Original Article

Evaluation of Cerebral Blood Flow Alterations and Acute Neuronal Damage due to the Water Pipe Smoking

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Background: Although water pipe smoking is a great public health problem, data regarding the acute and chronic effects and the degree of toxin exposure are limited. While water pipe-related malignancy, pulmonary, infectious, cardiac effects, infertility and biological effects have been described in a meta-analysis, there are no studies in the literature about its neurologic effects.
Aims: To evaluate water pipe-related acute neurological effects and cerebral blood flow through transcranial doppler ultrasonography and serum s100b protein level measurements.
Study Design: Prospective observational study.
Methods: Vital signs and baseline carboxyhemoglobin (COHb) and S100b levels, cerebral flood changes with Transcranial Doppler Ultrasound were evaluated and recorded before and after water-pipe smoking.
Results: The mean age of the 31 volunteers was 30,61 (±5,67) years and 24 of them (77,42%) were male. A statistically significant difference was determined in heart rate, oxygen saturation, systolic and diastolic arterial pressure values before and after water pipe smoking ($p<0,001$, $p=0,035$, $p=0,009$, $p=0,021$, respectively). Mean COHb level was 2,68 % (±1,68) before, 14,97 % (±4,83) after water pipe smoking ($p<0,001$). The S100b protein level was 25,05 μ/ml (±8,34) at the beginning, 40,71 μ/ml (±14,06) after water pipe smoking ($p<0,001$). An increase was determined in peak and median middle, anterior and posterior cerebrale artery blood flow rates, and a decrease was determined in the pulsatility index and resistivity index values after water pipe smoking through transcranial Doppler ultrasound.
Conclusion: Cerebral vasodilation develops due to the increase in cerebral blood flow rate and the decrease in pulsatility index, resistivity index values, and the elevation in COHb, S100b level indicates that water pipe smoking leads to neuron damage in the acute period.
Keywords: Water pipe, cerebral blood flow, transcranial doppler ultrasound, carbon monoxide, S100b protein

Water pipe (also known as hookah, sisha) is a traditional tobacco type, which has been used for more than 400 years. While it is widely used in Middle East countries, its use is gradually increasing among adolescents and young adults worldwide, mainly in the United States, Brazil, Europe (1). In a study conducted in the United States, 7.2% of young adolescents were found to have used water pipe during the last one month and 29.5% of these adolescents were determined to have used water pipe at least once during their lives (2). The main causes of this condition include its being interesting due to its structure and mechanism, the belief that it is less toxic than cigarettes due to the absence of direct tobacco exposure, and the smoke and the toxic substances being eliminated through water. Water pipe smoking is increasing today due to this belief. However, studies have indicated that subjects are exposed to more toxins than cigarette smoking and toxic exposure from the water pipe is equal to 100 cigarettes (3).
Although it is a great public health problem, the degree of toxin exposure and acute/chronic effects are limited. While water pipe-related malignancy, pulmonary, infectious, cardiac effects, infertility and biological effects

have been described in a meta-analysis (4), there are no studies in the literature about its neurologic effects. However, the neurological effects such as syncope, dizziness and headache are common among water pipe smokers (5,6). These symptoms were reported to result from elevated carbon monoxide level; however, there is insufficient data in the literature about acute brain damage and changes in cerebral blood flow.

Transcranial doppler ultrasonography is a non-invasive conventional method that does not lead to radiation exposure, and is used for detection of cerebral blood flow alterations. The potential risk of long-term cerebral effects may be determined through measuring the anterior, middle and posterior cerebral artery blood flow velocities. Water pipe smokers are subjected to an ample amount of toxic substances and the acute effects of these substances on central nervous system are not known. In particular, elevated carbon monoxide-related neurological symptoms are in the foreground; the carbon monoxide level can be measured with non-invasive tests. However, its measurement alone is not sufficient for determining the direct relationship between neurological effects and chronic effects; the correlation between the carboxyhemoglobin (COHb) level and the severity of intoxication has been reported to be limited and that it cannot be used as a neurological sequel marker (7). Therefore, different biochemical markers are required. The S100 calcium binding protein B (S100b) was reported to be able to be used as an independent marker for detection of acute injury in different patient groups (8).

