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Effect of Non-invasive Electrical Stimulation at the Level of Tragus on Blood Pressure and Heart Rate in Hypertensive Rats

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ABSTRACT

Background: As per the present scenario, increased incidences of side effects and the emergence of resistant cases is a big challenge for physicians in treating hypertension despite having multiple drug anti-hypertensive drug treatments, so a new way of treating hypertension by non-pharmacological method is warranted now. To study and compare the effects of non-invasive transcutaneous electrical stimulation (TES) of the vagus nerve on blood pressure and heart rate in rats.

Methods: The study was conducted on twelve male Wister rats (six normotensive and six hypertensive). Hypertension was induced using oral L-NAME administration for 21 days. Systolic blood pressure and heart rate were recorded at baseline and after 5, 10, and 20 minutes of TES applied at the tragus under ketamine/xylazine anesthesia.

Results: Systolic blood pressure was reduced from 135.14±3.50 mmHg to 119.74±3.06 mmHg and heart rate was significantly reduced from 234.00±20.01 to 212.83±6.79 beats/min after 20 minutes of TES in hypertensive rats. Similar trends were observed in normotensive rats. The reductions were statistically significant.

Conclusion: TES decreases both systolic blood pressure and heart rate in hypertensive as well as normotensive rats, suggesting its potential as a non-invasive approach for autonomic modulation in hypertension.

Key-words: Non-invasive, Electrical stimulation, Tragus, Blood pressure, Hypertensive rats

INTRODUCTION

Hypertension (HTN) till now is called when systolic blood pressure (SBP) level is more than 140mmHg and diastolic blood pressure (DBP) level is more than 90mmHg [1-3]. It is known to be a major risk factor for various cardiovascular diseases in developed as well as developing countries. HTN is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease (CHD) deaths in India [4].

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The estimated total number of hypertensive adults in 2010 was 1.33 billion, 346 million in developed countries and 985 million in developing countries [5]. The number of adults with HTN between the ages of 30–79 years has increased from 650 million to 1.28 billion in the last 30 years [6].

Poor control of blood pressure remains a big challenge nowadays for the physician despite having several types of drugs and drug combination therapies. Another big challenge in the drug treatment of HTN is that in some patients, it is resistant to optimal medical therapy. Resistant hypertension is defined as the inability to achieve normal blood pressure despite the use of at least three antihypertensive medications, or with controlled BP while receiving more than four BP-lowering medications [7]. Currently, an estimated one billion

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people carry a diagnosis of hypertension of which up to 15 % are considered to have resistant hypertension [8].

Based on the above literature it is clear that treatment of hypertension and resistant hypertension causes a significant decrease in cardiovascular co-morbidities but limitations of drug therapy include medication side effects, drug compliance, use of many drugs and even emerging cases of resistant hypertension after true treatment are of great concern nowadays. Thus, non-pharmacological management for hypertension has been attracting more interest. Over the last few decades, there has been an increasing understanding of the role of the sympathetic nervous system in the development and maintenance of hypertension. Electrical stimulation of the afferent arm of the baroreceptor–reflex alters the sympathetic and parasympathetic tone [9].

Electric stimulators that directly activate afferent baroreflex nerves were developed years earlier but failed for technical reasons [10]. Recently, a novel implantable stimulator was developed that may overcome some of these problems [11]. Till now, published literature showed that present devices are invasive and depend on an external complicated controlled system. Thus, further studies are warranted to probe the mechanism of blood pressure regulation and to develop non-invasive devices compatible with human physiology.

In a study, Low level–Transcutaneous Stimulation of Tragus (LL-TES) was able to inhibit Atrial Fibrillation (AF), suggesting a potential noninvasive treatment of AF [12]. In another study LL-TES of auricular branch of vagus nerve (ABVN) can attenuate left ventricular remodeling in conscious dogs with healed myocardial infarction and propose a new neural interface approach to modulate cardiac autonomic tone [13].

Now there is expanding interest in the role of tragus (supplied by ABVN) stimulation as an alternative, less-invasive method of vagus nerve stimulation. Therefore, we hypothesized that "Stimulation of the tragus may alter the blood pressure level in experimentally induced hypertension in rats by modulating the baroreflex and autonomic nervous system."

