Original Article

Median Nerves' Electrical Activation Reduces Ipsilateral Brachial Arteries' Blood Flow and Diameter

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ABSTRACT

Purpose: Our main objective in this study was to determine whether there is a difference between ipsilateral and contralateral brachial arteries' flow parameters in response to median nerves' electrical activation. **Material and Methods:** The study was conducted in healthy and active subjects. The arterial diameter and flow were measured using the probe from the brachial artery. Then, the median nerve was stimulated for 5 seconds via the bipolar stimulus electrode. Arterial diameter and flow were measured once more with the Doppler transducer, which kept going to monitor continuously just after the fifth stimulus. After a week, the same subjects are invited for the purpose of measuring the contralateral brachial arteries' vasomotor response to the same stimulus. **Results:** Before electrical stimulation, the median flow rate was 72.15 ml/min; after stimulation, the median flow rate was 39.20 ml/min. The drop in flow after stimulation was statistically significant ($P < 0.001$). While the median value of brachial artery vessel diameter before median nerve stimulation in the entire study group was 3.50 mm, the median value of vessel diameter after stimulation was 2.90 mm. After stimulation, the median nerve diameter narrowed statistically significantly ($P < 0.001$). As for the contralateral brachial in response to the right median nerves' activation, no significant flow or diameter change was found ($P = 0.600$, $P = 0.495$, respectively). **Conclusion:** We discovered that electrical stimulation of the median nerve caused significant changes in ipsilateral brachial artery blood flow and diameter in healthy volunteers. The same stimulation does not result in flow parameter changes in the contralateral brachial artery.

Keywords: Autonomous neuropathy, brachial artery, median nerve, neurophysiology, sympathetic nervous system

INTRODUCTION

Autonomic neuropathies are difficult to test in clinical practice, and a single test is insufficient to measure all autonomic functions. To determine total autonomic function, various tests that quantitatively measure the sudomotor, adrenergic, and cardiovagal systems should be considered together. In 2021, the American Autonomic Society, the American Academy of Neurology, and the International Federation of Clinical Neurophysiology have developed some preference criteria for autonomous tests that will be implemented. As a result, an autonomous test should be sensitive, specific, and reproducible, as well as physiologically and clinically relevant. Noninvasive, no time-consuming, and simple-to-use methods should be preferred.[1] The data of the method we will describe here for the first time mainly measure the sympathetic nervous system response and meet some of the above criteria as it is fast, simple, and noninvasive. Furthermore, by avoiding emotional and mental stress, external manipulations of intra-abdominal and intrathoracic pressure, and uncomfortable situations such as exposure to cold and heat, the reflection of adrenal gland activity to measured values is avoided, as these are false-positive results. Briefly, sympathetic activation is triggered through a specific peripheral nerve in this method rather than systemically.

As is well known, sympathetic nervous system activity causes vasospasm in the medium arteries and a decrease in blood volumetric flow.[2] Arteries are primarily controlled by the sympathetic nervous system, whereas the vasodilator response is provided by local autoregulation mechanisms rather than by parasympathetic nervous system action.[3] However, a parasympathetic nitrergic neuron network has also been discovered in mammals and humans in recent years, but its effectiveness in comparison with the dominancy of sympathetic nervous system is unknown.[4,5]

Some autonomic test-related clinical studies have reported changes in vessel diameters and volumetric flows with sympathetic nervous system activity. Dyson *et al*.[6] discovered that people who underwent a cold pressor test accompanied by Doppler ultrasound had significantly lower brachial artery blood flow than people who did not. Harris *et al*.[7] discovered that subjects' brachial artery diameter decreases during mental stress caused by various mathematical tasks. Similarly, Sinoway *et al*.[8] reported that ice compression reduced the total brachial artery area. Moreover, we have reported elsewhere that electrical stimulation of the median nerve triggers lower

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blood flow and narrower diameter of the ipsilateral brachial artery measured by Doppler ultrasonography.[9]

These findings are also supported by some invasive methods. Badal *et al*.,[10] for example, demonstrated that when the sympathetic nervous system was rendered dysfunctional by median nerve blockade, radial artery blood flow peak velocity increased. Li *et al*.[11] discovered that brachial plexus blockade increased ulnar artery flow. Finally, it has been demonstrated that patients with median nerve damage have impaired sympathetic nervous system control over the arteries. Ghasemi-Esfe *et al*.,[12] for example, demonstrated that in patients with moderate and severe carpal tunnel syndrome, sympathetic innervation of the radialis indicis artery innervated by the median nerve is significantly reduced.