The aim of the present study was to evaluate water pipe-related acute neurological effects and cerebral blood flow through transcranial doppler ultrasonography and serum S100b protein level measurements.

MATERIAL AND METHOD

Study design

This prospective observational study was conducted with healthy volunteers at a hookah cafe. Ethics committee approval was obtained from local ethics committee. The study was conducted in accordance with the Helsinki Declaration. Written and verbal informed consent was obtained from all participants prior to the study.

Volunteer population

The study was conducted with healthy volunteers who had gone to the hookah cafe, and who did not have an acute or chronic disease. No pressure was placed onto the participants for water pipe smoking; the potential harmful effects of water pipe smoking were explained verbally and in written form. Volunteers who had decided to smoke water pipe despite all warnings were included in the study. Volunteers under 18 years of age, pregnant women, volunteers who had coronary artery disease or disorders that could affect the cerebral blood flow such as ischemic stroke, A-V malformation, history of meningitis or central nervous system disease, those with history of intracranial surgery, those who were using anti-arrhythmic drugs, anti-hypertensive, anti-epileptic, hypnotic-sedative drugs; who had the history of alcohol, narcotics or substance use, those who smoked water pipe for shorter than 45 min, those who had a history of water pipe smoking during the recent 24 hours and who did not agree to participate were excluded from the study.

Study protocol

The participants who agreed for participation were taken to a closed room in the café before water pipe smoking. Age, gender, history of smoking or water pipe were questioned. The basal heart rate, oxygen saturation, blood pressure of systolic, and the diastolic were measured and recorded. The baseline COHb was measured using the non-invasive Masimo Root Rainbow Set (Masimo Rainbow SET Radical-7 Pulse CO-Oximeter, Masimo Corp., Irvine, CA) device. After the basal measurements, the volunteers rested for 5 minutes in the sitting position and transcranial doppler ultrasonography measurements were made from the temporal window. 5 ml of venous blood was placed into an EDTA tube for S100b protein measurement and stored at 4 °C in the refrigerator before second blood samples were taken.

The volunteers were taken to an open area after baseline measurements and re-evaluated after 45 minutes of water pipe smoking. Presence of symptoms like headache, dizziness, nausea, vomiting, syncope, palpitation and dyspnea were questioned. The volunteers were taken to the closed room again after 45 minutes of water pipe smoking, and vital signs, oxygen saturation and non-invasive COHb levels were measured with the same device again. After the measurements, transcranial doppler ultrasonography measurements were made again after the vital measurements. 5 ml of venous blood was drawn from peripheral blood into an EDTA tube one hour after the first blood test. All blood samples were transferred to the hospital in blood transfer bags within 30 minutes. The samples were stored at -80 °C after centrifugation. After the study had been completed, all blood samples were examined for S100b in the Elisa device using the S100b Elisa (S100b human serum or plasma) kit.

Ultrasonography measurement

All transcranial doppler ultrasonography examinations were performed by a single interventional neurologist with 10 years experience using the transcranial doppler ultrasonography device (DWL, MDT-2036, Germany). The transcranial doppler ultrasonography examination is performed using a 2 MHz frequency ultrasound probe. The measurements were made from the temporal window when the volunteers were in the seated position. The right and the left Anterior Carotid Artery, Middle Cerebral Artery, Posterior Cerebral Artery peak systolic flow rate, mean flow rate, pulsatility index (PI) and resistivity index (RI) measurements were made from the temporal window after the patient had been positioned before water pipe smoking (Figure 1). The volunteers were taken to