MATERIALS AND METHODS

Place of study- The study was conducted during the year 2017-18 in the Department of Physiology, King George Medical University, Lucknow, India.

Animals- Twelve male Wister rats aged about 4-6 weeks weighing about 210-250 mg were housed in the institutional animal house in standard environmental conditions: room temperature of 25±2°C, water and chow feed ad libitum, 12hr light-dark cycle. Animal care and experimental procedures were performed according to the principles of India's Committee for Control and Supervision of Experiments on Animals (CPCSEA) guidelines. The study was approved by the Animal Ethical Committee of King George Medical University, Lucknow, India.

Study Design- All twelve male Wister rats were acclimatized to the laboratory environment and restrainer (with tail cuff) for the first five days of the experimental period. They were divided into two groups Group A (n=6) and Group B (n=6). Baseline systolic blood pressure (SBP) and heart rate (HR) were recorded in both groups. L-NAME (induces hypertension) were given in Group B rats and converted into hypertensive rats (Group Bh). TES was done in both Group A and Group B_h rats in an anaesthetized state. Hemodynamic parameters (SBP, HR) were recorded at 5, 10 and 20 minutes of stimulation and were compared before and after stimulation.

Induction of Hypertension by L-NAME- L-NAME (nitro-l-arginine methyl ester) was purchased from Sigma Pvt. Ltd company, Lucknow. L-NAME was given to Group B rats for 21 days daily in the morning time between 9:00-9:30 IST in a dosage of 40mg/kg body weight. L-NAME was given orally in a palatable form mixed in a mixture of vegetable oil and roasted gram flour (vehicle). SBP and HR were recorded after every week of administration of L-NAME by NIBP instrument (AD Australia).

Anaesthesia Protocol- Ketamine/Xylazine cocktail anaesthesia was used for induction of anaesthesia before giving TES in both Group A and Group B_h rats. A cocktail of Ketamine (50mg/kg) and Xylazine (5mg/kg) was given through an intra-peritoneal route under aseptic conditions.

Stimulation Protocol- Transcutaneous electrical stimulation was given to both Group A and Group B_h rats after anaesthetization. The metal clip was designed in such a way that the two electrodes placed over the two

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arms of the clip face each other. A metal clip was placed over the tragus of the right ear of each rat to deliver TES.

Statistical Analysis- Data are expressed as mean±standard deviation (SD). Comparisons between groups were performed using unpaired Student's t-test, and changes within groups over time were assessed using repeated measures ANOVA followed by post-hoc comparisons, where applicable. A $p<0.05$ was considered statistically significant. All statistical analyses were performed using standard statistical software.

RESULTS

The present study was conducted on rats to know the effect of TES on SBP and HR and to compare the changes in cardiovascular parameters before and after the stimulation. Before intervention mean weight, mean systolic pressure and mean heart rate between Group A and Group B were not found to be statistically significant (Table 1).

Table 1: Between Group Comparison of Baseline Parameters (Before Intervention)

Parameters	Group A (n=6)		Group B (n=6)		Statistical significance
	Mean	SD	Mean	SD	'p'
Weight (gm)	234.17	15.94	231.67	17.51	0.801
Systolic Blood Pressure (mm Hg)	123.07	4.51	118.12	6.94	0.173
Heart rate (beats/min)	304.83	10.17	311.83	11.72	0.295

Mean SBP after 20min stimulation of rats of Group A (99.16±5.54 mmHg) and Group B_h (119.74±3.06 mmHg) was found to be decreased which was statistically significant with that before stimulation in Group A (107.95±5.92 mmHg) and Group B_h (135.14±3.50 mmHg) respectively (Table 2).

Table 2: Effect of Trans-cutaneous electrical stimulation (TES) on SBP (mmHg) in Group A and Group B_h rats

	Before TES	5 min TES	10 min TES	20 min TES
Group A (n=6)	107.95±5.92	110.05±4.88	106.15±4.10	99.16±5.54
Group B_h (n=6)	135.14±3.50	134.62±3.89	131.14±4.37	119.74±3.06

Mean HR after 20min stimulation of rats of Group A (217.00±5.97 beats/min) and Group B_h (212.83±6.79 beats/min) was found to be decreased and statistically significant with that before stimulation in Group A (235.83±10.98 beats/min) and Group B_h (234.00±20.01 beats/min) respectively (Table 3).

