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Adding Doppler Ultrasonography to the Follow-Up of Patients with Vasospastic Disorder Improves Objectivity

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AEF 1 **Kubilay Karabacak**
B 1 **Murat Kadan**
F 1 **Erkan Kaya**
C 2 **Gokhan Erol**
D 1 **Gokhan Arslan**
DG 3 **Murat Celik**
A 1 **Suat Doğanci**
A 1 **Ufuk Demirkilic**

1 Department of Cardiovascular Surgery, Gulhane Military Medical Academy, Ankara, Turkey
2 Department of Cardiovascular Surgery, Maresal Cakmak Military Hospital, Erzurum, Turkey
3 Department of Cardiology, Gulhane Military Medical Academy, Ankara, Turkey

Corresponding Author: Kubilay Karabacak, e-mail: kubilaykarabacak@yahoo.com
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Background: Assessing therapeutic efficacy and patient satisfaction objectively and quantitatively has always been a problem in patients with vasospastic disorders. We aimed to present the additive value of ultrasonographic assessment of peripheral arteries secondary to cold stimulation, as a test for treatment efficacy during follow-up.

Material/Methods: Arterial blood flow rates were measured from radial artery with Doppler USG in patients who presented to our department with vasospastic disorders. Ultrasonography was performed at the following intervals; before cold stimulation and at 5th, 10th, 15th, 20th minutes of cold stimulation. Patients were controlled by repeat cold stimulation test and Doppler US at the 2nd month of the treatment. Results were analyzed with SPSS for Mac 20.0 package program.

Results: We enrolled 46 patients in the study. All patients were male and mean age was 22.3±2.17 years. Most common symptoms were cyanosis and coldness. There were statistically significant differences between pre-treatment and post-treatment arterial blood flow rates at each measurement time point ($p < 0.001$) except initial measurement ($p > 0.05$). On post-treatment values, there were 10.04±0.78 cm/s increase in 5th minute, 6.25±1.39 cm/s in 10th minute, 6.43±2.13 cm/s in 15th minute, and 6.38±1.86 cm/s in 20th minute measurements. All increases at the 5 time points were statistically meaningful when compared to their pre-treatment corresponding time points ($p < 0.001$).

Conclusions: Doppler flowmetry added to standard cold stimulation test for evaluating the patients with vasospastic disorders provides better and more objective results when compared to the patient-oriented subjective scoring systems.

MeSH Keywords: Cold Temperature • Peripheral Vascular Diseases • Ultrasonography, Doppler

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Background

Vasospastic disorder (VD) is a relatively common disorder worldwide population, with a prevalence of 3.3% to 22% [1]. Episodic cyanosis, swelling, and pallor on the distal part of the extremities with cold exposure are the main characteristic features of this disorder. This disorder has female dominance and is especially seen in the 2nd and 3rd decades of life [2]. The disorder can be classified into 2 groups according to underlying etiologic factors. If the pathogenesis depends on an underlying disorder, it is called secondary (obstructive) form. The remaining form without any underlying disorders is called primary form [1,2].

Since the first description of this disorder, several etiologic factors have been reported to be responsible for the pathogenesis, but it is still not well known, and every possible etiologic factor is still controversial. In addition, no objective, quantitative diagnostic tool or objective follow-up method has been defined [3].

In this study, we aimed to answer the question “Can Doppler ultrasonography be used for objective follow-up of patients with vasospastic disorder?”

Material and Methods

This is a retrospective study, approved by the local ethics committee of Gulhane Military Academy of Medicine. We aimed to describe a quantitative method for the follow-up of patients with vasospastic disorder.

Patient's selection

Between April 2011 and October 2013, data were collected from files of 46 patients with the diagnosis of vasospastic disorder lasting more than 2 years. The diagnostic criteria, which were defined by Wigley et al. [4], were used as diagnostic criteria for the enrolled patients. Several etiologic disorders such as systemic sclerosis and SLE, which can cause secondary vasospastic disorder, were excluded, with detailed physical examination and several laboratory findings. After detailed examination, we only included the patients with primary vasospastic disorder. Demographic data and additional risk factors of patients were recorded.

Cold stimulation test

In our department, the cold stimulation test (CST) is routinely performed to all patients with vasospastic disorders symptomatology due to our national and military regulations. According to our protocol, application of the CST is as follows: 1. Hand

temperatures of the patients are measured with a probe, which is inserted between the pulp of first and second distal phalanges. At the same time, radial arterial blood flow rate is measured at the level of wrist by Doppler USG (detailed below). 2. The most affected hand is immersed into the iced-water at 4°C for 20 seconds. 3. After drying the hands, the temperature and the blood flow rate of the radial artery are measured again at the 5th, 10th, 15th and 20th minutes, with the same technique detailed before. 4. The rewarming time to initial temperature is also recorded. The test is performed after resting at room temperature (approximately 26°C) for at least 30 minutes. Patients are classified according to their smoking habits, but a standardized protocol about timing of refraining from tobacco prior to testing was not used. The Sonatemp™ 400/700 Monitor (Sheridan Catheter Corp. Argyle, NY, USA) device was used for temperature measurements.