the closed area after 45 minutes of water pipe smoking and the same measurements were made and recorded again (Figure 2).
Internal carotid artery bifurcation can be founded at 55 to 65 mm depth and identified by the current away from the probe. Internal carotid artery bifurcation continues as anterior and middle cerebral artery and also an important anatomic marker for locating the anterior circulation. Middle cerebral artery extends laterally and slightly anteriorly from the internal carotid artery root at a depth of 35-55 mm. The middle cerebral artery should be accurate until the trifurcation where the downstream flow becomes bidirectional. The anterior carotid artery, which can be seen at a depth of 60-70 mm, extends medial and anteriorly after the internal carotid artery bifurcation. The anterior carotid artery blood flow is visible at the proximal position. The posterior cerebral artery is displayed in the transtemporal window and usually located 1-2 cm posterior to the internal carotid artery bifurcation in the same plane as the wills polygon. Posterior cerebral artery, internal carotid artery and middle cerebral artery posterior and 60-70 mm deep. Flow towards the probe in the proximal posterior cerebral artery (P1 segment) and away from the probe in the distal posterior cerebral artery (P2 segment) (9).

STATISTICAL ANALYSES

Statistical analyses were performed using SPSS 15.0 (Chicago, IL). The Shapiro-Wilk test was used to assess the normal distribution of the variables. Non-parametric data were expressed as numbers, percentages, median values and min-max values, and parametric data were expressed as means and standard deviations (SDs). Non-parametric categorical parameters were analyzed using the Chi-square test, and non-parametric dependent ordinal parameters were analyzed using the Wilcoxon test. Dependent parametric data were analyzed using the Paired t-test. Paired t -tests were used to estimate the significance of differences in blood flow velocities, PI and blood pressure before and after water pipe smoking. Whenever appropriate, 95% confidence intervals were also calculated, and a p value less than 0.05 was considered statistically significant.

RESULTS

During study period 31 volunteers were included and evaluated. The mean age of the volunteers was 30,61 (±5,67) years and 24 of them (77,42%) were male. While 17 volunteers (58.84%) had a history of smoking, 14 volunteers (45.16%) had a history of regular water pipe smoking. Once the symptoms after water pipe smoking were analyzed, 18 volunteers (58.1%) were observed to have no symptoms, 9 volunteers (29%) had headache, 3 of them (9.7%) had dizziness, and 1 of them (3.2%) had dyspnea.
The heart rate, oxygen saturation, systolic and diastolic arterial pressure values before and after water pipe smoking have been summarized in Table 1. A statistically significant difference was determined in all parameters (p<0,001, p=0,035, p=0,009, p=0,021, respectively). Mean COHb level was 2,68 % (±1,68) before and 14,97 % (±4,83) after water pipe smoking. The water pipe smoking-related changes of COHb were statistically significant (p<0,001) (Table 1). The S100b protein level was 25,05 μ/ml (±8,34) at the beginning and 40,71 μ/ml (±14,06) after water pipe smoking. A statistically significant difference was determined in S100b protein after water pipe smoking (p<0.001) (Table 1). When the relationship between the S100b protein values of the subjects who smoked water pipe regularly and for the first time were analyzed, it was determined as 24,76 μ/ml (±8,19) in subjects who regularly smoked water pipe and 25,28 μ/ml (±8,7) in subjects who smoked it for the first time. No statistically significant difference was determined between the subjects who regularly smoked water pipe and subjects who smoked it for the first time with regard to the baseline S100b protein levels (p=0.875). When the S100b protein level alterations were analyzed before and after water pipe smoking, the increase in the S100b protein levels was 19,57 μ/ml (±13,5) in subjects who smoked water pipe chronically and 12,69 μ/ml (±6,48) in subjects who smoked for the first time. No statistically significant difference was determined between the two groups (p=0.085). While the mean baseline COHb level was 3,12 % (±1,83), S100b protein level was 27,04 μ/ml (±6,71) in smoking volunteers; these values were 2,14 (±1,35) and 22,64 μ/ml (±9,68) in non-smokers. No statistically significant difference was determined between smokers and non-smokers with regard to the baseline COHb and S100b levels (p=0,415, p=0,463, respectively).
The peak systolic flow rate anterior carotid artery, middle cerebral artery and posterior cerebral artery, and the mean flow rate, PI and RI values of volunteers have been summarized in Table 2. An increase was determined in the left and the right in peak and mean middle cerebral artery, anterior cerebral artery and posterior cerebral artery blood flow rates, and a decrease was determined in the PI and RI values after water pipe smoking. A statistically significant difference was determined in all measurements, except for the average left middle cerebral artery (p=0,072), left anterior cerebral artery PI (p=0,137) and left anterior cerebral artery RI (p=0,085) values. The mean transcranial doppler ultrasonography measurement values before and after water pipe smoking and the p values have been presented in Table 2. No statistically significant difference was determined between chronic cigarette or water pipe smokers and subjects who smoked for the first time with regard to baseline peak systolic flow rate, mean blood flow rates and PI and RI values (p=0,242, p=0,105, respectively).

