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Annals of Clinical and Experimental Hypertension

Short Communication

Aortic Arch Baroreceptor Stimulation: A Novel Method to Lower Blood Pressure

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Submitted: 01 January 2018
Accepted: 18 January 2018
Published: 31 January 2018
ISSN: 2373-9258

Keywords
- Aortic baroreceptor stimulation; Carotid baroreceptors; Autonomic nervous system

Abstract

Rationale: Hypertension is a common cardiovascular risk factor and is treated with pharmacological and non-pharmacological means. An aortic baroreceptor stimulation device based strategy has been tested for the manipulation of blood pressure in an experimental goat model. No prior clinical trials exist in this field. Twenty one experimental animals were used in this study. Long term effects of this procedure are unknown. No primate or human experiments have been conducted. This may be a novel therapy for the treatment of hypertension.

Objective: The study assessed the effect of aortic baroreceptor activation therapy on manipulation of systolic blood pressure.

Methods and Results: Twenty one experimental goat animals *Capra aegagrushircus* ranging from age 6 months to two years were enrolled in this cohort study. The study was conducted with intention to treat. This study was done as proof of concept/principle for manipulation of blood pressure and to assess whether the Octad stimulation system will result in significant blood pressure lowering.

Baseline blood pressure was a median of 111.8 mmHg with interquartile range of 16.8. After stimulation the median blood pressure was 88 mmHg with interquartile range of 21.0. The average lowering in blood pressure was 22.4 mmHg.

Conclusion: The results of this pilot study support the role of aortic baroreceptor stimulation to achieve significant blood pressure lowering. There might be an emerging role for development of a stimulation device for the treatment for high blood pressure. Aortic baroreceptor stimulation needs further investigation. First to be investigated would be the effect on diastolic blood pressure and mean arterial pressure. The second area that needs to be evaluated will be a cross species effect.

ABBREVIATIONS

UP: University of Pretoria; UPBRC: University of Pretoria Biomedical Research Centre

INTRODUCTION

Arterial hypertension is the most important risk factor for cardiovascular disease in humans resulting in premature death and disability globally. This cardiovascular disease includes coronary heart disease, stroke, heart failure, arrhythmias (such as atrial fibrillation) [1] Various drug trials and life-style change studies have been shown to significantly reduce cardiovascular events, but globally hypertension remains poorly controlled as less than a third of patients achieve target blood pressure [2]. This has led to the search for possible alternative methods to treat high blood pressure. An increased activity of the sympathetic nervous system, in part regulated by afferent input arising from arterial and cardiopulmonary baroreceptors has been demonstrated to play a critical role in developing and sustaining hypertension [3]. Activation of these receptors causes inhibition of the sympathetic system and potentially can reduce blood pressure.

Recently, electrical stimulation of the carotid sinus showed encouraging results in lowering blood pressure and reducing sympathetic drive. This was achieved both in short-term and long-term period of over 5 years and may have the potential to become a novel therapy for hypertension [4].

A variety of causes can stimulate the sympathetic nervous system to lead to hyper-activity of the system and one such cause is inactive baroreceptors. Low-pressure baroreceptors have an effect on renal-endocrine and circulatory systems, this having an effect on retention of salt and water and the intake of water. The neuro hormonal system resets the baroreceptor set point over time. Baroreceptor dysfunction leads to an increase in blood pressure [5].

The role of aortic baroreceptors in blood pressure control

Physiology of baroreceptors: Baroreceptors are located in blood vessels of all vertebrate animals. The sensory nerve endings of arterial baroreceptors are simple sprayed endings that lie in the adventitia of an artery. Changes in the arterial pressure and

thus stretching of the artery, results in action potentials triggered in these baroreceptors endings. Baroreceptors provoke action potentials with each heartbeat. Blood pressure changes act to maintain blood pressure and MAP.

These receptors work as a type of mechanoreceptor sensory system. The neurons are triggered by the stretch of a blood vessel wall. Increases in the pressure of arteries results in stretching of vessel walls. This produces action potentials that trigger the neuron stimulation which is conducted to the central nervous system [6,7] (Figure 1).

The neuron stimulation is mainly via the autonomic nervous system. This neuron stimulation modulates the heart rate, inotropic activity, thus cardiac output as well as vascular tone in the form of peripheral resistance [6] (Figure 2).

The release of hormones, such as adrenaline, that targets cardiac function can affect these baroreceptors instantly via sympathetic pathways. Baroreceptors respond immediately to maintain a stable blood pressure. Mean arterial pressure (MAP) and pulse pressure influence nerve firing so that the autonomic nerve system maintains near to the normal range of MAP. Physiological changes in the set point of blood pressure control occur in physical activity, hypertension and heart failure [3,7-9]. Adjustment over time occurs in this system which alters the sensitivity of these receptors. Changes in the set point explain why elevated blood pressure is maintained during exercise and in patients with chronic hypertension [10].

