The effect of a 30-minute water-pipe smoking session on cognitive measures and cardio-pulmonary parameters

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ABSTRACT

Introduction: One session of water-pipe tobacco smoking (WPS) can increase carboxyhemoglobin (COHb) to levels comparable to those reported in carbon monoxide poisoning, which may cause memory impairment and confusion.

Methods: A prospective study evaluating healthy volunteers pre- and post- 30-minutes of WPS session. Primary outcome parameters were executive cognitive measures [digit span test and Paced Auditory Serial Addition Test (PASAT)]. The effect of repeated cognitive testing 30 minutes apart without WPS was evaluated in age and sex matched healthy volunteers. Secondary outcome parameters included cardio-pulmonary, COHb, serum nicotine and cytokines changes.

Results: Thirty-five subjects aged 25.6±4.5 years smoked water-pipe for a 30-minute session. Control group included 20 subjects aged 25.2±5.1 years. Digit span test median score decreased after WPS (16 and 15, respectively, p=0.003); insignificant decrease in controls. Median PASAT score increased after WPS (49 and 52, respectively, p=0.009); however, a much larger significant increase was observed in controls (p=<0.001). One WPS session resulted in significant increases in heart and respiratory rates, and significant decrease in FEF25-75%. Post WPS, median COHb levels increased (from 2.2% to 10.7%, p<0.0001) as did median serum nicotine levels (from 1.2 to 26.8 ng/mL, p<0.0001). Serum cytokines levels: IL-2 and IL-6 increased (p<0.0001 for each), and IL-10 and IL-5 decreased (p<0.0001 and p=0.04, respectively).

Conclusions: One session of WPS resulted in significant negative effects on cognitive executive measures, significant increases in COHb and serum nicotine levels, and significant changes in serum cytokines. Our findings call for increasing awareness towards the possible consequences of cognitive alterations following a 30-minute session of WPS.

Keywords: water-pipe smoking, cognitive tests, carboxyhemoglobin, nicotine.

IMPLICATIONS

One 30-minute session of water-pipe smoking resulted in negative effects on executive cognitive measures, increased carboxyhemoglobin and serum nicotine, and significant changes in serum cytokine levels.

This study adds to the accumulating evidence on the harmful effects of water-pipe smoking, a growing epidemic, and calls for awareness of its possible consequences of acute cognitive alterations.

INTRODUCTION

Water-pipe (*narghile, shisha, hookah)* smoking (WPS), is an epidemic phenomenon with growing popularity through global social media[1].

Water-pipe tobacco smoke is known to contain many toxicants found in cigarette smoke, such as nicotine, tar, carbon monoxide (CO), polycyclic aromatic hydrocarbons, volatile aldehydes, phenols, carcinogens and heavy metals. A meta-analysis estimated that a single water-pipe tobacco smoking session was associated with significantly higher exposure to smoke nicotine, tar and carbon monoxide compared to smoking a single cigarette[2].

WPS session usually lasts 30 minutes up to several hours, and may take place indoors (cafes, homes and even cars) or outdoors[3]. Previous studies demonstrated an alarming increase in carboxyhemoglobin (COHb) levels after a single session of WPS[4,5]. Some individuals developed COHb levels higher than 25%, even above 40%. Higher COHb levels were observed in indoor group smoking (17.57%±8.79%)[5], compared with outdoor smoking (9.49%±5.52%)[4]. Only minor increase in COHb was observed among passive smokers after 30 minutes exposure (0.8%±0.25% *vs.* 1.2%±0.8%, respectively, $p = 0.003$)[5]. Such levels of COHb are significantly higher than those seen after smoking cigarettes[6]. They are comparable to levels reported in acute CO poisoning that may require hyperbaric oxygen treatment. Health effects associated with exposure to CO range from subtle cardiovascular, respiratory, gastrointestinal and neurobehavioral effects at low concentrations, to unconsciousness, seizures, myocardial ischemia, metabolic acidosis and death after acute or chronic exposure to higher concentrations of CO[7]. It should be noted that COHb levels are not well correlated with clinical manifestations and severity[8,9].

The main hypothesis attributes the toxic effects of CO to its high affinity to hemoglobin (200-240 times that of oxygen). Other suggested mechanisms include inhibition of mitochondrial cytochrome oxidase, inflammatory changes, production of free radicals (reactive oxygen species), and the production and release of nitric oxide (NO)[9–13].