DISCUSSION

Our study has revealed an increase in carbon monoxide level, heart rate, systolic and diastolic blood pressure and a decrease in oxygen saturation due to water pipe smoking. While water pipe smoking was found to lead to an increase in peak and mean anterior carotid artery, middle cerebral artery and posterior cerebral artery blood flow rates, it was observed to lead to a decrease in PI and RI values. A statistically significant increase was determined in S100b protein levels, which is used for detection of water pipe-related cerebral injury.

Water pipe smoking was shown to lead to an increase in systolic blood pressure, diastolic blood pressure and heart rate (10,11). A mean 45 min of water pipe smoking was shown to lead to a 6 bpm increase in heart rate (12), 16 bpm increase in heart rate, 6,7 mmHg increase in systolic blood pressure and 4,4 mmHg increase in diastolic blood pressure (13). The results of our study are similar to those of the literature; oxygen saturation was also observed to decrease in the volunteers. We consider that the reduction in oxygen saturation results from hypoxia. These hemodynamic changes are considered to result from the elevated nicotine level leading to an increase in nor-epinephrine, epinephrine and vasopressin or through its direct effect on endothelium and sympathetic nervous system activation.

A previous studies have shown positive correlation between water pipe smoking and the COHb level. In the study of Zahran et al. (14) conducted with 1832 volunteers who chronically smoked cigarettes and water pipe; the COHb level was shown as 6,47 ± 2,7 among cigarette smokers and 10,06 ± 2,5 in water pipe smokers. Al-Moamarly et al. (15) reported a 30% increase in the COHb level after water pipe smoking compared to healthy volunteers; Levant et al. (16) found this value as 20,8% and Yildirim et al. (17) determined this level as 23.7 % (minimum-maximum:6-44). Long-term inhalation of the smoke of the coal used for firing the tobacco in hookah prepared with conventional methods leads to an increase in COHb levels. Patients presenting to the emergency room due to COHb elevation-related symptoms such as headache, nausea, vomiting, dizziness, seizures and syncope have been reported in the literature (18,19). Similarly, a statistically significant elevation of COHb and related neurological symptoms were detected among subjects who smoked water pipe in our study.

Transcranial doppler ultrasonography is the most common non-invasive method for assessment of the cerebral blood flow. Smoking-related cerebral blood flow alterations have been reported in the literature despite the absence of studies about water pipe smoking. Varying degrees of distal blood flow increase were shown in intracranial vessels (anterior carotid artery, middle cerebral artery, posterior cerebral artery), and a decrease was shown in PI and RI as a result of smoking a single cigarette (20). In the posterior cerebral artery and middle cerebral artery the end diastolic volume increased (%7,8 in posterior cerebral artery, %14,4 in the middle cerebral artery) and peak systolic volume has been increased in anterior carotid artery (%1,1) and in middle cerebral artery (%7,5). Average rising end diastolic volume (%14) in the middle cerebral artery is more over than peak sistolic volume (%7,5). Pulsatility index of middle cerebral artery decreased at the same time. These results show that smoking causes reduces in vasculer resistance and rises cerebral blood flow. Cardiac output directly effected peak sistolic volume but end diastolic volume is thought to increased with peripheral vasculer resistance decrease. (21). The increase in peak sistolic volume in our participants after smoking showed that cigarette smoking increased cardiac output and that combined with low impedance indices should support cerebral blood flow. This result is supported by the fact that both blood pressure and heart rate have increased in our participants after smoking. The increase in blood pressure and the decrease in PI and RI values were reported to have a potential to play a role in chronic diseases like hypertensive encephalopathy and Alzheimer's disease in the long term due to vascular resistance (22). In our study, an increase was determined in the peak systolic and end diastolic blood flow rate, and a decrease was determined in the PI and RI values. In general, our results show that the immediate effects of cigarette smoking are reduced cardiac output by reducing peripheral cerebrovascular impedance and possibly promoting vasospasm of the middle cerebral artery and / or other basal cerebral arteries.