Previous investigators have evaluated the effect of carotid baroreceptor stimulation on hypertension [11]. New areas investigated in baroreceptor activity included hypertension treatment (carotid stimulation), sleep apnea syndrome and even diabetes control. This needs to be investigated further [4,12]. During these investigations it was found that diabetes control and sleep apnea improved.

Clinical trials

Carotid baroreceptor stimulation has already been evaluated in a double blind randomized placebo controlled Rheos Pivotal Trail in 2011. These results showed significant benefit for endpoints of sustained efficacy. The trial did not meet the endpoint for device and procedural safety [13].

A study that was done on the sensitivity between aortic baroreceptors and carotid baroreceptors indicated that the aortic depressor neurons possessed a higher percentage of mechano-sensitive neurons [14]. Due to this higher density of receptors we can predict that aortic baroreceptors stimulation will be more effective in lowering blood pressure.

However, no trials for aortic baroreceptor stimulation have yet been performed. Stimulation of the aortic arch baroreceptors has not been investigated. This study proved a novel mechanism in blood pressure manipulation. This research model determined the effect of aortic arch baroreceptor stimulation on blood pressure. The hypothesis was that stimulation of aortic arch receptors will cause a significant drop in systolic blood pressure.

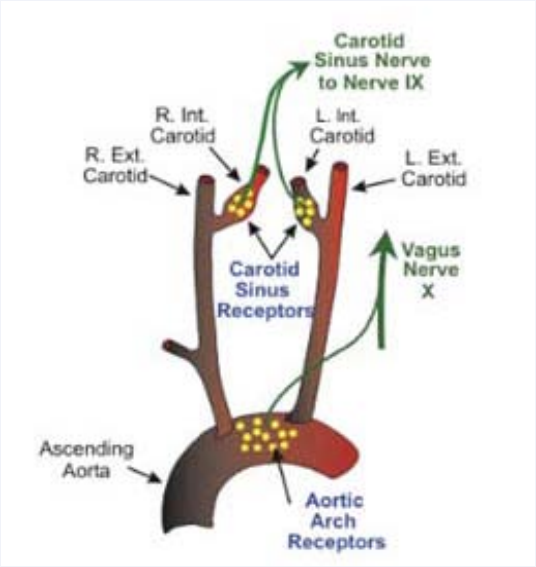

Figure 1 Location and innervations of arterial baroreceptors.
This illustrates the anatomical location and pathway innervations of the arterial baroreceptors which are located in the aortic arch and carotid artery sinuses. The innervation from the aortic arch via the vagal nerve X is shown. The baroreceptor innervation from the carotid artery sinus is shown via the carotid sinus nerve to the IXth cranial nerve.
This figure is freely available from the internet website: http://www.cvphysiology.com/Blood%20Pressure/BP012

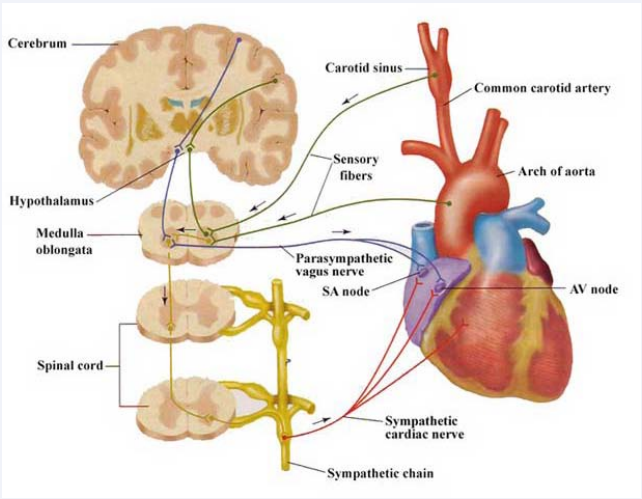

Figure 2 Afferent and Efferent autonomic pathways
This illustrates the afferent and the efferent pathways of the autonomic nervous system. Hormones such as adrenalin can affect cardiac function via the sympathetic pathway. The baroreceptors from the aortic arch and carotid sinus react immediately via the parasympathetic pathway to the brain.
This figure is freely available from the internet website: http://flipper.diff.org/app/items/info/5461

MATERIALS AND METHODS

Study design

This study is a proof of concept study approved by the

University of Pretoria Biomedical Research Council (Project no H007/14). In total 21 animals were subjected to aortic baroreceptor stimulation and the blood pressure response was measured.

UPBRC facility registration number with the South African Veterinary Council: FR15/1383.