Given this background, measuring sympathetic nervous system activity from a medium-sized artery in the upper extremity, such as brachial artery, which can easily be measured by Doppler in everyday practice, is both logical and physiologically and clinically relevant. However, which upper extremity nerve should be used for sympathetic activation should be determined. Anatomically, upper extremities' postganglionic sympathetic fibers connect to cervical nerve roots, enter the brachial plexus, and then travel to their target organs via various peripheral nerves.[13] Morgan *et al*.[14] discovered that sympathetic fibers in the median nerve were denser than those in the ulnar nerve, particularly at the elbow level, using dark-field fluorescence microscopy. In contrast, Balogh *et al*.[15] claimed that there was no significant difference in the density of sympathetic fibers between the median and ulnar nerves. We have also demonstrated in a neurophysiological study that median and ulnar nerves have a similar impact on brachial arteries' vasomotor response.[16] As a result, using the median nerve for sympathetic activation is consistent with current scientific evidence.

Our main purpose of this study was to measure the brachial arteries' blood flow parameters in response to electrical stimulation of median nerve and to record neurophysiological arterial changes in healthy subjects so that a clinically useful autonomous test model can be developed.

MATERIAL AND METHODS

Subjects: Written consent form was obtained from all participants. The studies conformed to the standards set by the latest version of the Declaration of Helsinki, and the procedures were approved by the Ankara City Hospital No. 2 Clinical Research Ethics Committee (Approval No.: E2-22-1307). The study included people who were active and healthy. Those with known polyneuropathy, autonomic neuropathy, or chronic diseases that may cause autonomic neuropathy (amyloidosis, diabetes mellitus, demyelinating neuropathy, etc.) and those with essential hypertension, heart disease, obesity (body mass index > 30), and peripheral arterial disease were excluded from the study. Those who reported numbness in their hands or feet and those with a history of median nerve traumatic injury or carpal tunnel syndrome were excluded from the study. In suspicious cases, those who had discomfort in their upper extremities, median nerve motor, and sensory conduction studies were performed in the electrophysiology laboratory 24 hours before the autonomic test to determine whether the median nerve was intact or not. Those who had abnormal electrophysiological findings were also excluded.

Experimental Design: The brachial arteries' sympathetic activation was to be measured in the study through electrical stimulation of the median nerve. A model like "sensory nerve conduction study" technique, which is a noninvasive method commonly used in electrophysiology laboratories, was developed for this purpose [Figure 1]. Four hours before the main test, three electrical stimuli were delivered to the median nerve in the left wrist using a bipolar stimulus electrode on the functional direction of the sensory fibers, that is, orthodromically, with an intensity of 10 milliamperes and frequency of 1Hz. An electrical stimulus of this intensity is sufficient to elicit sensory and autonomic responses in the upper extremity, that is, to activate the small fibers. It is, however, a painless and nonirritating dose and has little influence on muscle activity. The first stimulus group given to the volunteers' left wrist is for them to recognize the electrical current. It is hoped that this will prevent emotional and physical stress, as well as exaggerated reactions, from impairing the objective responses to be measured. People who are emotionally or physically sensitive more than expected to low-intensity electrical current were again excluded from the study at this stage. These were one male and two female subjects.

Alcohol, caffeine, thein, and nicotine consumption and exercise are restricted for 4 hours. At the beginning of the main test, blood pressure, heart rate, and body temperature of the subjects were measured, and subjects who had abnormal values are again excluded. These were two male subjects with high blood pressure (>135/85 mmHg). The same bipolar stimulus electrode was then orthodromically placed on the median nerve at the level of the right wrist. The subject was rested for 5 minutes in the sitting position with forearms supinated.

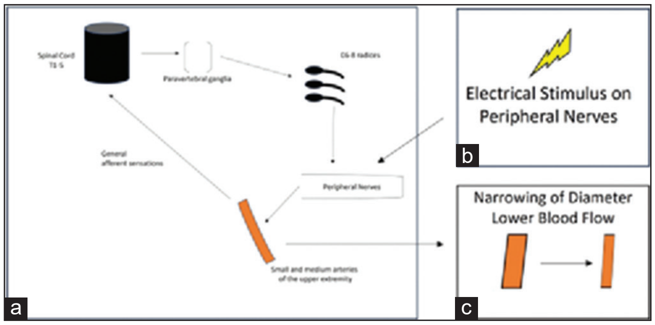

Figure 1: (a) Afferent–efferent circuit of sympathetic innervation of medium- and small-sized arteries of extremities. (b) In this experimental study, electrical stimulus has been applied to efferent peripheral nerves. (c) Electrical stimulus of sympathetic efferents results in narrowing of the peripheral arteries and lower blood flow