S100b protein is widely available in high concentrations in astroglial cells and white matter besides being produced in Schwann cells and peripheral nerve cells. S100b protein rapidly transfers to the cerebrospinal fluid and secondarily to the circulation if these cells are damaged and blood-brain barrier is impaired. S100b protein is reported to be effective for prediction of neurological brain damage, which may develop in hypoxic brain damage (23). S100b protein is recommended for rapid detection of neuronal damage resulting from traumatic brain damage, stroke or subarachnoid hemorrhage, synthetic cannabinoid use (24-27). Carbon monoxide elevation-related brain damage is assumed to develop secondary to hypoxia. However, inflammation and oxidative stress may also lead to neuron damage (7). In our study, the S100b protein level was observed to significantly increase due to water pipe smoking. The absence of a significant difference between chronic cigarette or water pipe smokers and the subjects who smoke for the first time with regard to COHb and S100b protein level has indicated that the effect is acute, and not associated with chronic use. Although no studies are available in the literature investigating water pipe smoking-related neurological damage, neuronal damage

develops due to indirect carbon monoxide elevation. Carcinogenic aromatic hydrocarbon, nitric oxide and nicotine may also lead to neuronal damage through oxidative stress. Despite the limited number of studies about oxidative stress, we consider that toxic substances in hookah may act through a similar way as with cigarettes, based on the study of Golbidi et al. (28) investigating the effects of smoking on oxidative stress.

LIMITATIONS

Our study was a single center study conducted with a small number of volunteers; furthermore, the small number of female subjects and narrow age range led to a limitation for making a general conclusion. The study group was not distributed homogenously due to the history of smoking cigarette or water pipe in a portion of the volunteers. However, we consider that this limitation is not significant as there was no significant difference between the smoking and the non-smoking groups, and the subjects who had a history of water pipe smoking and who smoked water pipe for the first time with regard to baseline COHb and s100b protein levels. Although all volunteer groups constantly smoked water pipe for 45 minutes, the duration, number and depth of inhalations were not constant. However, an increase was determined in the COHb and S100b protein levels, an increase in cerebral blood flow, and a decrease was determined in PI and RI values compared to baseline values.

CONCLUSION

While water pipe smoking is an important public health problem, and it is believed to be less toxic than cigarette. Many neurological symptoms may develop due to water pipe smoking, and we consider that these symptoms develop due to the elevation in the COHb level. Cerebral vasodilation develops due to the increase in cerebral blood flow rate and the decrease in PI and RI values, and the elevation in S100b level indicates that water pipe smoking leads to neuron damage in the acute period. We consider that progressive and chronic effects may develop in volunteers in the long term due to progressive neuron damage and decreased vascular resistance. Therefore, we believe that all government and civil society organizations should direct the same efforts against smoking narghile as they do against smoking cigarettes in the past.

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Table 1. Characteristics of vital signs, COHB levels and S100b levels on before and after water pipe smoking

	5 Minutes Before Water Pipe Smoking	45 Minutes After Water Pipe Smoking	P Value
Sistolic blood pressure (mmHg) Med (Min-Max)	110 (80-140)	120-(90-150)	0,009
Diastolic blood pressure (mmHg) Med (Min-Max)	70 (50-80)	80-(60-110)	0,021
Heart Rate (beat/minute) Med (Min-Max)	82 (58-102)	98 (67-121)	<0,001
SPO_2 (%) Med (Min-Max)	99 (96-100)	97 (89-99)	0,035
COHB (%) Med (Min-Max)	3 (0-6)	14 (9-26)	0,001
S100b (μ/ml) Med (Min-Max)	22,3 (7,28-48,72)	36,8 (15,19-68,67)	<0,001

