventable diseases that result in early death. A multitude of research has verified that decreasing one's blood pressure decreases the risk of cardiovascular disease. Padmanabhan et. al. (2010) indicated that "for every 2 mm Hg decrease in mean systolic blood pressure, there is a 7% reduction in the risk of ischemic heart disease mortality, and a 10% reduction in the risk of stroke mortality." The authors also go on to state that individuals of any age who decrease their blood pressure by 20mmHg, decrease their risk of cardiovascular disease by 50% **(38)**. Figure 5 below depicts reductions in blood pressure from a studied population, and the resultant reductions in mortality percentages for associated diseases.

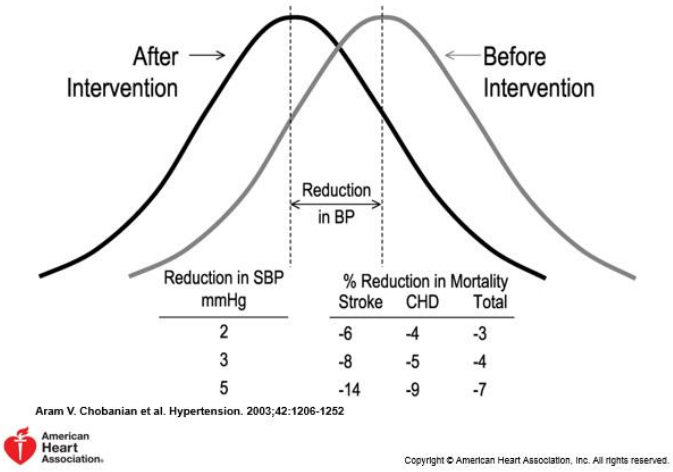

Figure 5. Population-based distributions of systolic blood pressure after intervention. Systolic blood pressure distributions pre- and post- therapeutic intervention in a population-based intervention strategy, as well as the decrease in mortality. Public health approaches of intervention include: decreasing sodium or caloric density in supplied foods, providing desirable exercise opportunities and increasing access to appropriate community facilities. SBP, systolic blood pressure; BP, blood pressure; CHD, coronary heart disease. Figure taken from **(39)**.

Several distinguishable patient risk factors have been identified for diagnosing individuals at risk for hypertension. These identifiers consist of, but are not limited to: advancing age, high BMI, ethnicity, sex, hereditary factors, baseline blood pressure and measurements of aldosterone secretion in the urine and plasma renin activity. **(38)** Other lifestyle factors include increased alcohol ingestion, high sodium and low potassium intake through diet and an inactive standard of living. **(39)**

Blood pressure regulation is clearly affected by several factors, some of which are out of an individual's control, and others which can be modified by lifestyle changes. Diet and exercise play a key role in blood pressure regulation and can be driven prophylactically to prevent cardiovascular disease, or introduced as lifestyle adjustments as first steps to treat and manage hypertension. For the treatment of hypertension, patients are informed to maintain a healthy diet, become more active through regular physical exercise and lose weight if they are currently overweight or obese. **(40)**

There are many established diets that individuals with hypertension are recommended to follow in order to lower blood pressure and reduce the risk of significant morbidity and mortality **(40)**. Although slightly different in each approach of various food groups and daily recommended intake, each diet is heavily focused on wholesome and natural foods instead of processed and artificial ingredients. Three diets that aim to reduce elevated blood pressure and therefore, alter blood pressure regulation, will be briefly discussed here. These diets include the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet and the less commonly known, Nordic diet. **(40)**

The Mediterranean diet was recognized from different countries around the Mediterranean basin in the 1950's for its emphasis on rural and agriculturally-based foods. **(41)** Foods typically consumed in this diet include fresh produce, olive oil, legumes, fish, nuts and whole grains, as well as a reasonable intake of red wine. The diet also recommends a low consumption of red meats, sugar and dairy products. The latter food groups, in combination with artificial and processed foods, are what characteristically make up the Western diet that is more commonly adapted in unhealthy lifestyles. Literature reviews of randomized controlled trials have concluded that individuals following a Mediterranean diet lowered their blood pressure significantly, along with several other cardiac risk factors such as LDL and total cholesterol and body weight. **(42)**

The DASH diet was created by the National Heart, Lung and Blood Institute to advise individuals with hypertension on how to manage and, potentially reduce their blood pressure, both in the chronic and acute settings, through diet alterations. Generally, a DASH diet is low in all fats (particularly saturated fats), sodium, sugars and cholesterol. Published research has shown that people following a DASH diet have a reduced "risk of coronary heart disease that can result from hypertension." Research has also shown that people living with chronic hypertension have the potential to be medication-free if they maintain their blood pressure through healthy diet and lifestyle choices. **(43)** In addition to the positive effects of chronic modification and maintenance of hypertension, the DASH diet has been shown to lower ambulatory blood pressure levels measured at 24

hours, as well as throughout time points during the day and evening. These results were viewed across several classifications, such as ethnicities, sex and age groups. **(44)**

The Nordic diet, also known as the Baltic Sea diet, incorporates foods that are understood to have properties that promote good health. The Nordic countries of Norway, Sweden, Finland and Denmark cultivate and consume low-fat dairy products, barley, oats and rye, salmon, fruits including berries and apples, and vegetables including leafy greens, root vegetables, tomatoes, cucumbers, peas and cabbages. All of these foods are considered to have "health-enhancing features." Additionally, low amounts of alcohol, red meats and fat are consumed. **(45)** Results from studies have shown that this less-commonly known diet has produced significant effects in reducing blood pressure in the compared trials. Further investigation of the Nordic diet to manage hypertension is warranted. **(40)**

Other interesting dietary factors come into play with blood pressure regulation. One particular group of metabolites has gained interest in the cardiovascular community for its correlation with cardiovascular and chronic disease. Quercetin is a metabolite of many common foods consumed in the Nordic diet, and is a polyphenolic flavonoid. It is found in berries, onions, apples, red grapes, citrus fruits, bark roots, broccoli, tea, red wine and flowers, and has been shown to have blood pressure lowering effects in hypertensive human and animal models. Due to a limited amount of published literature on quercetin its impact on cardiovascular heath, the exact mechanism by which quercetin's effects are carried out are still uncertain. Some hypotheses include: enhanced endothelial function, reduced oxidative stress, direct impact on vascular smooth muscle,

angiotensin-converting enzyme (ACE) inhibition and alteration of gene expression and cell signaling. Although an exact mechanism has yet to be determined, it is evident that quercetin interacts with several targets that are of future interest in studying its blood pressure lowering properties. **(46)**

As previously discussed, diet undoubtedly plays an important role in blood pressure regulation and the serious impact on long-term health and wellbeing. It is interesting to note, however, that there are acute effects on blood pressure, immediately after food consumption. When food is consumed, signals from different areas of the body are relayed to the brain in order to prepare for digestion, metabolism and appropriate storage of nutrients. "Postprandial activation" occurs through nervous and hormonal system participation, and in particular, through sympathetic nervous system activation. This activation, which is governed in part by the baroreceptors, is necessary to direct blood flow and moderate blood pressure in order to support the digestion of food intake. After a meal, the relocation of blood flow also produces thermogenic responses due to the energy expenditure necessary for tissues to absorb nutrients needed instantaneously, or to be stored for later use. The baroreceptors play a role in food digestion during the post-prandial state as vessels begin to vasodilate. As food is consumed, vessels within the periphery vasodilate, which is immediately sensed by the baroreceptors as a decrease in blood pressure, causing afferent signaling to the central nervous system and activation of the sympathetic nervous system. Consequently, it is quite clear that diet, in the acute sense of meal-to-meal activity, has a rapid effect on blood pressure regulation and the baroreceptor response. **(47)**

Along with diet, physical exercise is another non-pharmacological factor constantly influencing blood pressure regulation. As exercise is initiated, the baroreceptors are key players in modifying the cardiovascular response to support the body's demand for an adequate oxygen supply and tissue perfusion. Beat-to-beat fluctuations in blood pressure are sensed by the stretch receptors in the carotid arteries and aortic arch and an autonomic nervous system response is generated, ensuring sufficient cardiac output and appropriate changes in TPR are maintained. Research has shown that throughout low, moderate and heavy exercise, the baroreceptors will "reset" to adjust to the blood pressure increases produced during exercise. This resetting is thought to be a combination of several mechanisms; the baroreceptors appear to work in conjunction with central signaling from higher brain centers, an "exercise pressor reflex," caused by contracting skeletal muscle and signals generated from the cardiopulmonary receptors in the heart, lungs and large veins. The influence of physical exercise on the baroreflex has clearly been shown to have significant impact on blood pressure regulation. **(3)**