Table 3: Effect of Trans-cutaneous electrical stimulation (TES) on HR (beats/min) in Group A and Group

	Before TES	5 min TES	10 min TES	20 min TES
Group A (n=6)	235.83±10.98	226.67±9.46	224.22±12.02	217.00±5.97
Group B_h (n=6)	234.00±20.01	232.67±17.96	227.67±15.83	212.83±6.79

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DISCUSSION

In our study, we intended to evaluate the effect of non-invasive transcutaneous stimulation over the tragus (supplied by the auricular branch of the vagus nerve) in experimentally induced hypertensive male Wister rats. Initially, we successfully induced hypertension in rats in our laboratory by giving L-NAME by oral route for 21 days. L-NAME treatment increases blood pressure and vascular reactivity due to decreased nitric oxide (NO) bioavailability [14]. We also observed that while inducing HTN, the elevated blood pressure which was increased after 21 days of L-NAME administration, lowers down to a normal level within 15 days. The weight of the rats was found to be significantly reduced (p=0.0001) after L-NAME administration which was also documented in previous studies [14,15].

We stimulated the auricular branch of the vagus nerve of all the animals (hypertensive and normotensive) by applying electrodes transcutaneously over the anterior and posterior aspects of the right tragus. Till now, no published data has reported the effect of transcutaneous stimulation of the auricular branch of the vagus nerve at the level of the tragus on systolic blood pressure in rats. In this study, to avoid the frequency/voltage-based changes in blood pressure, we applied a constant 5V induced current at the frequency of 30 Hz to all animals. Previous studies pointed out that tragus stimulation activates a series of neurotransmission between ABVN, nucleus tractus solitaries, and other nuclei in the brain participating in cardiovascular control by eventually activating the efferent vagal fibers. In this study, we recorded the systolic blood pressure every five minutes after electrical stimulation and observed that 20 min stimulation of the auricular branch of the vagus nerve in anaesthetized rats significantly reduces SBP and heart rate in normotensive as well as hypertensive rats.

Although we did not estimate the NT level in the serum of animals, we can speculate that a duration of twenty-minute stimulation is required to form the optimum number of NTs at the level of NTS or at the level of Neuro-muscular junction to generate an action potential in afferent/efferent arm of baroreflex. Our data revealed that stimulation of the auricular branch of the vagus nerve certainly gives input to the baroreflex arc which in turn inhibits the sympathetic activity leading to a decrease in blood pressure and heart rate as observed in invasive stimulation of the vagus nerve in previous studies [16,17].

CONCLUSIONS

This study shows that non-invasive transcutaneous electrical stimulation (TES) at the tragus significantly lowers systolic blood pressure and heart rate in both normotensive and hypertensive rats. The effect is likely mediated through the modulation of autonomic tone via the auricular branch of the vagus nerve, influencing baroreflex pathways. These findings support TES as a potential non-pharmacological approach for blood pressure control, especially in resistant hypertension. However, as the study was conducted under anesthesia, further research is needed in conscious models to confirm its effectiveness and clinical relevance.

LIMITATIONS

This study was conducted in anaesthetized animals therefore its implication in conscious animal is doubtful and needs further study to rule out the confounding effect of anaesthesia.

CONTRIBUTION OF AUTHORS

Research Concept- Dr. Ankit Gupta, Dr. Pradeep Kumar
Research Design- Dr. Ankit Gupta, Dr. Pradeep Kumar, Dr. Piyush Gupta
Supervision- Materials- Dr. Piyush Gupta, Dr. Ankit Gupta
Data Collection- Dr. Piyush Gupta
Data interpretation- Dr. Piyush Gupta, Dr. Sudhir Yadav
Literature- Dr. Sudhir Yadav, Dr. Piyush Gupta
Writing Article- Dr. Sudhir Yadav, Dr. Piyush Gupta
Critical value- Dr. Ankit Gupta, Dr. Pradeep Kumar
Final approval- Dr. Ankit Gupta, Dr. Pradeep Kumar

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