Med:Median , COHB: Carboxyhemoglobin, Min: Minimum, Max: Maximum

TABLE 2. Transcranial Doppler Measurement Before And After Water Pipe Smoking				
	5 Minutes Before Water Pipe Smoking Med, (Min-Max)	45 Minutes After Water Pipe Smoking Med, (Min-Max)	95% CI	p
Right Middle Cerebrale Artery				
Peak SFR cm/s	85 (58-114)	99 (58-156)	[(-24,26) - (-6,06)]	0,002
Average cm/s	55 (42-80)	67 (34-110)	[(-19,44) - (-3,72)]	0,005
Pulsatility index	0,9 (0,64-1,45)	0,8 (0,42-1,2)	[(0,04) - (0,22)]	0,006
Resistivity index	0,6 (0,44-1,6)	0,57 (0,21-0,77)	[(0,04) - (0,23)]	0,007
Right Anterior Cerebrale Artery				
Peak SFR cm/s	76 (55-130)	89 (51-41)	[(-21,08) - (-1,76)]	0,022
Average cm/s	56 (35-98)	64 (28-123)	[(-19,66) - (-2,99)]	0,009
Pulsatility index	1 (0,7-1,58)	0,83 (0,48-1,48)	[(0,04) - (0,28)]	0,012
Resistivity index	0,66 (0,51-1,3)	0,58 (0,36-0,82)	[(0,07) - (0,24)]	0,001
Right Posterior Cerebrale Artery				
Peak SFR cm/s	55 (29-122)	71 (32-120)	[(-25,26) - (-9,32)]	<0,001
Average cm/s	38 (21-98)	46 (21-112)	[(-21,97) - (-8,61)]	<0,001
Pulsatility index	0,98 (0,75-2)	0,76 (0,45-1,8)	[(0,11) - (0,37)]	0,001
Resistivity index	0,7 (0,5-1,1)	0,54 (0,32-0,9)	[(0,09) - (0,23)]	<0,001
Left Middle Cerebrale Artery				
Peak SFR cm/s	99 (52-144)	110 (58-150)	[(-22,45) - (-0,64)]	0,039
Average cm/s	67 (29-104)	79 (34-123)	[(-18,3) - (0,82)]	0,072
Pulsatility index	0,9 (0,6-1,3)	0,76 (0,45-1,2)	[(0,01) - (0,23)]	0,028
Resistivity index	0,58 (0,4-1,2)	0,56 (0,31-0,69)	[(0,03) - (0,2)]	0,007
Left Anterior Cerebrale Artery				
Peak SFR cm/s	79 (50-108)	99 (44-157)	[(-30,98) - (-9,99)]	<0,001
Average cm/s	53 (31-90)	74 (20-118)	[(-25,24) - (-7,28)]	0,001
Pulsatility index	0,9 (0,6-1,4)	0,82 (0,45-1,6)	[(-0,03) - (0,21)]	0,137
Resistivity index	0,63 (0,46-1)	0,58 (0,31-1)	[(-0,01) - (0,16)]	0,085
Left Posterior Cerebrale Artery				
Peak SFR cm/s	64 (30-105)	73 (31-136)	[(-22,24) - (-3,37)]	0,009
Average cm/s	41 (16-88)	51 (21-116)	[(-20,44) - (-3,31)]	0,008
Pulsatility index	0,98 (0,7-2,13)	0,83 (0,45-1,9)	[(0,06) - (0,34)]	0,006
Resistivity index	0,73 (0,5-1,2)	0,56 (0,42-0,78)	[(0,09) - (0,23)]	<0,001
Peak SFR: peak systolic flow rate, Med: Median, Min: Minimum, Max: Maximum, CI: Confidence interval cm/s:centimeter/second				