Memory impairment and confusion are initial neurological manifestations of acute CO poisoning. Previous studies have reported neurological sequelae after the poisoning[14,15]. Intellectual function impairments, short-term memory loss, amnesia, psychosis, irritability, dysfunctional gait, speech disorders, Parkinson-like disease, depression and even increased rate of dementia were reported as poisoning sequelae, also known as delayed neuropsychiatric syndrome[16–18]. A recent meta-analysis assessed the immediate and delayed neuropsychological effects of prolonged or accidental exposure to CO. This meta-analysis concluded that patients with CO poisoning performed significantly worse on measures of divided attention, immediate memory, and processing speed compared to healthy controls; some measures improved over time[19].

The growing popularity of WPS is spreading to the Western hemisphere. It is estimated that >100 million people experience daily exposure to WPS and preform daily activity immediately following WPS. As previously reported, a single WPS session is associated with acute increase in COHb and serum nicotine levels[4,5]. But the effect of WPS on cognitive performances was not fully examined.

Our hypothesis was that a single session of WPS for a period of 30 minutes might have a negative effect on executive cognitive functions. The term "executive functions" refers to mental activities that involve control of cognitive processes (e.g., planning, energizing, switching, inhibiting and monitoring), and enable behavioral and emotional self-regulatory functions[20]. Executive functions are frequently sensitive to toxic and metabolic effects[21]. Our main aim was to evaluate the effect of a single 30-minute session of WPS on measures of executive functions.

METHODS

Ethics Statement

The Institutional Review Board approved the study. Written consents were obtained from all participants prior to the study.

Study group

Inclusion criteria: Healthy volunteers aged 18 years or older with previous experience of WPS.

Exclusion criteria: Pregnant or lactating women, acute viral or bacterial illness, oral or intravenous steroid treatment in the previous two weeks, history of WPS during the previous 24 hours, cigarette smoking during the previous six hours and exposure to fire smoke during the previous 24 hours[4,5].

Study Design, Materials, and Procedure

This was a prospective study carried out in an indoor setting (Outpatient Pulmonary Service office area). The study was performed during evening hours when no patients were on the same floor. Immediately after the end of the WPS, the facility was kept ventilated for two consecutive days (over the weekend); no patients or employees were on the premises. Water-pipes (WPs) were prepared by one of the investigators, as previously reported[4,5]. The WPs were of similar size, and all subjects smoked 10 g of double-apple-flavored tobacco moasel of the same brand (Nakhla; El Geish St. Cairo, Egypt). The tobacco was lit with the same instant-light charcoal disks (Bright Star Charcoal, 3.5 cm diameter, 1 cm width; Nakhla group). Subjects were instructed to smoke at their own regular pace and pattern mimicking regular smoking. Puff topography data was not assessed.

Study parameters were evaluated immediately before and after the 30-minute session of WPS. Evaluation included two cognitive tests, cardio-pulmonary parameters, and COHb, serum nicotine and serum cytokines levels.

The cognitive tests administered included the digit span subtest (Wechsler Adult Intelligence Test WAIS-III heb battery[22], and the Paced Auditory Serial Addition Test (PASAT)[23]. In the digit span task, participants hear digit sequences of increasing lengths and have to recall them forward and in reversed order in one trial option. Each level contains two equal number series with different numbers. The test was terminated after three successive failures of repetitions or reversal of digits presented. In the PASAT, single digits are presented every three seconds and

the participant must add each new digit to the one immediately prior to it. The score is the total number correct out of 60 possible answers.

We applied different Record Forms of the PASAT (Form A or B) and consistently administered PASAT-A pre-manipulation and PASAT-B post-manipulation. Cognitive test score administrators were not blinded; cognitive test score raters were blinded.

Participants: WPS group included 35 subjects (age 25.6±4.5 years; 69% males). They used to smoke WP 3-4 times a week; each session lasted up to two hours.

The effect of repeated cognitive testing 30 minutes apart without WPS was evaluated in a group of 20 non-smokers volunteers. The control group was similar in age (25.2±5.1 years), gender (70% males), educational (university students in their final stages of studies) and socioeconomic status.

All other parameters were evaluated only in WPS: Cardio-pulmonary parameters included vital signs, spirometry–and lung clearance index (LCI) value. Systolic and diastolic blood pressures and heart rate were measured using an Omron HEM-712 C BP monitor (Houston, Texas); respiratory rate was measured manually. Spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society Task Force, using a KoKo spirometer (nSpire Health, Inc.; Louisville, Colorado). Each maneuver was repeated for at least three technically acceptable forced expiratory flow volume curves; the best results were used for analysis[24]. LCI was measured by multiple breath washouts (MBW) using Easy-One Pro, MBW Module (NDD Medical Technologies, Zurich, Switzerland). LCI was calculated as the cumulative expired volume during the nitrogen washout phase divided by the functional residual capacity (FRC)[25]. An increased LCI indicates more FRC turnovers required for nitrogen washout, reflecting small airway disease and ventilation inhomogeneity[26]. At least three technical acceptable MBW tests were required for inclusion of the participants in the final analysis.