Exercise and the arterial baroreflex response is mediated in an "intensity-dependent" fashion, although as previously described, a range of intensities from low to extreme do evoke a baroreceptor signaling reaction. The neural inputs from the carotid and aortic baroreceptors, central command of higher brain centers and the exercise pressor reflex are well understood, whereas the literature published focused on the cardiopulmonary receptor response is limited. Once thought to be absent during exercise, the baroreceptor response functions to maintain an unchanged reflex sensitivity as heart

rate and blood pressure increase, which allows for its resetting and ability to operate at demanding MAP levels as well as it does at rest. The baroreflex, along with the aforementioned neural inputs, generates the body's response to exercise as a complex system of sympathetic and parasympathetic mechanisms in order to maintain adequate blood pressure levels. Figure 6 below highlights these inputs and their outcomes to modulate MAP via changes in heart stroke volume, heart rate, cardiac output and vasculature alterations in peripheral vessels. **(21)**

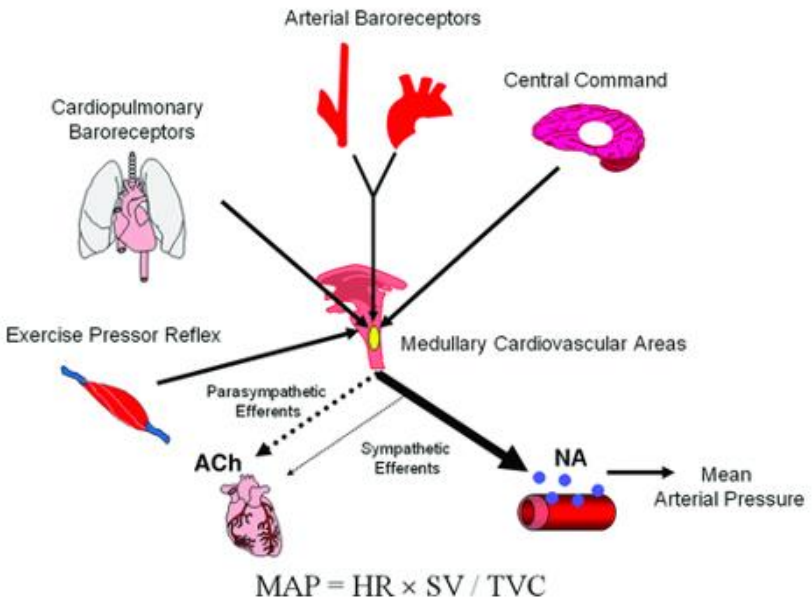

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Figure 6. Afferent and efferent signaling with resultant cardiovascular changes during exercise. Contributions of the neural mechanisms involved with adjustments to cardiovascular hemodynamics during exercise. Central command signals from the brain, arterial baroreceptors, cardiopulmonary receptors and the exercise pressor reflex influence the sympathetic and parasympathetic activity modifications during exercise. The resultant changes in autonomic output modify heart rate, contractility, vessel diameter and total vascular conductance to allow for proper blood pressure levels during exercise. MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; TVC, total vascular conductance; ACh, acetylcholine; NA, noradrenaline. Figure taken from **(21)**.

Pharmaceutical agents

The targets of antihypertensive medications focus on specific areas of blood pressure regulation, with each pharmaceutical agent having its own unique mode of action. **(38)** There are currently several antihypertensive drugs available by prescription. Common oral antihypertensive agents include: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor (ARB) blockers, calcium channel blockers, alpha 1-receptor blockers, beta receptor blockers, central alpha-2 receptor agonists, diuretics and direct vasodilators. If necessary to achieve optimal blood pressure levels, some medications may be used in combination. Additionally, the dosage and frequency of medication vary between and within groups of drugs. **(48)** For the purposes of this review, a brief overview of the more common antihypertensive medications will be discussed.

ACE inhibitors play a role in reducing elevated blood pressure by stabilizing the renin-angiotensin-aldosterone and kallikrein-kinin systems. This class of medications stops the production of the angiotensin II by inhibiting the enzyme that converts angiotensin I to angiotensin II. As the angiotensin-converting enzyme is inhibited, the result is a reduction in TPR. This decrease in vessel resistance allows for increased renal plasma flow within the vasculature of the kidneys and thereafter, an increased excretion of sodium. A "renoprotective" result is also generated through increased dilation of the nephron's efferent arteriole, which reduces pressure within the nephron and the amount of protein that is filtered and excreted. Moreover, ACE inhibitors have anti-inflammatory effects and reduce growth factor release that are beneficial to the health of the kidneys.

(49) As ACE inhibitors take effect by modifying the balance between these two systems, the overall result is a tightly regulated extracellular fluid volume and a reduction in blood pressure. **(50)**

Antihypertensive angiotensin receptor blocker (ARB) medications are similar in fashion to ACE inhibitors in that the renin-angiotensin-aldosterone system is again targeted; their mode of action, however, differs. ARB's act by blocking the stimulation of the angiotensin II receptor, while ACE inhibitors halt the production of the angiotensin II enzyme itself. **(51)** Angiotensin II targets two receptors for its physiological effects: Ang II type 1 receptor and type 2 receptor. The pharmacological properties of ARB medications have their methods of action targeted to the type 1 receptors to produce the antihypertensive effects of this drug class. **(52)**

Calcium channel blockers are pharmaceutical agents which inhibit vascular voltage-gated calcium channels, diminishing the amount of free intracellular calcium. This results in less available calcium, and therefore decreased smooth muscle contraction. As the smooth muscle relaxes within the arterial blood vessel, blood vessel diameter increases and thus, blood pressure decreases. **(53)** Additionally, as arterial diameter increases, the arterial resistance in the vessel decreases, adding to calcium channel blocker's antihypertensive properties. **(54)**

Alpha and beta blockers are classes of medications which target adrenergic receptors located throughout the body. From a cardiovascular standpoint, the receptor types that play a major physiological role are alpha-1, beta-1 and beta-2. Alpha-1 receptors have been viewed as pharmaceutical targets for their involvement in

vasoconstriction of large resistance blood vessels, the aorta and the coronary arteries, contraction of the heart and heart rate. Beta-1 receptors serve to alter the activity of catecholamines centrally within the heart, whereas beta-2 receptors effect the peripheral tissue vasculature with vasodilating methods of action. It has been clearly established that blocking the alpha-1 receptor results in lowered blood pressure by reducing its vasoconstrictive actions; what is not clear is precisely how beta blockers produce reduced arterial blood pressure effects. Suggested methodologies consist of beta blockers effecting the renin-angiotensin-aldosterone system by decreasing renin formation, controlling the sympathetic nervous system, or reducing cardiac output. The antihypertensive result is proposed to potentially be a mixture of all three physiological responses. **(55)**

Diuretics for the treatment of hypertension are typically in the form of thiazide or thiazide-like diuretics, or non-thiazide loop diuretics. Both classes generate their pharmacological properties by causing the kidneys to get rid of excess sodium in the body. Certain types of thiazide and thiazide-like diuretics also produce vasodilation in the vasculature. **(56)** By inhibiting the sodium-chloride cotransporters in the distal convoluted tubule of the nephron, sodium and water are unable to be reabsorbed, therefore, allowing for excess excretion and an overall decrease in fluid volume. This characteristic of thiazide and thiazide-like diuretics has been well established in the acute setting, but similar to beta blockers, the long-term overall hypotensive effects of these medications are not fully understood. **(57)** Loop diuretics also produce inhibitory actions on the nephron, however, their pharmacologic target are the sodium-potassium-chloride

cotransporters located in the in the loop of Henle. The overall result of diuresis causes similar hypotensive results as fluid is lost from the body. Additionally, similar to thiazide and thiazide-like diuretics, loop diuretics also have vasodilatory properties that contribute to their antihypertensive effects. **(58)**

Interventional and device therapies

During the 1950's, the significance of autonomic regulation of the cardiovascular system was discovered as sympathectomy was observed to cause strong antiarrhythmic properties in experiments. Since then, the importance of the baroreflex and its regulation of blood pressure has been of great interest in the interventional and device therapeutic worlds. A subset of therapies will be discussed briefly here, before delving deeper into three specific cardiovascular devices. The first set of interventional approaches that have an impact on the baroreflex to be considered here are lower body negative pressure, vagal nerve stimulation, renal denervation, spinal cord stimulation and carotid angioplasty and stenting. **(59)**