The experiment was conducted at a room temperature of 22–24 degrees Celsius. After 5 minutes of rest, the volunteers were instructed to remain as stationary as possible throughout the test, and they were informed at each stage of the procedure (e.g. before the Doppler measurement was taken and before the electrical stimulation was started). The right brachial arteries' baseline diameter and flow were measured using a 9 Hz linear transducer of the General Electric (GE) LOQIC P9 USG Doppler machine from 2 cm superior of the antecubital fossa. These measurements were taken by a radiologist with 8 years of experience in the Doppler field. The imaging was carried out without changing the position of the transducer and while continuously measuring. The right median nerve was then activated by the intensity of 10 mA and frequency of 1 Hz electrical stimulus for 5 seconds, delivered through the bipolar stimulus electrode of the Nihon Kohden MEB-9400A EMG/EP System (five repetitive stimuli in total). Arterial diameter and flow were measured once more with the Doppler transducer, which kept going to monitor continuously just after the fifth stimulus, or at the 5th second [Figure 2].

According to the first observations we made while designing the study, the vasomotor response, ie. reduction in blood flow in the brachial artery, began within the first two seconds, and the reflex vasodilation response reappeared with possible local autoregulation mechanisms from the 20th second. Consequently, it was determined that recording physiological responses in the fifth second and ending the test at this point was rational and sufficient.

After a week, the same subjects are invited for the purpose of measuring the contralateral brachial arteries' vasomotor response in the same stimulation. Hence, electrical stimulation was applied from the right median nerve once again; conversely, the left brachial arteries' baseline and poststimulus flow and diameter values were recorded.

Statistical analysis: For statistical analysis, the Statistical Package for Social Sciences (SPSS) version 25 software was used. Visual (histograms and probability graphs) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk tests) methods were used to assess the variables' conformity to the normal distribution. Correlation coefficients and their significance were calculated using the Spearman test.

Figure 2: Positioning of bipolar stimulator on median nerve and ultrasound probe

Changes in diameter and flow rate were measured as a percentage of baseline values before and after nerve stimulation. When the parametric test assumptions were met, the numerical variables in independent groups were compared using the Student's *t*-test; otherwise, the Mann–Whitney U-test was used. When parametric test assumptions were met, numerical variables in dependent groups were compared using the Student's *t*-test; otherwise, the Wilcoxon test was used. Cases with a type 1 error level of less than 5% were considered statistically significant.

Results

The median age of the 62 volunteers who took part in the study was 28.5 years, with a range of 19 to 61 years. Males make up 54.8% of the participants. The median age for women is 28 and 31 for men; there was no significant difference in age distribution by gender between the groups ($P = 0.254$) [Table 1].

Before stimulation, the median flow rate was 72.15 (52.38–107.93) ml/min; after stimulation, the median flow rate was 39.20 (27.95–54.03) ml/min. The drop in flow after stimulation was statistically significant ($P < 0.001$) [Table 2].

While the median value of brachial artery vessel diameter before median nerve stimulation in the entire study group was 3.50 (3.00–3.80) mm, the median value of vessel diameter after stimulation was 2.90 (2.50–3.30) mm. After stimulation, the median nerve diameter narrowed statistically significantly ($P < 0.001$) [Table 3].

The median absolute change in flow rate after median nerve stimulation was 27.15 (19.70–38.10) ml/min in women and 39.75 (24.80–70.00) ml/min in men. The decrease in flow following stimulation was significantly greater in men than in women ($P = 0.018$) [Table 4].

Table 1: Gender and age distribution of the subjects

	Median	25P	75P	p
Gender				
Female	28,00	23,50	35,50	0,254
Male	31,00	24,00	44,00	

Table 2: Median nerve's pre- and poststimulation flow rates (ml/min)

	N	Median	25P	75P	p
Flow rate before stimulation (ml/min)	62	72,15	52,38	107,93	<0,001
Flow rate after stimulation (ml/min)	62	39,20	27,95	54,03	

When the difference in flow rate after median nerve stimulation is expressed as a percentage compared with the initial value, there is a 47.30 ± 15.04% decrease in females and a 48.07 ± 14.26% decrease in men. There was no statistically significant difference between gender groups ($P = 0.84$) [Table 5].