The laboratory analyzing the blood samples was blinded to the sequence of smoking. Analysis included COHb levels, serum nicotine and cytokines levels. COHb levels were measured in venous blood samples using an Illex co-oximeter (IL-682; Instrument Laboratory; Lexington, Massachusetts). Serum was stored at -20°C for analysis of nicotine and cytokine levels; each was performed in one run within 3 months. Serum nicotine concentrations were determined by liquid chromatography-tandem mass spectrometry, with a limit of detection of 1 ng/mL, lower limit of quantitation 2 ng/mL, and upper limit of quantitation of 5 ng/mL (Quattro micro API equipped with Waters 2795 HPLC; Waters Corp)[27].

The serum cytokines interleukin (IL) 2, IL-5, IL-6, IL-10, tumor necrosis factor alpha (TNFα) and transforming growth factor beta (TGF-β) were measured and analyzed using Human Inflammatory Cytokines Multi-Analyte ELISArray™ Kit [Qiagen, kit# 336161, Hilden, Germany].

Statistics

Sample size was calculated by http://biomath.info/power[28]. The primary outcome was the effect of WPS on cognitive function tests following smoking.

Sample size calculation assuming a power of 80%, setting alpha at 0.05 for statistical testing mean difference in cognitive score of two units and SD=4, determined the requirement of 34 subjects. Based on the sample size calculation, effect size was found to be 0.5, considered moderate. Cardio-pulmonary parameters, including vital signs, pulmonary function tests, LCI, COHb, nicotine and cytokines levels, were considered as secondary outcomes parameters.

Results are expressed as mean±SD, median and interquartile range (IQR25-75). Kolmogorov-Smirnov test was used to assess normality of distribution. Paired Student's t-test and Wilcoxon signed rank paired test were used for within group comparisons, and unpaired Student's t-test and Mann-Whitney test for between groups comparisons of the within group score differences (pre- and post-WPS score delta), where relevant.

P-value less than 0.05 was considered statistically significant.

RESULTS

The results of the executive cognitive tests are shown in Table 1. Post-WPS digit span raw score significantly decreased, unlike in controls. Post-WPS PASAT score significantly increased, but to a much lesser extent than in controls. Comparison of within group difference in the executive cognitive tests between the two groups is presented in Table 2. The magnitude of change was significantly different between the WPS and control groups for both tests.

Cardio-pulmonary parameters before and after WPS are presented in Tables 3 and 4. Heart and respiratory rates significantly increased post-WPS (Table 3). FEF25-75% significantly decreased; a downward trend was found in FEV1, LCI remained unchanged (Table 4).

Laboratory parameters are presented in Tables 5 and 6. Post-WPS median COHb levels significantly increased (from 2.2% to 10.7%, $p<0.0001$), as did median serum nicotine levels (from 1.2 ng/mL to 26.8 ng/mL, $p<0.0001$). The pro-inflammatory cytokines IL-2 and IL-6 serum levels significantly increased, while anti-inflammatory cytokines IL-10 and IL-5 serum levels significantly decreased. No change was observed in the serum levels of TNFα and TGF-β (Table 6).

DISCUSSION

Our hypothesis was that a single session of WPS resulting in increased COHb level comparable to levels seen in acute CO poisoning, may cause negative cognitive alterations. Our study showed that one session of WPS resulted in a negative effect on executive cognitive tests compared to non-smokers control group. In addition, we found significant increases in COHb and serum nicotine levels, and significant changes in serum cytokines levels in WPS.

WPS has gained global popularity in recent years[29]. We previously showed that a 30-minutes session of WPS could result in increased COHb levels comparable to that seen after acute CO poisoning[4,5]. Therefore, WPS might be considered as a recreational but unaware self-exposure to CO.

Regular daily tasks, such as driving, studying and working require meticulous attention and executive cognitive performance. Half-life of COHb in CO poisoning is relatively short (320 minutes)[30], hence we chose validated, relatively simple, short duration tests that can be completed within a short period after the end of WPS.

Our current study shows that one session of WPS resulted in significant changes in executive cognitive tests scores compared to the scores achieved without WPS. We evaluated healthy non-smokers rather than smokers in order to avoid possible misinterpretation that may result from a carry-over effect and long-standing cognitive impairment in smokers.