Lower body negative pressure is a technique designed to decrease central blood volume by shunting blood from the thoracic region to the lower half of the body. This technique has been used typically to study hemorrhage, aerospace physiological changes and orthostatic blood pressure. As a therapeutic machine delivers lower body negative pressure to an individual, the venous return of blood is reduced, creating a lessened stroke volume and preload on the heart. **(60)** This relocating of blood volume produces orthostatic stress, which is sensed by the baroreceptors as a hypotensive state; studies

have referred to this as "baroreceptor unloading." As this occurs, the baroreflex activates the sympathetic nervous system to attempt to bring the body back to a hemodynamically stable state. **(61)**

A technique less commonly adapted in the clinical setting is vagal nerve stimulation. Immense research and development have gone into producing therapies for sympathetic activation, however, parasympathetic activation by interventional approaches remains to be explored. Parasympathetic innervation of the heart derives from the vagus nerve, as well as contributions from parasympathetic thoracic ganglia, which allow for mechanisms of "negative inotropic and chronotropic effects." **(62)** When applied at low levels, vagal stimulation has been shown to improve cardiovascular functioning in certain patient populations. It appears that this "cardioprotective" result is implemented in both the atria and ventricles. Studies of patients with heart failure have shown improved cardiovascular functioning in the chronic setting through vagal nerve stimulation. **(63)**

The range of literature surrounding vagal nerve stimulation and its impact on the baroreflex and blood pressure regulation in the acute setting is currently quite narrow. One report describes patients going through coronary artery bypass graft (CABG) surgery or carotid endarterectomy who had vagal nerve stimulation during these procedures. The resulting blood pressure effects were a "frequency-dependent" decrease in systolic blood pressure only, as well as a reduction in heart rate. **(62)** The obstacles found when attempting to evaluate changes in the baroreflex response and cardiovascular hemodynamics during vagal nerve stimulation were estimating heart rate during a

continual balance of efferent and afferent signals. Published work has described heart rate to be changed very minimally, which makes evaluating an actual autonomic response difficult. As afferent and efferent signals are produced, they are roused in a stable fashion, which improve parasympathetic vagal activation in the heart and a result in a nominal change in heart rate. **(63)** Therefore, it is clear that continued research efforts are necessary to understand the effects of parasympathetic activation on the baroreflex via vagal nerve stimulation, and resultant acute alterations in blood pressure.

Hypertension treatment for patients who undergo procedural interventions to reduce the sustained high levels of MAP may target the elevated sympathetic stimulation. As previously discussed, the baroreceptors and cardiopulmonary receptors are principal targets for treatment focused on sympathetic activation. Renal denervation is another therapeutic technique that demonstrates an influence on blood pressure regulation through the renin-angiotensin-aldosterone system. The afferent and efferent signaling from the kidneys are also considered central sympathetic nervous system stimulation as the kidneys receive and distribute sympathetic action. **(64)** While the baroreceptors alter sympathetic and parasympathetic activities, renal afferent signaling only plays a role in central sympathetic activity. By inhibiting this signaling through renal denervation, sympathetic afferent action is dampened, reducing overall central sympathetic output. Ultimately, this reduction serves to decrease blood pressure, as well as other cardiovascular hemodynamics controlled by sympathetic nervous system activity. **(65)**

An important pathophysiological condition directly related to the renin-angiotensin-aldosterone system to note, besides blood pressure dysregulation, is heart

failure (HF). As a disease, HF is a major concern in the healthcare world as it is associated with extreme mortality and morbidity; in 2013, the cost was roughly $32 billion within the United States alone. Renal denervation (Figure 7) has become an important method of HF treatment as patients with HF have an increased stimulation of the renal sympathetic system. This results in fluid volume overload, sodium retention and additional renal sympathetic system activation, thereby creating a continual cycle of recurring disease. **(66)**

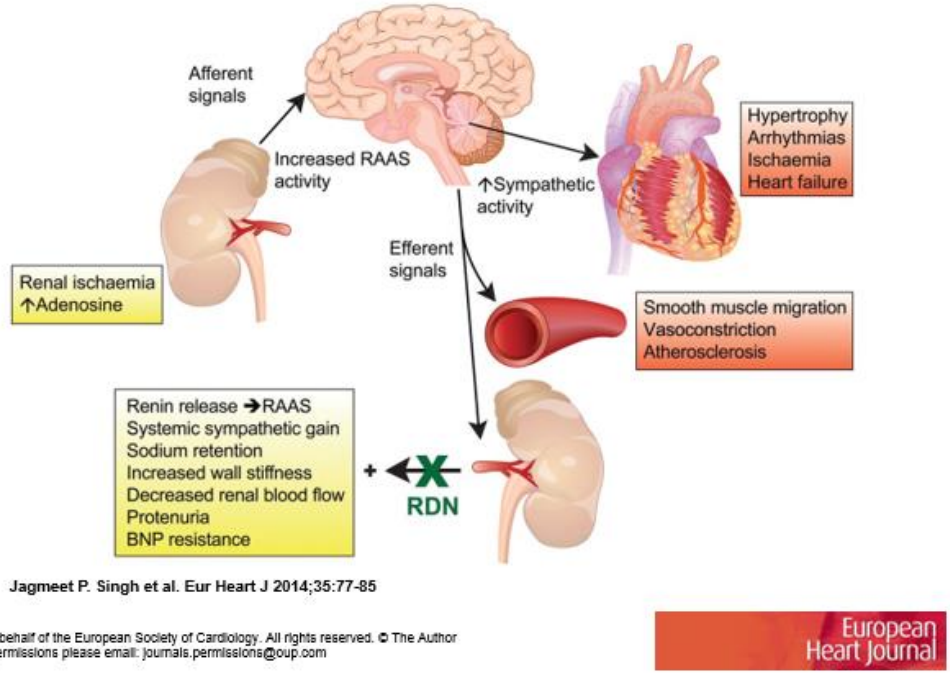


Figure 7. Physiological impact of hypertension and heart failure. The renin-angiotensin-aldosterone system is triggered by the kidneys and brain in pathological states of hypertension and heart failure. Renal denervation is illustrated as a non-pharmacological method of intervention for the treatment of resistant hypertension and heart failure. RAAS, renal-angiotensin-aldosterone system; RDN, renal denervation. Figure taken from **(66)**.

Another therapeutic method of interest in blood pressure regulation is spinal cord stimulation. Along with vagus nerve stimulation, spinal cord stimulation is considered

neuromodulation that has been employed in the clinical setting since the 1980's. Initially used for epilepsy, depression, refractory angina and chronic pain management, spinal cord stimulation has gained interest in the research world for its use in patients with HF. **(67)** Through clinical investigation, spinal cord stimulation has shown to produce a "cardioprotective effect." This is substantially achieved through parasympathetic stimulation via the vagus nerve, which serves to decrease blood pressure and heart rate. Continued preclinical efforts are currently being done to evaluate the cardioprotective results of this therapy in the hopes of gaining further insight into the treatment of HF and other cardiovascular diseases. **(66)**

A final therapeutic method to be considered briefly here is carotid angioplasty and stenting (CAS). CAS is a procedure used to treat carotid stenosis in patients for the prevention of ischemic stroke. Well-known complications for this intervention have been identified, including alterations in the baroreflex. "Hemodynamic depression" can result during or after the CAS procedure due to activation of the baroreflex by the stenting balloon or carotid stent pressing against the baroreceptors. This mimicking of elevated blood pressure can lead to hypotension, decreased TPR and lowered heart rate. Studies have shown that CAS can decrease the baroreceptor function or increase parasympathetic nervous system action in the acute setting. **(68)**

Very limited published research has been provided for the chronic effects of CAS on the baroreceptors and the consequential alterations in cardiovascular hemodynamics. **(69)** One case study from 2014 of a patient undergoing CAS reported the patient experiencing hemodynamic instability following stenting and for a sustained period

thereafter, which required vasopressor support for the following week. **(68)** Vasopressors are pharmaceutical medications which serve to increase blood pressure in the acute, critical setting. **(70)** Other studies have attempted to review longer periods of time post-carotid artery stenting, however, many limitations, including small numbers of studied patients, have made this area of study challenging. It has been proposed that the underlying disease, such as carotid atherosclerosis, coronary heart disease and stroke, is the contributor to decreased baroreceptor sensitivity, rather than CAS itself. Therefore, further investigation is warranted to determine the effects of CAS on baroreceptor function and blood pressure regulation in the chronic setting. **(69)**

SPECIFIC AIMS

The immense amount of published research on the aortic and carotid baroreceptors and the use of different cardiovascular devices in the clinical setting reflects the importance of each subject in its own separate element. However, it is of great speculation that research published reflecting both considerations together is quite limited. This literature review section therefore serves to summarize the current understanding of the effects of three different cardiovascular devices on the baroreflex in the cardiovascular system. The three devices to be reviewed include: intra-aortic balloon pumps (IABP), left ventricular assist devices (LVAD) and carotid sinus stimulators.