UP Animal Ethics Committee registration with the National Health Research Ethics Council: AREC-261110-001.

Research animal population

The goat species Capra aegagrushircus was used in this research project. This species was chosen due to the convenient size, especially of the aortic arch and consequently the ease to identify the sites of the aortic baroreceptors. Both sexes were included in this study. The age of the animals varied from 6 months to 2 years.

Anesthetic procedure

All research animals received anesthesia according to the anesthesia protocol. The protocol made provision to have the least possible effect on systolic blood pressure. The anesthetic induction and procedure included a single bolus of Alfaxalone (5mg per Kg) combined with intramuscular Midzolam via a Jab stick.

This was followed by a face mask through which Isoflurane and oxygen were continued. Maintenance fluid was administered via an auricular vein. The femoral artery catheter was connected to the Vigeleo system that measured blood pressure intra-arterially. Stimulation was only done after the blood pressure was stable during 5 measurements taken at 5 minute intervals.

Surgical procedures

This procedure consisted of a left lateral thoracotomy incision and the aortic arch dissected down to the adventitia. A bolus of Buprenorphine was administered prior to the surgical procedure to ensure that there was no pain to influence systolic blood pressure. The Octad probe was placed on the outer surface of the aortic arch. This probe is designed as an 8 contact probe, bended to fit over the aorta. The 8 contacts provide optimum contact area to cover the baroreceptors on the aortic wall. Data was collected using the Vigileo System. This system was connected to a femoral artery canalization probe. Blood pressure response was measured via the arterial pressure wave. Stimulation was continued until no further blood pressure reduction could be achieved. All animals were euthanized after the procedures.

Primary endpoints

The end-point of the study was the maximum reduction in systolic blood pressure that could be achieved with baroreceptor stimulation.

Statistical analysis

Per trial design assumptions, sample size was calculated to adequately power endpoint results for a power of 90% at the significance level of 0.05. Sample size was determined as 17 experimental animals. Twenty one animals were included in the study. The first four animals were used to determine the technical aspects. These four animals were included in the final data analysis.

For this research the null hypothesis of no relationship between stimulation of aortic baroreceptors and a drop in blood pressure was applied. By rejecting the null hypothesis would then conclude that there are grounds for believing that there is a relationship between stimulation of the receptors and lowering of blood pressure.

The null hypothesis is rejected if a significant blood pressure lowering, defined as a 20mmHg decrease in blood pressure, is achieved. The control measure is defined as the blood pressure reading before stimulation of the receptors. The effect is measured by applying the relevant statistical tests as described below.

For this study, which is proof of concept, a significant drop in SBP of 20mm Hg (due to stimulation) sample size determination was applied. A standard deviation of 23.62mmHg is assumed ($\sqrt{2}$* expected range for drop in SBP/∂ = $\sqrt{2}$ * 100/∂). A sample size of 17 animals had 90% power to detect a change from baseline of at least 20mmHg when the standard deviation is 23.62mmHg and testing is two-sided at the 0.05 level of significance.

During this study baseline and endpoint blood pressure results were compared.

Main endpoints

Efficacy analysis was conducted according to the principle of intention to treat. Change in BP was calculated using the average of the 5 measurements from the stable anesthetic phase against the maximum blood pressure drop in the stimulation phase.

RESULTS AND DISCUSSION

Twenty one animals were used in this research. The initial four animals were allocated to perfect the technique. The data from these four animals were added to the remaining seventeen as per protocol.

The final results were analyzed with the Kolmogorov-Smirnov test that showed that both pre-stimulation and post-stimulation data were non-parametrical. The Wilcoxon Signed Rank Test was therefore applied for the final results.

The baseline blood pressure (before stimulation) had a median value of 111.8 mmHg with the interquartile range value of 16.8. After stimulation blood pressure was 88mmHg with the interquartile value of 21.00. This showed a significant lowering of blood pressure with a mean reduction of 22.4 mmHg. Blood pressure lowering was observed in all experimental animals.

Pre- and post-stimulation results for each animal are shown in Figure (3).

The results of the median for both pre- and post- stimulation data is shown in Figure (4).