In addition to CST, we routinely use a scale (verbal complaint severity scale, VCSS), which is used by our department for evaluating the progress in the follow-up period. In this scale, a physician asks all of the patients about their symptoms for determining their progress. The scale is detailed in Table 1.

Doppler ultrasonography

Simultaneously with CST, patients' radial arterial blood flow rate was measured at the level of the wrist. For this measurement, a 12-MHz linear probe was used. Radial arterial blood flow velocity was calculated at the level of the wrist on color Doppler ultrasonography (Figure 1). LOGIQ Book XP scanner (GE Medical Systems, USA) is used as the Doppler USG device.

Treatment

In our clinic, we routinely use a combination therapy for vasospastic disorders for a 2-month period. This combination includes pentoxifylline 1200 mg/d bid (2×600 mg) as a vasodilator molecule, nifedipine 60 mg/d bid (2×30 mg) as a calcium-channel blocker, and acetylsalicylic acid 300 mg/d (1×300 mg) as an antiplatelet agent. After 2 months, we evaluate all patients again to observe their progress. After the second evaluation, patients who do not respond to treatment are referred to interventional treatment methods, or they are not allowed to continue their military duties.

Study protocol

Demographic data, co-morbid disorders, VCSS, and blood flow rates of the included patients at pre-treatment and post-treatment period were all recorded. Patients' arterial blood pressures were also recorded during cold stimulation test. After data collection, the results were compared.

Table 1. Verbal complaint severity scale.

Verbal Complaint Severity Scale	Definition
I	Symptoms start with cold exposure, and stop with cessation of cold exposure
II	Symptoms start with cold exposure, but not stop cessation of cold exposure, rewarming is almost necessary
III	Symptoms start with cold exposure, course with painful swelling and movement restriction. Rewarming is mandatory, and usually extended up to 30 minutes



Figure 1. Ultrasonographic measurement technique.

Statistical analysis

SPSS for Mac 20.0 package program (SPSS Inc, Chicago, IL) was used for statistical evaluation. Descriptive results are expressed as mean ± standard deviation for normally distributed continuous variables and median values for abnormally distributed continuous variables. Categorical variables are reported as numbers and percentages. Before analyses, the Kolmogorov-Smirnov test was used for analyzing the distribution pattern of data. Comparisons of the parametric values were performed with Student t test for normally distributed groups and with Mann-Whitney U test and Wilcoxon signed ranks test with abnormally distributed groups. Pearson’s chi-square test, Fisher’s exact test, and McNemar-Bowker test were used for the comparisons of categorical variables.

A p value of <0.05 was considered as statistically significant with a 95% confidence interval.

Table 2. Demographic data of patients.

Age (year)	22.3±2.12 (20–29)
Gender (male/female)	46/0
Smoking (n)	32
Co-morbidity (n)	
Hypertension	0
Diabetes mellitus	0
Renal insufficiency	0
Vasculitis	0
COLD	0
Other	0
Symptoms	
Cyanosis (n, %)	34 (73.9%)
Numbness (n, %)	30 (65.2%)
Hyperhidrosis (n, %)	29 (63.0%)
Hand swelling (n, %)	18 (39.1%)
Pain (n, %)	1 (2.2%)
Duration of symptoms (year)	4.39±2.68

Results

Patients’ characteristics

In Turkey, military service is mandatory for every male aged 20 years. Therefore, all the study population was young males; 32 of the patients (69.5%) were smokers and 14 of these 32 patients were smokers for more than 10 years. None of the patients had co-morbid disorders such as hypertension or diabetes mellitus. The most common complaints were cyanosis (34 patients, 73.9%), numbness (30 patients, 65.2%), and hyperhidrosis (29 patients, 63%).

Mean duration of symptoms from onset to present was 4.39±2.68 years. There were no treatment-related adverse effects. Demographic data of patients are given in Table 2.

Table 3. Verbal complaint severity scale distribution of patients.

Verbal Complaint Severity Scale	Before treatment		After treatment		p value
	n	%	n	%	
I	11	23.9	10	21.7	0,223
II	31	67.4	34	73.9	
III	4	8.7	2	4.3	

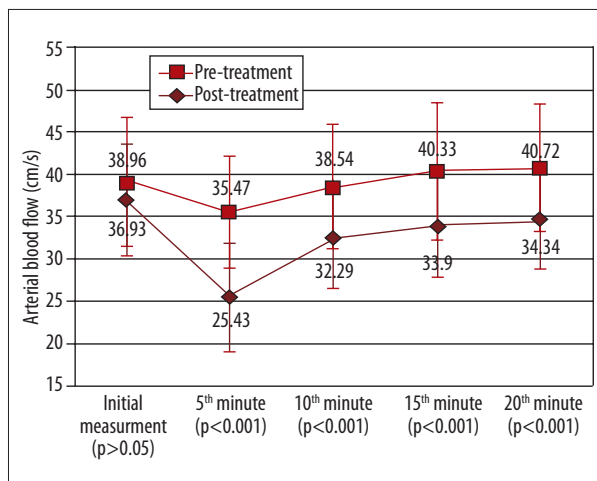


Figure 2. Changes of the blood flow rates during cold stimulation test.