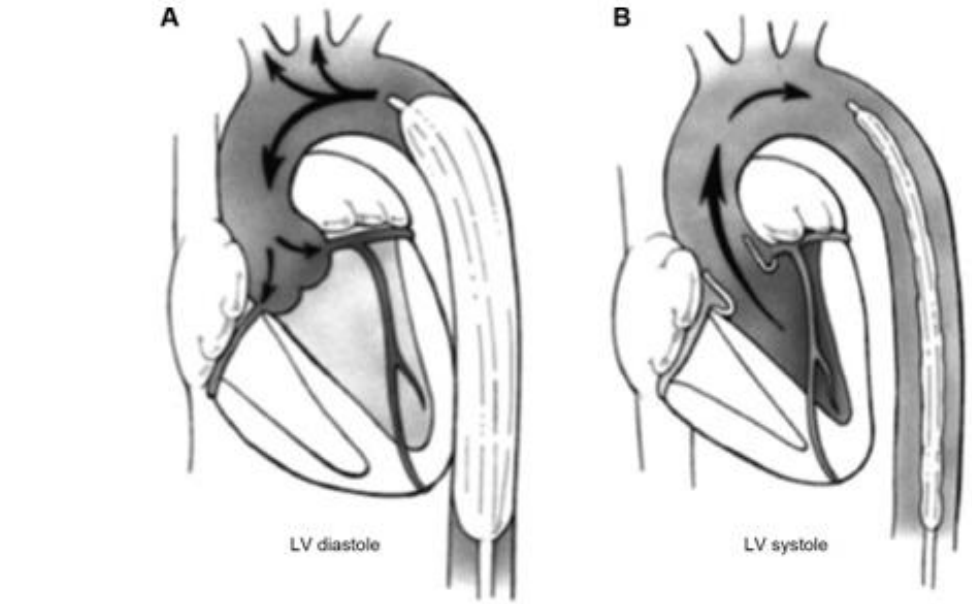
An investigation into the current evidence about standard treatment with IABPs, LVADs and carotid sinus stimulators in cardiology patients may shed light on baroreceptor activity involvement and any potential implications. Conclusions will be drawn on the significance of the physiological role baroreceptors play in modulating blood pressure during the use of these cardiovascular devices in the clinic. Given the limited amount of published work, it will most likely be determined that further research and consideration will need to be established from a cardiovascular standpoint in order to better understand the relationship between all components.

PUBLISHED STUDIES

Intra-aortic balloon pumps

The intra-aortic balloon pump is a device used for its counterpulsation mechanism and has been considered "the most widely used mechanical circulatory support device because of its ease of use, low complication rate, and fast manner of insertion" **(71)**. Mechanistically, the device functions within the descending aorta to inflate during diastole and deflate during systole, mainly to increase oxygen delivery in the coronary arteries and reduce the afterload on the heart, in turn reducing oxygen demand and myocardial workload. IABPs are used for temporary cardiovascular circumstances, such as during a percutaneous coronary intervention (PCI), to allow for sufficient myocardial oxygen perfusion to make up for a heart that cannot pump efficiently on its own. **(72)** The standard patient case that warrants use of an IABP typically is for cardiogenic shock, high-risk PCI and acute myocardial infarction. **(71)**

An IABP is made up of generally three main parts: the console, a balloon catheter and driving gas that fills the balloon. The console functions to provide a precise amount of gas into the balloon catheter, typically helium, at a set time point, followed by removal of the gas thereafter. It is important to note that patients undergoing procedures with IABPs also have constant measurements of heart rate and blood pressure through the use of electrocardiograms. These measurements come from a monitoring system within the console, which then processes the information and generates a "trigger signal" to increase or stop gas flow into the balloon. **(73)**



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Intra-Aortic Balloon Counterpulsation in Contemporary Practice – Where Are We?

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Figure 8. IABP placement and balloon use. Diagram depicting balloon placement and mechanism. During diastole, the balloon inflates and allows for increased perfusion of the heart vessels, while during systole, the balloon deflates and lessens the afterload on the left ventricle. Figure taken from **(74)**.

The concept of counterpulsation (Figure 8) was initially established during the 1950's in dogs when researchers discovered that impeding systolic blood pressure, enhanced diastolic or coronary blood pressure and, thereby significantly increased coronary blood flow to the heart. Further studies built onto this new concept by discovering experimental techniques of augmenting aortic diastolic pressure, as well as reducing systolic blood pressure through an arterial cannula and coordinated infusion and extraction of blood. It was during this time that experimental techniques of modifying

blood pressure changes were found to be dependent on a few factors, which Weber et. al have described as "the volume of blood displaced, the pressure-volume relationship of the aorta, the position and size of the arterial cannula, and proper synchronization with the cardiac cycle." **(75)**

By the 1960's, the earliest forms of IABPs were created through the implementation of latex tubing wrapped around the end of a catheter containing several holes in its side, and blocking one end of the catheter in order to expand and depress the latex balloon through the side holes. This mechanistic approach formed a "closed system" through which carbon dioxide could be contained for balloon expansion through alternating employment of air pressure. Pairing this approach with measurements from an electrocardiogram, the balloon was timed to deflate during systole and inflate during diastole. This novel method was further implemented within the aorta to manipulate cardiovascular hemodynamic responses of decreased end diastolic blood pressure and increased diastolic blood flow within the arterial circulation. **(73)**

The same investigators who performed novel IABP experiments in dogs continued their efforts in the clinical setting through studies of small numbers of patients who suffered from cardiogenic shock following myocardial infarctions. Their efforts showed promising results as the initial devices provided hemodynamic support for patients, reversing the infarction shock state with minimal side effects after device use. This discovery in the clinical setting set the stage for others to begin implementing IABPs in their research, which eventually lead to further positive results of the device's use. Patients with myocardial infarction-induced shock had enhancements in "myocardial

metabolism" while using the device, as well as implementation during critical procedures; procedures including "coronary angiography and left ventriculography" during IABP use were successfully completed in emergency situations. **(75)**

Continued efforts in the research and development of IABPs lead to several discoveries of valuable information for the device's use in a range of clinical settings. By the 1970's, researchers were implementing the device in HF models, showing beneficial effects (Figure 9). The topic of HF patients and IABP use will be discussed in greater detail in upcoming sections of this literature review. Additional studies found further promising results in improved cardiovascular hemodynamics while using counterpulsation techniques; the detection of improved patient prognosis provided the basis for IABP support immediately following cardiogenic shock. **(73)**

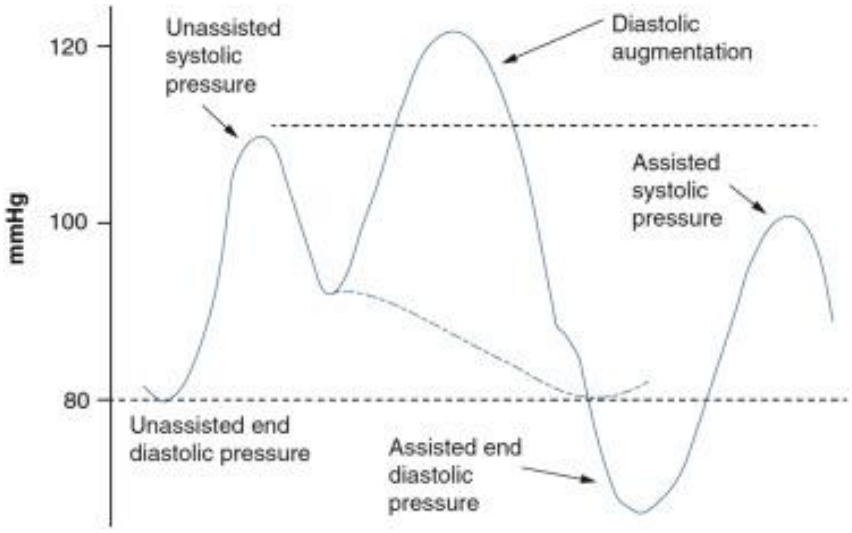

Figure 9. Hemodynamic changes with and without implementation of an IABP. Waveform alterations demonstrating the differences in blood pressure between assisted and non-assisted device counterpulsation. Figure taken from **(71)**.