The median absolute diameter difference between before and after stimulation was 0.65 (0.40–0.95) mm in women and 0.40 (0.30–0.60) mm in men. The decrease in vessel diameter after stimulation was greater in women than in men ($P = 0.024$) [Table 6].

When the change in diameter from the initial value after median nerve stimulation is expressed as a percentage, women have a 19.68% (13.20–31.00) decrease and men have a 10.36% (8.11–15.79) decrease. The percentage decrease in diameter after stimulation compared with the initial vessel diameter was significantly greater in women than in men ($P = 0.001$) [Table 7].

No statistically significant correlation was found between age and flow rate difference and between age and diameter difference [Table 8].

As for the contralateral brachial artery in response to the right median nerves' activation, no significant flow or diameter change was found ($P = 0.600$, $P = 0.495$, respectively) [Table 9].

Discussion

The neurophysiological method, which we describe for the first time in our article, is based on the principle of measuring brachial artery diameter and flow changes combined with an electrically stimulated median nerve [Figures 3 and 4]. These findings are most probably dependent on the activation of sympathetic fibers of the median nerve, since, according to the literature, systemic sympathetic activation also causes similar results in medium and smaller arteries.

Peripheral blood flow is already known to decrease with sympathetic activation and increase with peripheral nerve blockade. However, a test to assess sympathetic nervous system health in clinical practice has yet to be developed based on this mechanism. In this study, we found a statistically significant decrease in brachial artery blood flow and diameter after electrical current in both gender groups. These findings indicate that the test we developed is promising for clinical settings.

Several studies, in some respects similar to our method, have obtained vasomotor responses with electrical stimulus. Mandel *et al*.[17] used electrical stimulation to induce peripheral vasoconstriction in an animal experiment and reported that this method was promising in traumatic acute hemorrhage. Again, Brinton *et al*.[18] were successful in reducing femoral artery flow with an electric current in animal experiments. In a slightly different way, Kezurer *et al*.[19] reported that a vasoconstriction response was obtained using endovascular electrodes. The goal of this research is to effectively stimulate sympathetic nerve endings without causing thermal damage and to develop a new treatment method for hemorrhagic shock.

Moreover, while electrical stimulation of a nerve carrying sympathetic fibers causes peripheral vasoconstriction, activation of a nerve carrying parasympathetic fibers causes increased blood flow in the periphery. Yagi *et al*.[20] discovered that electrical stimulation of the vagal nerve increased

Table 3: Median nerve diameter (mm) before and after stimulation

	N	Median	25P	75P	p
Diameter before stimulation (mm)	62	3,50	3,00	3,80	<0,001
Diameter after stimulation (mm)	62	2,90	2,50	3,30	

Table 4: Flow rate by gender before and after stimulation

	Median	25P	75P	p
Gender				
Female	27,15	19,70	38,10	0,018
Male	39,75	24,80	70,00	

Table 5: Change in flow by gender

	Median	Standard deviation	p
Gender			
Female	47,30	15,04	0,84
Male	48,07	14,26	

Table 6: Diameter difference following stimulation

	Median	25P	75P	p
Gender				
Female	0,65	0,40	0,95	0,024
Male	0,40	0,30	0,60	

Table 7: Change in diameter following stimulation

	Median	25P	75P	p
Gender				
Female	19,68	13,20	31,00	0,001
Male	10,36	8,11	15,79	

Table 8: Correlation between age and flow difference and diameter difference

	Flow difference	Diameter difference
Age		
Spearman's rho	0.221	0.096
p	0.085	0.456
n	62	62

Table 9: Changes in diameter and flow in the contralateral brachial artery before and after stimulation

	Flow before stimulation (n=62)	Flow after stimulation (n=62)	Diameter before stimulation (n=62)	Diameter after stimulation (n=62)
Mean±SD	85.77±46.79	85,68±46.54	0.38±0.06	0.38±0.06
Median (25P-75P)	71.50 (51.75-107.75)	71.50 (51.75-107.75)	0.38 (0.35-0.43)	0.38 (0.35-0.43)
p	0.600		0.495	