Verbal complaint severity scale

Patients were categorized into 3 groups according to VCSS. There were no statistically significant differences in patient VCSS distribution. Distribution of patient VCSS is given in Table 3.

Ultrasonographic data

There was a significant decrease in arterial blood flow after cold exposure in both pre-treatment and post-treatment measurements. In the rewarming period, flow rate did not reach its basal values over the test time (20 minutes) in pre-treatment measurements, but it reached its basal value by approximately 10 minute in post-treatment measurements. The changes of arterial blood flow rates during the CST are given in Figure 2.

There were statistically significant differences between pre-treatment and post-treatment arterial blood flow rates at each measurement time points ($p<0.001$) except initial measurement ($p>0.05$). On post-treatment values, there were 10.04 ± 0.78 cm/s increase in the 5th minute, 6.25 ± 1.39 cm/s in 10th minute, 6.43 ± 2.13 cm/s in 15th minute, and 6.38 ± 1.86 cm/s in 20th minute measurements. All increases at the 5 time points were statistically meaningful when compared to their pre-treatment corresponding time points ($p<0.001$).

Discussion

Several diagnostic methods and invasive and non-invasive techniques were defined for the diagnosis of vasospastic disorders over time. However, no definitive diagnostic tool or objective and quantitative follow-up method has been defined [5]. The main cause of this failure is the complexity of the etiopathogenesis, which is still unclear.

Patients' symptoms subjectivity is the other possible reason for this diagnostic problem. Most patients usually complain of many subjective symptoms such as cyanosis, numbness, or painful attacks, which are often aggravated by cold exposure [6]. Therefore, objective diagnosis of primary vasospastic disorders is often not possible.

To address this diagnostic problem, several tools (e.g., triphasic color changes of hands, finger systolic blood pressure, finger-brachial index, plethysmography, capillaroscopy, and rarely, more invasive techniques) were used in the history of treating this disorder [2,3,7]. Unfortunately, most of these diagnostic tools require special conditions – special technicians, devices, and sometimes laboratory conditions – that cannot be used in outpatient conditions. It is also too hard to use these techniques in follow-up, even if they could be used for diagnosis [8].

Assessment of treatment efficacy in the follow-up period is another therapeutic controversy. This mainly depends on subjectivity of patients' symptoms. Most patients with vasospastic disorders consider their treatments as ineffective regardless of their types. However, for evaluating patient progress, objective, quantitative, and easily performed tests are necessary.

CST and its application method are still not standardized worldwide and there are few studies about this method in the literature. We have used our clinical protocol, as detailed above, for approximately 3 years [3]. Toprak et al. used 5°C water for cold stimulation in their study and they declared that this temperature is better for provoking the vasospasm than water at 10°C [9]. Therefore, we routinely used 4°C ice-water for provoking the vasospasm, as in our present study.

In the literature there are few studies about cold stimulation and its effect on ultrasonographic arterial blood flow rates. Most of these studies are focused on the differential diagnosis of the primary form vs. secondary form by using Doppler ultrasonography [9–11]. There have been no studies on its usefulness as a marker of treatment efficacy in the follow-up period. We consider that our present study is the first in this area.

When we analyzed the ultrasonographic parameters of our study, we observed different patterns of blood flow rates. In pre-treatment measurements, flow rates were not able to reach their basal value throughout the test, which suggests that vasospasm lasts longer. In contrast, in the post-treatment tests, flow rates increased quickly to their baseline values by approximately just 10 minutes. In addition, different from the pre-treatment test, flow rates were above baseline values at the 15th minute measurements, which suggests that vasospasm lasts less than the 15 minutes.

In our department, we use the verbal complaint severity scale (VCSS) for classification of disease severity. In our study population, despite the given treatment modality, there were no statistically significant changes in patient VCSS. Three patients changed their VCSS throughout the study. When we analyzed these 3 patients and compared their CST results independent from the study group, we found that there were no statistically significant differences between ultrasonographic flow rates before and after treatment ($p>0.05$). In this regard,

ultrasonographic flow rate measurements added to CST in our study seem to be helpful for follow-up of patients with VD, both quantitatively and objectively.

Conclusions

Doppler flowmetry added to standard cold stimulation test for evaluating patients with vasospastic disorders provides better and more objective results when compared to patient-oriented subjective scoring systems.

Study limitations

This study was performed in a military hospital; therefore, all of the patients were male. For this reason, it may be difficult to generalize our results to women. The smoking time, smoking cessation time, or the correlation between smoking habits and study protocol were not detailed in this study. More studies in these subgroups may be performed later on this topic. The significant cut-off value of ultrasonographic blood flow rate changes (positive or negative) is not well known and was not defined in this study. To define clear-cut values of this parameter, we need to perform studies with larger populations.

Disclosure statements

The authors declared that they have no conflicts of interest.

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