In current medical practice, the most typical indication for use of an IABP is for patients who have had a myocardial infarction, trailed by cardiogenic shock, the two pathologies most studied during the development of modern-day IABP devices. The largest randomized clinical trial studying cardiogenic shock involving IABPs showed that most patients presenting with myocardial infarctions ended up having a PCI, as well as stent deployment in the affected vessel, or vessels, if multi-vessel disease was present. During use, the device's mechanical support allows for enhanced coronary blood flow and peak diastolic blood pressure, which are beneficial to patients in the acute, emergency situation involving a heart attack and ensuing infarction shock. **(76)** Problems observed from IABP use have been noted as "aortic wall damage, femoral artery insufficiency, and thrombocytopenia," though patient cases have shown these complications to be uncommon. **(75)** The researchers concluded that further investigation was warranted to prove a stronger indication for IABPs in the setting of cardiogenic shock post-myocardial infarction, as compelling evidence to show a robust clinical impact was not seen. **(76)**

In addition to myocardial infarction followed by cardiogenic shock, other recognized indications for IABP use include myocardial infarction alone, cardiac surgery and patients undergoing high-risk PCI's. On the other hand, patient profiles that contain contraindications for use comprise severe peripheral vascular disease, significant aortic regurgitation, active bleeding, uncontrolled coagulopathy, sepsis and severe aortic vessel pathology. As previously mentioned, the lack of robust clinical data supporting the use of IABPs for these clinical indications contributes to the current ambiguity surrounding

the appropriate use of the device; therefore, continued research efforts are needed to provide more insight. **(74)**

Additional patient profiles of interest are those suffering from HF. IABPs are most commonly used in acute HF to improve myocardial recovery through mechanical circulatory support until the patient can be weaned off of the device. Although most published literature discusses IABP use in the setting of acute HF, a recent preliminary study has shown promising results for the use of IABPs long term for patients with chronic HF. **(77)** Chronic heart failure is a disease characterized by a worsening of HF symptoms, either acutely, or a slow deterioration of previously diagnosed chronic HF. The left ventricle function is usually compromised, though there are HF patients with preserved left ventricular function. Patients with HF tend to present with "acute pulmonary edema, hypertensive heart failure, decompensated chronic heart failure, and cardiogenic shock." Most organ systems are affected as blood flow is reduced, leading to decreased tissue and organ perfusion, as well as congestion. **(78)**

Given the now widely accepted use of IABPs in the clinical setting, it is of interest to discover that very limited published literature has been established for the effects of IABP use on the baroreceptors. As previously considered, IABPs have been intensely studied for their effects on the left ventricle and the device's intended use, but effects on the autonomic system regulation in comparison have been almost nonexistent. **(79)** In 1971, Normann et. al. published a paper investigating arterial "baroreceptor output (BRO)" during IABP use in dogs. Heart rate and aortic arch pressure were measured, while electrocardiogram readings were monitored for proper timing methods.

Aortic and carotid baroreceptor activities were monitored during each circulatory cycle on a beat-by-beat basis. The investigators found that the BRO readings typically seen during systole were lessened, and were also equivalent to or less than BRO readings during diastole. It was also noted that baroreflex responses from both the carotid and aortic locations were similar in their hemodynamic modifications. From these experiments, it was clear that IABPs altered baroreceptor responses in the acute setting. Immediate changes during systole and diastole can be seen, demonstrating the high sensitivity of the baroreceptors while the device is in use. The experimental data from these studies show that IABPs produced a similar effect to that of increasing heart rate two-fold, therefore altering autonomic output to the heart and peripheral vasculature. Their discussion reiterates the concerns and potential benefits surrounding baroreceptor control and ensuing autonomic hemodynamic changes during procedures with mechanical circulatory assist devices, such as IABPs. **(80)**

Another publication by Feola et. al. reviewed IABPs and the baroreflex in dogs during their considerations of hemodynamic changes in induced acute left ventricular HF. Measurements of BRO were recorded, and similar results to Normann et. al. were observed. IABP use again increased BRO during diastole and decreased BRO during systole, with the overall result being greater during diastole. Therefore, it again was detected that IABP use significantly changed the output signals of the baroreceptor response, and that acutely, the association between the device and the body's autonomic response are of vital importance to consider during similar procedures. **(81)**

Fresiello et. al. produced a paper focused on observing the baroreflex while IABPs were in use, while noting changes in heart rate, venous tone and TPR, to evaluate the potential positive effects the device may have on cardiovascular hemodynamics. As HF and hypertensive patients could benefit from a reduction in heart rate and TPR, thereby decreasing the workload of the ventricles, the investigators aimed to create a "hybrid model" to test their hypotheses. This model was "computational and hydraulic," and studied timing effects of IABPs on the baroreflex, as well as how alterations in baroreflex activity would change cardiovascular hemodynamics in a simulated patient. The hybrid model was a combination of physical and computational submodels based off of previous work that mimicked systemic and pulmonary circulation. Within this system, experiments within a mock aorta could be produced to mirror actual baroreceptor responses to pressure changes. As discovered in previously mentioned work, the investigators found that IABP use impacted baroreceptor activity; counterpulsation during diastole stimulated the baroreflex, with an overall result of an increase in afferent signaling. The outcomes reiterate the knowledge that during device use, the inflation of the balloon stimulates the baroreceptors by causing additional pressure during the diastolic phase, thereby increasing baroreflex action and the resultant hindering of the sympathetic nervous system. Additionally, they also noted that the timing and duration of the balloon inflation was vital to altering TPR, heart rate and venous tone, as the counterpulsation created opposing effects of the sympathetic system depending on when inflation occurred. **(79)**

Left ventricular assist devices

Mechanical circulatory assist devices have evolved tremendously since their initial development during the 1950's. The class of devices known as left ventricular assist devices, or LVADs, have gained immense clinical use as device development has progressed over time. **(82)** The main elements of LVADs are a cable, known as a driveline, that is inserted into the patient's chest, pump and inflow and outflow cannulas, which serve to supplement the role of the patient's own heart. The pump is placed at the apex of the left ventricle and is connected to the inflow and outflow tubes. Blood from the inflow side of the left ventricle is sent through the pump, followed by passage into the outflow side and through the aorta. Various types of LVADs allow for differing blood flows, as well as pulsatile or continuous pumping. The driveline serves to link the heart pump to a driver outside of the patient's body that houses a system controller. A battery-operated unit is connected to the system that serves as a power source, regulator of system speed and power, establishes data collection, provides alarms and completes diagnostic monitoring of the device. **(84)** Figure 10 below illustrates the overall device placement for patient use.

A major clinical indication for LVAD use is HF. As previously discussed, HF poses a high risk for morbidity and mortality while contributing to immense financial burdens within the healthcare world. Regardless of continued efforts in resynchronization devices and pharmacotherapy, several patients suffering from the disease reach end-stage HF. Options for patients during end-stage HF are limited; LVAD use or a heart transplant are typically the only therapeutic approaches remaining. Given

that heart transplant procedures are restricted due to the number of available donor organs, LVAD use has been established as a "bridge to transplant or as a destination therapy" for those who do not meet the criteria for a heart transplant. **(83)**

With the development of the first mechanical circulatory assist devices in the 1950's, many efforts were made thereafter to produce device pumps for short-term support during surgeries and interventions. Patients undergoing cardiopulmonary bypass surgery were placed on pump therapy if their cardiac output was decreased post-procedure. In a little more than ten years since the first mechanical circulatory device was implemented in the clinical setting, the "Artificial Heart Program" was developed for the research and development of devices, which could provide not only acute, emergency circulatory support, but also long-term support for patients with failing hearts. By 1969, the first implantable LVAD was successfully implemented. As physicians began regressing from the use of total artificial hearts due to their increased risk of complications, LVAD therapy was moving forward with development of long-term use. Many generations of the device have been modified over time through current medical practice; LVAD therapy can be used for patients awaiting donor hearts who need bridge to treatment support, or others who are ineligible for heart transplants and receive long-term support, also known as "destination therapy." **(83)**