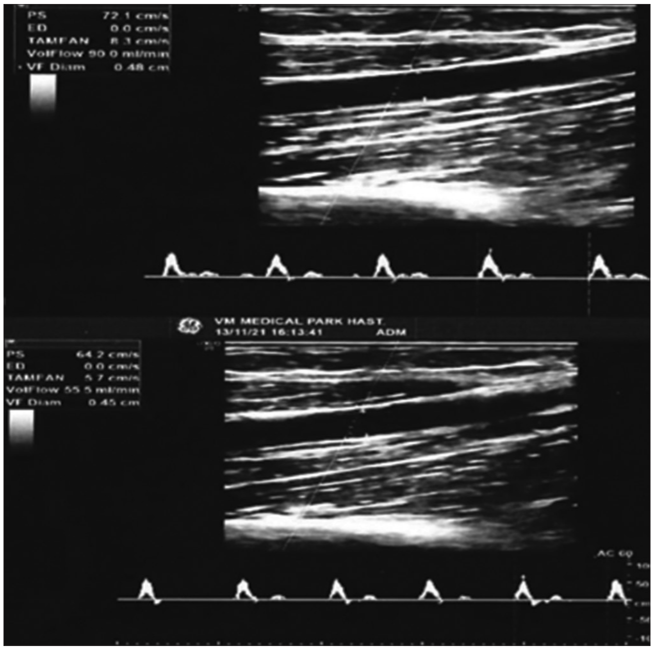

Figure 3: Brachial artery flow rate of a 55-year-old female volunteer participant was 90 ml/min before stimulation and 55 ml/min after stimulation

intestinal blood flow. This was especially evident in trauma and hemorrhagic shock.

The sympathetic skin response (SSR), which surveys the dermal sympathetic sudomotor response secondary to the electrically activated peripheral nerve, has found more widespread use in clinical practice in both autonomic neuropathies and small fiber neuropathies to date. However, it is well known that body temperature and mental stress influence the sympathetic skin response. For this reason, it is extremely difficult to establish test standardization and distinguish between normal and abnormal responses in humans.[21,22] Quantitative sudomotor axon reflex testing (QSART) is another method that measures sudomotor sympathetic activity and employs electrical stimulation. However, there have been reports that the test is not reproducible.[23]

There have also been studies that apply the activation of sympathetic nervous system without using the electrical stimulus. Various studies have found that ice compression reduces peripheral arterial flow[6,8] Such tests, however, are extremely difficult to use routinely in clinical practice since they require both time and finance. Furthermore, adrenal gland activity cannot be ruled out during these warnings and probably has an impact on the results.

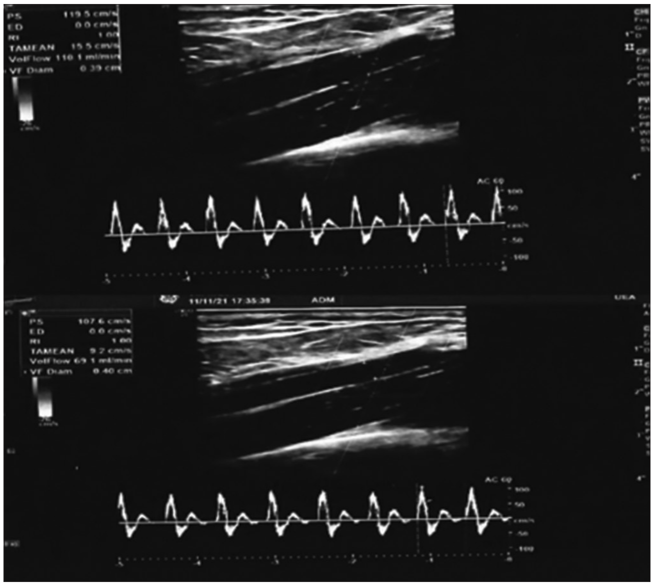

Figure 4: Brachial artery flow rate of a 28-year-old male volunteer participant was 110 ml/min before stimulation and 69 ml/min after stimulation

The brachial arteries' sympathetic activation, however, induces sympathetic activation through a selective peripheral nerve. It can measure sympathetic nervous system activity objectively, irrespective of adrenal gland activity and sudden body maneuvers that may cause blood pressure and heart rhythm changes. Because the procedure is based on measuring the alterations of brachial artery diameter and blood flow after 5 seconds of applying an electrical current to the median nerve, other humoral and environmental factors are unlikely to have an impact on the test results within these first 5 seconds.

The limitation of this study is that it has not been able to draw a framework of normal and abnormal values in humans since no study in patient groups has yet been conducted (e.g. diabetic autonomous polyneuropathy). Investigations that will be expanded to include patient groups will be useful in distinguishing between normal and pathological values.

CONCLUSION

We discovered that electrical stimulation of the median nerve caused significant changes in ipsilateral brachial artery blood flow and diameter in healthy volunteers. The same stimulation does not result in flow parameter changes in contralateral brachial artery.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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