Water-pipe smoke contains CO, nicotine, and many other compounds[31]. Multiple studies showed that in acute CO poisoning, cognitive tests may be impaired with COHb levels as low as 5%. More than 50% of patients with COHb levels higher than 10% after acute CO exposure may develop neuropsychiatric sequela[32].

Several studies, including our previous and the present one, showed that a single WPS session resulted in significant increases in COHb and serum nicotine levels[4,5,31]. The effect of nicotine on various cognitive domains is controversial[33]. Nicotine has structural similarity to acetylcholine, and acetylcholine receptors are dispersed throughout the brain[34]. While nicotine was shown in an experimental model to be neurotoxic in young animals[35], nicotinic acetylcholine receptor agonists were found to improve cognitive performance[35]. It is unclear whether the worse cognitive performance after WPS found in our study is due to increased COHb, nicotine, or the many other smoke constituents. We are unaware of humane studies assessing cognitive functions following a single session of WPS. One animal study showed a

decrease in cognitive performance and an increase in oxidative stress at the hippocampus level after WPS[36].

Cigarette smoking differs from WPS in many aspects. WPS results in significant higher COHb concentration and nicotine compared to acute cigarette smoking[2].

Several studies evaluated cognitive function in chronic cigarette smokers, and reported poorer global cognition and impaired performance on specific measures of working memory, cognitive flexibility, visuospatial learning and memory, and processing speed studies, compared with nonsmokers[37]. Studies indicated that tobacco smoking during adolescence increases the risk of developing psychiatric disorders and cognitive impairment in later life. In addition, adolescent smokers suffer from attention deficits, which aggravate with the years of smoking[38,39] .

In addition to cognitive functions, we evaluated multiple cardio-pulmonary parameters and serum cytokines levels.

Similar to previous studies, we found significant increases in heart and respiratory rates after WPS[4,5] and a significant decrease in FEF25-75% predicted[4]. There is evidence that cigarette smoking has detrimental effects on small airways assessed by FEF25-75%[40]. A recent human study demonstrated that WPS is associated with epigenetic changes and related transcriptional modifications in the small airway epithelium. This is the cell population demonstrating the earliest pathologic abnormalities associated with cigarette smoking[41].

LCI is a relative novel marker of small airway disease and deranged ventilation. LCI has been recently suggested as a diagnostic marker of small-airway disease in deployment-related distal lung disease[42]. We are not aware of previous studies assessing LCI in WPS. Our study shows that one session of WPS did not affect LCI measurements. It is suggested that LCI is less sensitive than FEF25-75% for detecting WPS-induced acute changes in small airways.

In order to evaluate possible systemic effect of WPS, we chose to measure serum levels of some pro- and anti-inflammatory cytokines[43]. We previously assessed cytokines levels in exhaled breath condensate[4]; serum cytokines in WPS have not been studied. We found an increase in

serum levels of the pro-inflammatory cytokines IL-2 and IL-6, and a decrease in serum levels of anti-inflammatory cytokines IL-5 and IL-10; serum levels of TNFα and TGF-β did not change. More studies are required to evaluate the systemic inflammatory effects of WPS.

Limitations

The main limitations of our study are the relatively small sample size and inclusion of only healthy volunteers. We evaluated exposure to CO and nicotine, but not exposure to other smoke constituents known to exert health effects (e.g., aldehydes, polycyclic aromatic hydrocarbons). We used a small number of cognitive tests; time elapsing from the end of WPS limited the number of tests that could be done. We did not evaluate the effects of WPS several hours after a single session, nor the long-term sequela of repeated WPS.

In conclusion, our study demonstrates that one 30-minute session of WPS significantly affected executive cognitive tests performances in healthy volunteers. WPS may have systemic effects as suggested by the change in serum cytokines levels, in addition to the known effects on COHb and serum nicotine levels, and cardio-pulmonary parameters.

This study adds to the accumulating evidence of the harmful effects of WPS. Awareness towards the high COHb levels and possible cognitive impairment that may affect real time reaction, should be raised. It is suggested that WP smokers should refrain from doing tasks that require high attention such as driving immediately following WPS. The possible consequences of the cognitive impairment and the effects of repeated exposure to WPS should be further studied.

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DISCLOSURE OF INTEREST

The authors report no conflict of interest.