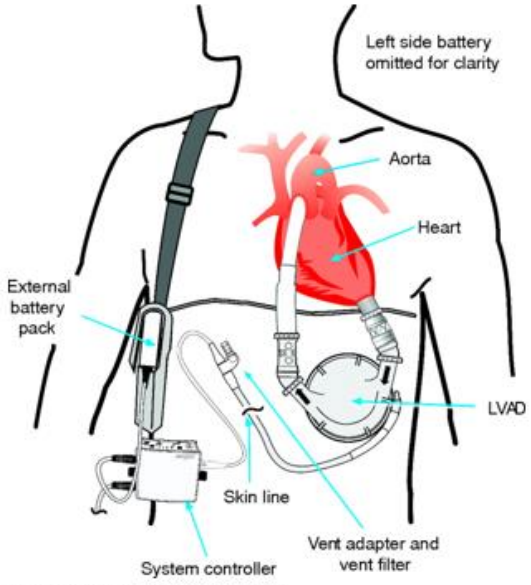

Figure 10 Left ventricular assist device. Components of a current standard LVAD for patients with an indication for device use. The pump is located near the left ventricle and contains a tube which sends blood through the aorta. The driveline is seen inside and outside of the body via the skin line, where it connects the pump to the system controller and external battery pack. Figure taken from **(85)**.

The current indications for LVAD therapy are provided as guidelines for device use, however, the final decision to implant the device in a patient is the product of several consults with different specialists and collaborative efforts of many teams. Suitable patients must have previously exhausted all optimal medical therapy options, as well as have at least one of the following clinical indications: three or more hospitalizations within the last year, a left ventricular ejection fraction of less than 25%, ionotropic support dependence, early right ventricular dysfunction, or advanced kidney and/or liver failure "secondary to hypoperfusion" and to elevated "left ventricular filling pressures."

It is important to note that patients who are considering LVAD therapy are typically also presented with the option of total heart transplant, given that their end-stage HF meets the criteria for either therapeutic technique. **(86)**

Similar to IABPs previously reviewed, LVADs and the baroreflex have been frequently researched; however, their considerations together are sparse in the scientific literature. The LVAD has established its critical use for patients needing mechanical circulatory support, especially those with HF. Jansen-Park et. al. have discussed the importance of considering the effects of LVADs and the baroreflex to gain further knowledge of the physiological changes taking place during device use. The investigators implemented a hydraulic model, named "mock heart circulation loops," that mimic the cardiovascular system and have reproducible effects similar to the human body. While using this model, investigators found it challenging to establish autonomic regulatory function of cardiac output and MAP. The background information supporting their investigation described the baroreceptor response as altering the afterload of the hydraulic model, as well as TPR, venous tone and heart rate; their new model took all autonomic regulation into consideration and adjusted accordingly in order to study LVADs without confounding issues. The results indicated that changes in LVAD speed, which served to alter the preload on the heart, altered cardiovascular hemodynamics. As the device increased in speed, the pressure within the aorta increased, whereas the pressure in the left ventricle decreased, and were the result of baroreflex alterations. The investigators discussed that studying further baroreflex fluctuations could shed additional light on pathophysiological states. The mock heart circulation loop model proved to be a

vital tool for observing LVAD effects and the baroreflex, which investigators concluded provides potential benefit for future research on mechanical circulatory assist devices, their clinical application and resulting physiological outcomes. **(87)**

Another publication by Tank et. al. studied nine HF patients with implanted LVADs and the device's direct effect on the baroreflex. The investigators hypothesized that LVADs with a continuous flow, as opposed to pulsatile flow, would alter the baroreflex ability to control sympathetic output to the heart, and ultimately intensify sympathetic activity. The newly established continuous flow systems have proven superior to pulsatile flow devices in "cardiovascular morbidity, reoperations for device repair or replacement, and total mortality," providing a promising option for patients suffering from end-stage HF. However, the investigators argued that as these more modern devices have been implemented, their resulting effects on cardiovascular hemodynamics may be problematic as continuous flow is linked with significant baroreflex regulation issues. Hemodynamic variables measured in the nine patients studied included: brachial and finger blood pressure, respiration, muscle sympathetic nerve activity and heart conductance via electrocardiograms. The patients went through a series of autonomic function testing, as well as changing seven of the patient's devices to have an increased speed. Baroreceptor function was evaluated and the investigators concluded that low pressure pulses from LVAD use is adequate enough to generate sympathetic activity via baroreflex activation. One of the experiment's significant findings showed that the regulation of baroreflex muscle nerve sympathetic activity was unexpectedly conserved, resulting in decreased sympathetic output. Additionally, given

the compromised contractility status of each patient's heart, it was surprising to discover that sympathetic activity was low. The results from this study contest the concept that pulsatile flow and normal pressures are necessary in order to preserve cardiovascular hemodynamic stability. The investigators concluded that continuous flow LVAD use in patients with HF is satisfactory to conserve cardiovascular functioning through baroreceptor regulation. **(88)**

A paper published in 2014, not long after the work produced by Tank et. al., stated that Tank's group was the only paper published examining continuous flow LVAD use and effects on the baroreflex within the clinic setting. Fresiello et. al. therefore wanted to implement different study models *in vivo* in order to determine which model may be realistic for the study of the device and autonomic functioning. The baroreflex involvement in varying cardiovascular hemodynamic states creates a challenging situation when analyzing data from animal models, which the investigators state is due to the intricacy of several physiological interactions. The investigators used a hybrid device model that analyzed data generated during LVAD use within animal models in normal, pathological and device-assisted states. Their findings revealed that the hybrid device was able to mimic physiological and pathological hemodynamic states within the animal model, as well as the effects of LVAD use on baroreceptor regulation and unloading of the left ventricle at altering pump speeds. One component of the study looked at afferent and efferent sympathetic nerve action during LVAD use, and found similar results to the work produced by Tank et. al. in patients with end stage HF; as device speed increased, sympathetic action declined, indicating the baroreceptor control of autonomic activity.

Fresiello et. al. concluded that the model used in their experiments was able to adjust without difficulty to generate varying hemodynamic states and study the effects of LVAD use, and should be considered for future work in human studies. The paper discusses the importance of further studying mechanical circulatory assist devices, such as the LVAD, given their increasing usage and development, in order to understand the devices in varying physiological states and modify their use to maximize potential benefit in the experimental and clinical setting. **(89)**

A final reviewed paper by Markham et. al. compared physiological responses in patients with and without pulsatile LVADs. As previously mentioned, the early generation of pulsatile flow devices were succeeded by continuous flow, or nonpulsatile, devices as device development matured. The investigators in this study wanted to examine the long-term effects of continuous flow LVADs in patients who would not be receiving a constant pulse from their devices. The paper describes the challenges surrounding blood pressure measurements without a consistent device pulse, which can contribute to "an increased risk of uncontrolled hypertension and possibly stroke," as well as other potential complications. They speculated this could be due to the constant, and at times increased, sympathetic output due to the lack of device pulsation. Without a consistent pulsatile mechanism, the baroreflex is not triggered as effectively, reducing the afferent nerve signaling and causing an increased sympathetic response. The increased sympathetic activity is the result of a decreased inhibition via the baroreceptor response, as the lack of continual pulsation did not stimulate the reflex as effectively. The study's hypothesis was that patients with continuous flow LVADs would have increased

sympathetic activity compared to those with pulsatile devices. Measurements were taken while patients were at rest and while upright. Results showed that for both resting and upright patients, those with continuous flow devices did indeed have elevated sympathetic nerve activity compared to patients with pulsatile devices and healthy control individuals. The investigators discussed different prospective mechanisms for their results; the most plausible idea was less baroreceptor activation, but they also discussed other potential mechanisms. For example, constant baroreceptor activation, as in the case of pulsatile flow devices, quickly causes baroreceptor desensitization, which does not occur in continuous flow devices. The paper describes that theoretically, endothelial cell function could play a role in increased sympathetic discharge as a decrease in pulsation reduces shear stress, and less nitric oxide is generated. A decrease in nitric oxide weakens the vasodilatory effects of endothelial cells, as well as produces an escalation in sympathetic activity. Another potential mechanism the researchers postulated was humoral factors, such as products of the renin-angiotensin-aldosterone system, may add to the observed increased sympathetic activity in patients with continuous flow LVADs. As described in other papers reviewed in this section, Markham et. al. also expressed the need for further investigation in order to gain more advanced knowledge on the clinical impact of continuous flow LVADs and their effects on cardiovascular hemodynamics in patients implanted with these devices for chronic use. **(90)**