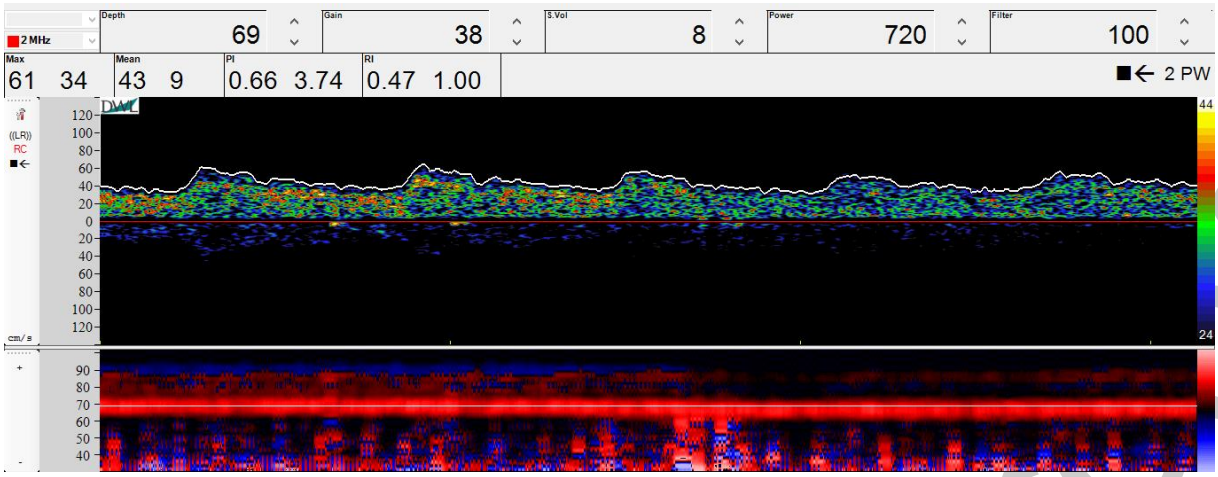

Figure 1. An example of transcranial doppler ultrasound in the target vessel before water pipe smoking (flow analysis in right MCA)

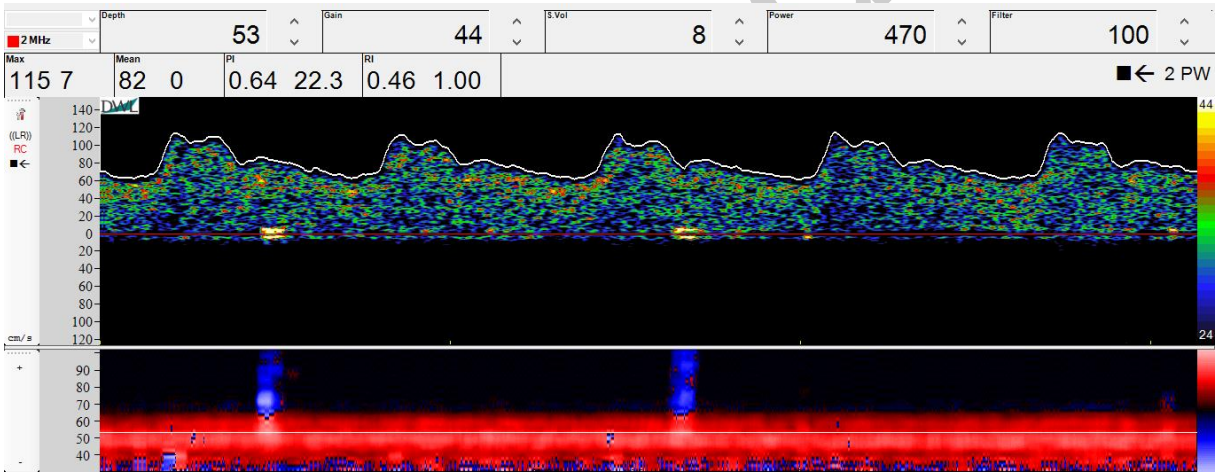

Figure 2.An example of transcranial doppler ultrasound in the target vessel after water pipe smoking (flow analysis in right MCA)