The difference between pre- and post- stimulation was highly significant with a p-value of 0.0001. The null hypothesis was thus rejected and aortic baroreceptor stimulation is associated with lowering in blood pressure

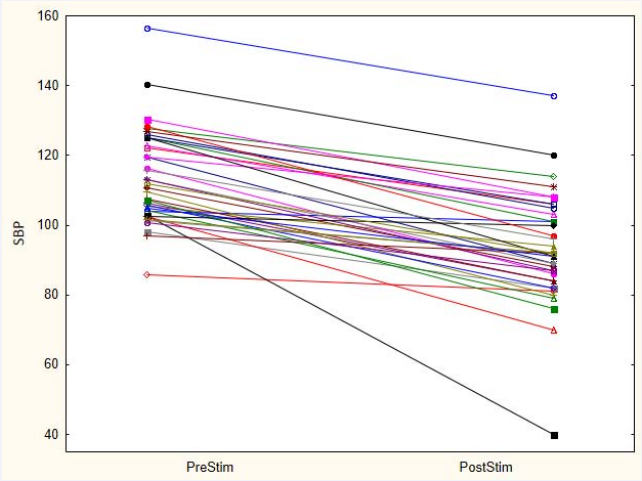

Figure 3 Octad stimulation results
Results of pre and post stimulation for each research animal are plotted in this figure. This was the results of aortic arch baroreceptor stimulation with the Octad experimental probe. Systolic blood pressure values are represented in mmHg.

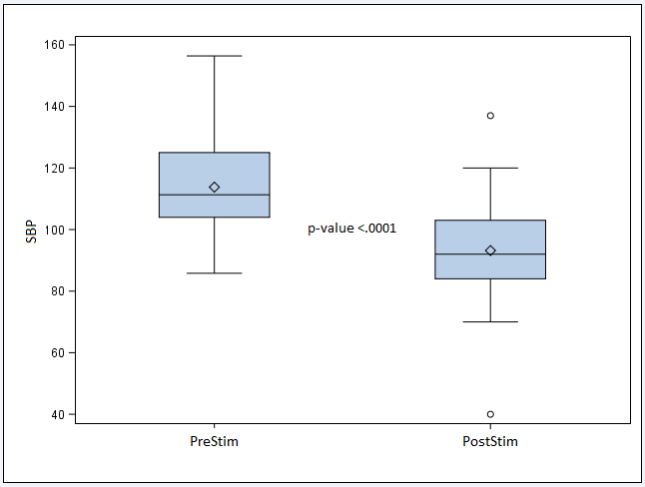

Figure 4 Pre- and Post-stimulation data
The results of the distribution of the median are shown in the figure, together with the p-value after applying the Wilcoxon rank test. Systolic blood pressure values are represented in mmHg.

CONCLUSION

Hypertension is an important cause of morbidity and mortality worldwide and significant resources are utilized annually for medication to treat hypertension [1,15]. However, compliance with pharmacological therapy is relatively inadequate and few patients achieve target blood pressure [16,17]. Side effects of medication contribute to poor compliance and some patients with resistant hypertension require multiple agents [16,18-20].

The findings of the current study suggest that stimulation of aortic baroreceptors in an animal model may represent a viable method to decrease arterial pressure.

Aortic baroreceptor stimulation caused a significant decrease in systolic blood pressure in all animals tested. Importantly, the median decrement in systolic blood pressure observed in this study was highly significant with a magnitude of 22.4 mmHg and was sustained for the duration of the procedure without serious adverse effects. A surgical procedure was used to place the probe close to the aortic baroreceptors and this may have had an effect on the pre-stimulation systolic pressure. This effect was not observed. However, general anesthesia and appropriate analgesics were administered to the animals to minimize sympathetic stimulation during the procedure. The blood pressure response to baroreceptor stimulation was carefully monitored to ensure the accuracy of all measurements taken.

The current study did not evaluate the effects of the aortic baroreceptor stimulation during sleep and therefore the effects of this procedure on nocturnal dipping cannot be determined. In addition, significant autonomic sympathetic activity may transiently overcome the effects of aortic baroreceptor stimulation and the animals used in this study were healthy and normotensive. A similar study using animals with hypertension will be required to determine whether or not the response to aortic baroreceptor stimulation is comparable to that observed in normotensive animals.

Despite these limitations, aortic baroreceptor stimulation is a novel method to decrease systolic blood pressure and may provide an alternative method for the treatment of hypertension if these results in an animal model are repeatable in human trials.

We postulate that aortic baroreceptor stimulation will be more effective than carotid baroreceptor stimulation in regulating systemic blood pressure due to the sensitivity and density of the aortic baroreceptors. This difference between this two stimulation sites is not well known and should be investigated further.

The potential utility of this form of therapy may include subgroups of patients with resistant hypertension or those who experience significant side effects from pharmacological therapy.

In conclusion, stimulation of aortic baroreceptors in an animal model produced a significant decrease in systolic pressure and may represent a novel method to modulate systemic blood pressure in subjects with hypertension.

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Cite this article

Benson JF, Venter FJ, Ker JA, Zeiler G, Bester E, et al. (2018) Aortic Arch Baroreceptor Stimulation: A Novel Method to Lower Blood Pressure. Ann Clin Exp Hypertension 6(1): 1054.