Carotid sinus stimulators

As the baroreflex and its association with blood pressure regulation became better understood, interest arose amongst the scientific community to further explore potential beneficial methods of therapeutic intervention. As early as the 1850's, *in vivo* studies were conducted on the carotid sinus and the discovery of the baroreflex in modulating blood pressure was established. In the 1960's, the development of an implantable device with two carotid sinus electrodes was created to study blood pressure changes in dogs with hypertension. A short time thereafter, the first clinical implementation of this same procedure in two patients with hypertension was performed. **(91)** Hypertension was the first disease of interest given its direct relation to blood pressure dysregulation. Early clinical stages of research and development were slow in nature due to the limitations of the then present technology, as well as the introduction of favorable pharmaceutical agents. **(92)** Additionally, initial clinical data supporting baroreflex mechanisms in hypertensive patients was only understood in an acute sense; baroreceptor activation was viewed as a short-term mechanism with transient properties. **(91)**

Currently, the most studied carotid sinus stimulator undergoing clinical investigation is made up of three parts: leads for use within the carotid sinus, a programmer that is used externally and an implantable pulse generator. Both carotid sinuses may be targeted for stimulation, or a single side is intervened on through newer device systems. The ends of the leads contain electrodes, or a single electrode in newer device systems, which deliver stimulation to the baroreceptors either in bursts or continuously. The stimulation can be adjusted for different "voltage protocols" that

allow for modifiable impulse amplitudes and intervals. The leads are attached to the implantable pulse generator that is surgically inserted into an infraclavicular pocket within the patient. The external programmer is not connected to the patient and serves to test the patient's device routinely for cardiovascular hemodynamic changes. **(92)** Figure 11 below demonstrates the internal location of the carotid sinus leads and location of the pulse generator.

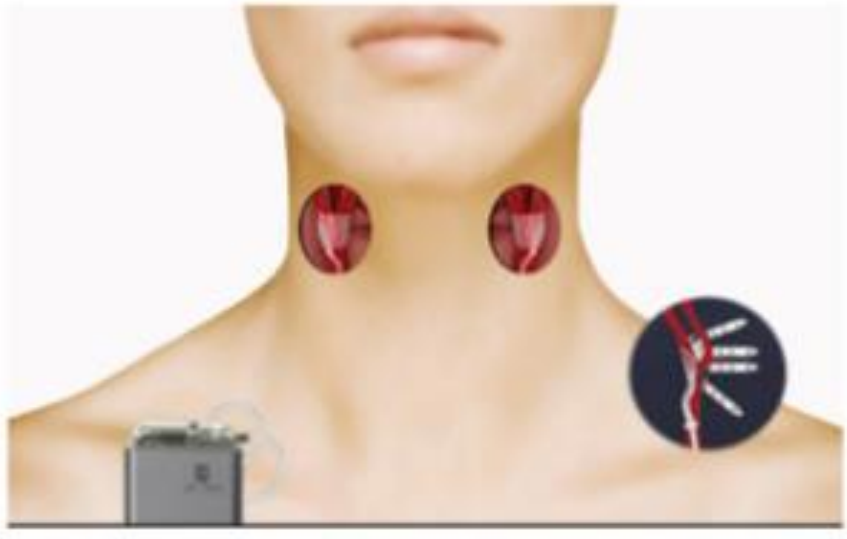

Figure 11 Carotid sinus stimulator. Depiction of a carotid sinus stimulator set of leads affixed within the carotid sinus and a pulse generator that is implanted within the patient's infraclavicular pocket. Figure taken from **(92)**.

Due to the fact that carotid sinus stimulators are still in clinical trial investigational phases, there are no current Food and Drug Administration indications for use. Patients who enroll into clinical trials involved with carotid sinus stimulators typically have either treatment resistant hypertension or chronic HF. Patients who present with treatment resistant hypertension are generally categorized as those with

"blood pressure that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes." **(93)** These patients present with elevated sympathetic nervous system activity, as well as decreased parasympathetic activity of heart rate control. Carotid sinus stimulators promote baroreflex activation in order to reverse these autonomic functions by increasing parasympathetic activity and decreasing sympathetic activity, ultimately serving to establish an equilibrium between the two opposing outputs and depressing blood pressure. **(94)** It is also important to note that as sympathetic tone is lessened through this therapeutic approach, the renin-angiotensin-aldosterone system output is decreased, thereby increasing excretion by the kidneys. **(95)** Although this newer therapeutic approach has shown promising data and hope for patients suffering from treatment resistant hypertension, the response is not consistent, and some individuals undergoing carotid sinus stimulation do not generate a response whatsoever. **(94)**

Chronic HF has been a more recent disease of interest by investigators studying carotid sinus stimulators, with a patient population focused on those with reduced left ventricular ejection fractions. Similar to treatment resistant hypertension, patients suffering from chronic HF have increased sympathetic and decreased parasympathetic activity imbalances that advances the development of HF over time. Current therapies concentrate on balancing neurohormonal factors via pharmacotherapy; typically, renin-angiotensin-aldosterone inhibitors and beta-blockers are prescribed. With a lowered left ventricular ejection fraction, the chronic HF patient's heart is unable to provide adequate systemic and organ perfusion on a continuous basis. These conditions place the body

into a state such that sympathetic activation and parasympathetic inhibition are constantly attempting to supply the necessary neurohormonal means of restoring physiological homeostasis. Due to this, the stress on the heart causes further decrease in cardiac output and function, and a perpetual cycle continues. As with treatment resistant hypertension, carotid sinus stimulation (Figure 12) looks to activate the baroreflex in an attempt to reverse the autonomic disparity in chronic HF patients. **(96)**

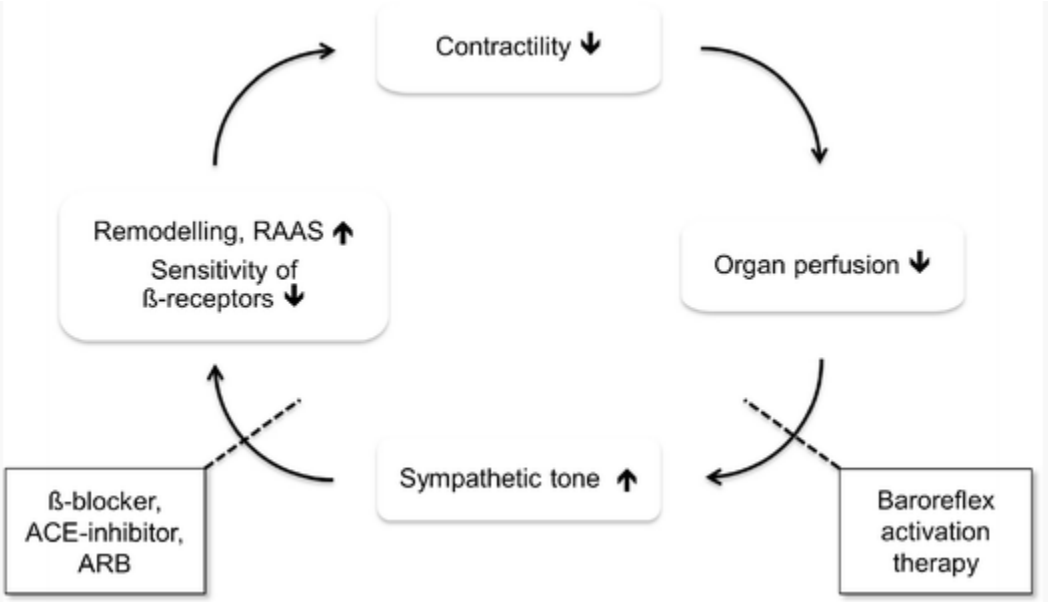

Figure 12 Carotid sinus stimulation intervention in patients with chronic heart failure. Baroreflex activation therapy is modeled with the intent of breaking the continual cycle of sympathetic nervous system activation in patients with chronic HF. Pharmacotherapy interventional options are also noted. Figure taken from **(96)**.