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Table 1: Executive cognitive tests in water-pipe smokers (before and after 30-minutes smoking) and non-smokers controls (repeated testing 30 minutes apart)

		Mean±SD	Median [IQR25-75]	p-value*
Water-pipe smokers				
Digit span	Before	15.40±3.42	16.0 [14–17]	0.003
	After	14.29±2.78	15.0 [12-16]	
PASAT	Before	46.47±9.95	49.0 [39-54]	0.009
	After	49.10±9.31	52.0 [45-57]	
Controls, non-smokers				
Digit span	Before	20.60±3.49	21.5 [18-23]	0.21
	After	20.95±3.56	20.5 [18.3-25]	
PASAT	Before	44.70±9.24	47 [38-51]	<0.001
	After	51.60±9.95	54 [50-58]	

* Wilcoxon signed rank paired test.

Table 2: Within group difference in executive cognitive tests, water-pipe smokers *vs*. non-smokers controls

		Mean±SD	Median [IQR25-75]	p-value*
Digit span	Smokers	-1.11±0.32	-1.0 [(-3) - (0)]	0.003
	Controls	+0.4±0.04	0 [0 - 1]	
PASAT	Smokers	+2.63±0.78	+1.5 [(-1) - (6)]	0.001
	Controls	+6.95±1.03	+7.0 [5 - 10.5]	

* Between groups comparisons of the within group score differences were done using Mann-Whitney test.

Table 3: Cardio-pulmonary parameters before and after WPS

		Mean±SD	Median [IQR25-75]	p-value*
Heart rate (beats/min)	Before	85.3±11.6	82.00 [78–90]	0.001
	After	95.4±15.7	96.0 [83-108]	
Oxygen saturation%	Before	98.8±0.9	99.0 [98-100]	0.84
	After	98.9±1.1	99.0 [98-100]	
Systolic blood pressure (mmHg)	Before	132.0±14.5	135.0 [122-140]	0.28
	After	134.3±17.3	133.0 [120-148]	
Diastolic blood pressure (mmHg)	Before	74.0±8.6	76.0 [66-80]	0.46
	After	74.9±9.7	75.0 [70-83]	
Respiratory rate (breaths/min)	Before	15.2±2.1	16.0 [14-17]	<0.0001
	After	19.1±4.7	18.0 [16-20]	

* Wilcoxon signed rank paired test

Table 4: Spirometry and lung clearance index before and after WPS

		Mean±SD	Median [IQR25-75]	p-value*
FEV1% predicted [a]	Before	96.2±10.0	98.0 [91-103]	0.059
	After	95.3±11.0	98.0 [87-102]	
FVC% predicted [b]	Before	92.0±11.2	93.0 [84-102]	0.61
	After	92.3±11.4	95.0 [85-100]	
FEF 25-75% predicted [c]	Before	97.6±20.3	95.0 [84-111]	0.02
	After	94.4±20.1	92.0 [81-108]	
LCI [d]	Before	6.51±0.7	6.4 [6.0-6.9]	0.12
	After	6.27±0.6	6.2 [5.9-6.7]	

[a] Forced expiratory volume in the first second

[b] Forced vital capacity

[c] Forced expiratory flow at 25-75% of the pulmonary volume

[d] Lung clearance index

* Wilcoxon signed rank paired test

Table 5: COHb and serum nicotine levels before and after WPS

		Mean±SD	Median [IQR25-75]	p-value*
COHb (%)	Before	2.6±1.6	2.2 [1.3-3.20]	<0.0001
	After	11.5±5.5	10.7 [7.2-13.3]	
Serum nicotine level (ng/mL)	Before	5.5±9.3	1.2 [0.6-7.6]	<0.0001
	After	29.2±16.4	26.8 [14.4-43.4]	

* Wilcoxon signed rank paired test

Table 6: Serum cytokines levels before and after WPS

		Mean±SD	Median [IQR25-75]	p-value*
IL-2 (pg/ml)	Before	4.7±1.9	4.6 [3.3-6.7]	<0.0001
	After	17.0±3.2	16.7 [14.6-16.7]	
IL-6 (pg/ml)	Before	1.2±0.7	1.17 [0.67-1.84]	<0.0001
	After	4.9±1.8	4.6 [3.2-6.5]	
IL-10 (pg/ml)	Before	7.4±2.15	7.3 [5.9-9.1]	<0.0001
	After	3.3±1.9	3.3 [2.1-4.4]	
IL-5 (pg/ml)	Before	5.3±4.13	5.0 [1.9-8.7]	0.04
	After	5.0±3.8	4.1 [2.4-7.9]	
TNFα (pg/ml)	Before	16.3±13.1	12.2 [7.9-22.3]	0.31
	After	17.4±17.4	10.1 [5.4-23.5]	
TGF-β (pg/ml)	Before	14.6±12.6	8.0 [3.9-25.6]	0.25
	After	15.5±11.3	12.1 [4.1-26.2]	

* Wilcoxon signed rank paired test