Unlike the previous cardiovascular devices discussed in this literature review, it is much more clear the effects that carotid sinus stimulators have on the baroreflex. For consistency, a few published articles will be reviewed briefly here. A publication by Gronda et. al. looked at the effects of baroreflex chronic activation in eleven patients with

chronic HF at a single investigational center. Data measured included muscle sympathetic nerve activity, blood pressure and heart rate, as well as electrocardiogram measurements. Also, quality of life, HF classifications, walk tests, lab data, left ventricular ejection fraction and safety data were assessed. Two weeks after patients were implanted with the carotid sinus stimulator, the device was turned on, and baroreceptor stimulation therapy was increased, as tolerated, to a stimulation protocol desired pulse level. The investigators followed the study participants for six months; their results concluded that chronic carotid sinus stimulation of the carotid baroreceptors decreased sympathetic activity in these patients. Additionally, they noted that there was marked improvement in baroreflex response, which is normally compromised in chronic HF patients, in turn generating an overall positive effect on cardiovascular health. **(97)**

Another publication by Wallbach et. al. aimed to study the effects of carotid sinus stimulation on ambulatory blood pressure for patients with treatment resistant hypertension. Ambulatory blood pressure measurements provide insight to regular blood pressure levels that may be hindered by "white coat hypertension" that is prevalently seen in some patients while blood pressure measurements are taken in a clinic setting. **(98)** The investigators pointed out that inadequate data are currently present for day-to-day blood pressure alterations for patients implanted with baroreflex activation devices, in comparison to blood pressure readings produced in the clinic. Measurements of ambulatory blood pressure were taken pre-procedure and six months after device activation. The investigator's results showed that ambulatory blood pressure readings were significantly lowered, along with a decrease in prescribed antihypertensive

medications. As a novel investigation on ambulatory blood pressure and carotid sinus stimulators, the investigators concluded that for patients living with treatment-resistant hypertension, baroreflex activation therapy could be a potential innovative approach to decrease overall cardiovascular risk factors. **(99)**

A third publication by Georgakopoulos et. al. presented a literature review focused on carotid sinus stimulation in patients with chronic HF who maintained preserved left ventricular ejection fractions. HF with preserved ejection fraction (HFpEF) is considered to be as serious of a public health concern as HF with diminished left ventricular ejection fraction. The investigators point out that as of the paper's publication in 2011, there have not been any randomized clinical trials showing significant benefit for HFpEF patients in any therapeutic approaches. **(100)** A further investigation into the literature provided very little additional information. An abstract from a more recent publication in 2014 again confirmed that there has not been a successful treatment option discovered for HFpEF patients, with researched potential therapeutic approaches including pharmacotherapy, carotid sinus stimulation, heart pacing and lifestyle modification through diet and exercise. At this time, it appears that the goal is to manage HF symptoms while research and development continues to search for a more promising therapy. **(101)** Georgakopoulos et. al. describe in their review that hypertension is the chief comorbidity in HFpEF patients, therefore current efforts in studying carotid sinus stimulation and hypertension may provide promising insight for future therapeutic options. Also, the review summarizes other potential advantages of baroreflex activation besides hypertension management, including "regression of left

ventricular hypertrophy," equilibrium establishment between autonomic imbalances, disruption of the renin-angiotensin-aldosterone system, vessel dilation and kidney function conservation. The review reiterates that although there are no currently available treatments, great efforts are being put forth to research carotid sinus stimulation in the hopes of developing the first effective therapy for patients living with HFpEF. **(100)**

CONCLUSIONS AND FUTURE DIRECTIONS

Blood pressure regulation is managed on an instantaneous basis in order to maintain cardiovascular homeostasis. As mechanosensitive receptors activated by distension, the baroreceptors play a crucial role in modulating MAP through autonomic system balances. Located within the aortic arch and carotid sinuses, baroreceptor activation provides signaling for sympathetic activation and parasympathetic inhibition, whereas baroreceptor disengagement produces the opposite, with inhibition of sympathetic nerve signaling via increased parasympathetic activity. These actions result in physiological changes in MAP, heart rate, heart contractility and TPR.

Alterations from a steady state in blood pressure management are swiftly adjusted in order to reduce any unwanted stressors on the cardiovascular system. Over time, however, continued stress eventually leads to dysregulation. In the case of MAP, hypertension is the main pathophysiological state that results from continued, elevated blood pressure levels. As the leading risk factor for disease, hypertension therapy and management efforts have been robust as a remarkable proportion of the population are effected and as healthcare costs continue to skyrocket. Lifestyle modifications through diet and exercise are executed as initial and continued efforts to attempt to reduce elevated blood pressure levels. Additional therapeutic approaches are provided, as needed, to patients living with hypertension. An abundance of pharmaceutical agents has been established for use in the clinic that target different components of blood pressure regulation. Several antihypertensive agents can be provided as potential therapies, with

options to alter dosage, switch to a different class of drugs, or to use as a combination therapy with multiple antihypertensive agents.

In cases where lifestyle modification and pharmacotherapy options have been exhausted, patients may seek help through interventional and device therapies. As the baroreflex provides the integral role in blood pressure regulation, different interventions and devices have been shown to have varying effects on the aortic and carotid baroreceptors and their ensuing actions. As previously considered, much published literature has been produced on the baroreflex and its role in cardiovascular hemodynamic stability, as well as a vast abundance of knowledge surrounding device therapies. It is the combination of these efforts that is lacking in established data and knowledge that makes the considerations for this literature review so intriguing.

With the development of IABPs, patients needing temporary mechanical support have found profound success. Strong efforts have been made to develop next generation models based on prior safety and efficacy data in order to provide topline healthcare options for those with significant cardiovascular disease. Given that the device is inserted into a location in close proximity to the aortic baroreceptors, IABPs can be anticipated to prompt changes in autonomic nerve output and therefore may alter cardiovascular function. Changes in IABP counterpulsation also may play a role in varying physiological responses, which could serve as a potential therapeutic modification in future studies. Additionally, further investigation into short versus long term IABP use may shed additional light on physiological changes produced by device effects, and how to transform these responses into positive therapeutic benefit for

patients. As very limited published information is known about IABP influence on the baroreflex, additional pre-clinical and clinical work needs to be performed in order to better understand short and long term effects of device use.

Heart failure is a disease which plagues a significant portion of the patient population and causes many clinical complications, healthcare cost burdens and a decreased quality of life for those suffering from the disease. For several, heart transplantation is a typical therapeutic option for those with HF, however, there are some individuals who are not suitable candidates for a heart transplant, and therefore need to seek other options. Like IABPs, LVADs are mechanical circulatory assist devices that assist HF patients either awaiting heart transplants, or those who are not indicated to have the procedure and require chronic support. Given that HF patients have extremely increased sympathetic activity and impaired baroreflex function, further investigation into LVAD use is warranted. Pulsatile and continuous flow LVADs allow for prospective insight into the realm of baroreflex control of cardiovascular hemodynamics and physiological changes that may be inducible through different flow patterns. A continuous flow and constant baroreflex activation may produce an overall decrease in blood pressure and potentially the negative effects produced by hypertension, but additional research is required to evaluate long term physiological effects. New data could offer better comprehension on the controlling of LVADs and how this may induce positive results in HF patients. Newer hybrid models mimicking the human cardiovascular system can be utilized to test LVADs, as well as other mechanical circulatory assists devices, with the potential to delve into more complex clinical

situations without direct patient involvement. As with IABPs, clearly additional research and development is warranted to better characterize LVAD pump speed, understand and modify blood pressure via baroreflex activation and ultimately alter the path of cardiovascular disease through novel therapeutic treatment.

As the baroreflex became more established through a vast amount of contributors to blood pressure regulation research, its impact on cardiovascular physiology in healthy and diseased states warranted greater investigational efforts. The baroreceptors became a critical target for potential new treatments for blood pressure dysregulation, as hypertension was already known to be a significant risk factor for many comorbidities. Through the development of initial carotid sinus stimulators, a hypothetical novel therapeutic device for the management of hypertension was established. Clinical trials with early stage device models also showed promising data for patients with chronic HF. The device has allowed researchers to manipulate the baroreflex via pulsatile and nonpulsatile settings, along with amplitude and interval voltage protocols that provided more precise control of baroreceptor activation. Additional research and development is warranted in order to determine the fine-tuning of these settings for device safety and efficacy, and in theory, on certain patient populations and on an individual case-by-case basis in the future. With promising pivotal data and current robust efforts in clinical research trials, carotid sinus stimulators may one day become the next therapeutic option for patients living with treatment resistant hypertension or chronic HF. As with IABPs and LVADs, however, there still remains numerous questions regarding device use,

patient selection factors and augmentation of ideal device voltage protocols that are to be answered in order to find successful implementation in the clinical setting.

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