

Central and Peripheral Hemodynamics in Young Adults Who Use Water Pipes and the Acute Effects of Water-Pipe Use



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BACKGROUND: Tobacco use via water pipe (commonly referred to as water-pipe smoking [WPS]) is popular among young adults globally and exposes those who smoke to toxicants.

RESEARCH QUESTION: Is WPS associated with impaired measures of arterial function and does WPS acutely impair these measures in young adults?

STUDY DESIGN AND METHODS: We assessed heart rate (HR), brachial and aortic BP, HR-adjusted augmentation index (AI), and carotid-femoral pulse wave velocity (CFPWV) in 62 individuals who use water pipes and 34 individuals who have never used a water pipe recruited from the community (mean age, 22.5 ± 3.0 years; 48% female). Measurements were obtained before and after an outdoor session of WPS among participants who use water pipes and among the control group of participants who have never used a water pipe. Measurements were compared after vs before exposure and between those who use and those who do not use water pipes, adjusting for possible confounders using linear regression.

RESULTS: Participants who use water pipes and control participants had similar demographic characteristics. BP and HR increased acutely after WPS (brachial systolic BP by 4.13 mm Hg [95% CI, 1.91-6.36 mm Hg]; aortic systolic BP by 2.31 mm Hg [95% CI, 0.28-4.33 mm Hg]; brachial diastolic BP by 3.69 mm Hg [95% CI, 1.62-5.77 mm Hg]; aortic diastolic BP by 3.03 mm Hg [95% CI, 0.74-5.33 mm Hg]; and HR by 7.75 beats/min [95% CI, 5.46-10.04 beats/min]), but not in the control group. AI was significantly higher in participants who use water pipes compared with those who do not (9.02% vs 3.06%; $P = .03$), including after adjusting for BMI and family history of cardiovascular disease ($\beta = 6.12$; 95% CI, 0.55-11.69; $P = .03$) and when assessing habitual tobacco use via water-pipe extent (water pipes used/day \times water-pipe use duration) in water-pipe-years ($\beta = 2.51$ /water-pipe-year; 95% CI, 0.10-4.92/water-pipe-year; $P = .04$). However, CFPWV was similar in those who use water pipes and those who do not, and AI and CFPWV did not change acutely after WPS.

INTERPRETATION: In apparently healthy young individuals from the community, habitual WPS was associated with increased AI, a predictor of cardiovascular risk, and one WPS session acutely increased HR and brachial and aortic BP. CHEST 2023; 164(6):1481-1491

KEY WORDS: cardiovascular function; hemodynamics; water-pipe use

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ABBREVIATIONS: AI = augmentation index; AI@75 = augmentation index adjusted to a heart rate of 75 beats/min; CFPWV = carotid femoral pulse wave velocity; CO = carbon monoxide; HR = heart rate; PP = pulse pressure; WPS = water-pipe smoking

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Take-home Points

Study Question: Do habitual and acute tobacco use via water pipe affect measurements of arterial function in young adults?

Results: In apparently healthy, young individuals from the community, habitual tobacco use via water pipe is associated with increased augmentation index, a predictor of cardiovascular risk, and one water-pipe smoking session acutely increased heart rate and brachial and aortic BP.

Interpretation: Water-pipe smoking is associated with both acute and chronic adverse effects on arterial function in young, apparently healthy individuals.

Tobacco use via water pipe (commonly referred to as water-pipe smoking [WPS]) originated centuries ago in the Middle East and has become more popular during the past 2 decades in other parts of the world, including Europe and North America, especially among young individuals.^{1,2} The prevalence of WPS is reported to be 9% to 15% among middle-school students from the Arabian Gulf; 16% among girls and 25% among boys from Estonia; 7.6% to 10% among high or secondary school students in the United Kingdom, United States, and Canada; and 8.4% among US college students.¹ WPS often occurs in social settings, is affordable, and is perceived to be less harmful than cigarette use; furthermore, the advent of heavily flavored water-pipe tobacco products has made WPS highly attractive to new and young populations.¹⁻³ Water-pipe tobacco smoke contains the major classes of toxicants that are thought to cause tobacco use-related diseases in individuals who use cigarettes, including large quantities of carbon monoxide (CO), nicotine, polyaromatic hydrocarbons, volatile aldehydes, and heavy metals.^{4,5} Indeed, nicotine levels in individuals who use water pipes were equivalent to levels recorded after using 10 cigarettes/d,⁶ and exhaled CO after up to 45 min of WPS was nine times higher than levels recorded after using one cigarette.⁷

Few studies have evaluated the association of WPS with cardiovascular disease.⁸ Studies that evaluated the acute

cardiovascular effects of WPS have shown an acute increase in BP and heart rate (HR) afterward.⁹⁻¹¹

Arterial stiffness and pulse wave reflection measured using carotid-femoral pulse wave velocity (CFPWV) and augmentation index (AI) acutely increased after WPS.¹² WPS also was associated with a sustained increase in AI in middle-aged and older adults, but not with CFPWV.¹³

CFPWV and AI are validated measures of arterial stiffness and relative wave reflection, respectively, and can be measured noninvasively using applanation tonometry and arterial pulse wave analysis. Arterial pulse waves reflect along the arterial tree at sites where the transmission properties change. When pulse wave velocity increases, the reflected waves return to the heart earlier in systole and augment the aortic systolic pressure, rather than the diastolic trough, and thus amplify the pulse pressure (PP).¹⁴ This increased PP could damage blood vessels in target organs such as the brain or kidneys.^{14,15} Furthermore, early return of the reflected arterial pulse wave during systole increases cardiac afterload¹⁶ and over time causes left ventricular hypertrophy and remodeling, which could cause heart failure.¹⁷

Indeed, increased CFPWV has been associated with atherosclerosis among asymptomatic patients¹⁸⁻²⁰ and is an independent predictor of longitudinal increases in BP and hypertension onset.²¹ AI is the magnitude of reflected pressure wave contribution to the systolic aortic BP expressed as a percentage of the aortic PP. Thus, AI estimates the percentage of aortic PP attributed to the reflected pressure wave. Higher AI has been associated with the presence of coronary artery disease in asymptomatic individuals¹⁸ and in patients undergoing coronary angiography.^{22,23} AI may predict cardiovascular outcomes in patients with coronary artery disease,²⁴ but evidence is conflicting.²⁵

Considering the limited evidence implicating WPS in vascular disease, especially in young individuals, and increasing prevalence of WPS among youth, we evaluated the association of WPS with these validated noninvasive markers and predictors of vascular disease in asymptomatic young individuals. We hypothesized that AI, CFPWV, and peripheral and central BP are increased in young asymptomatic individuals who use water pipes from the community compared with individuals who have never used a water pipe, and that these parameters increase acutely after a session of WPS.

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Study Design and Methods

Study Sample

This study included 96 healthy young adults aged 18 to 30 years recruited from the community in Beirut through advertisements at college campuses and cafes that offer WPS. Participants comprised 34 individuals who have never used (water pipe, cigarette, cigar, or e-cigarette) and 62 individuals who had been using a water pipe for > 1 year, but who did not use other tobacco products. Individuals who used cigarettes or cigars and those with a history of asthma, diabetes, renal failure, atherosclerosis, hypertension, cardiovascular disease, coronary artery disease, or hematologic disease and pregnant women were excluded. The study protocol was approved by the American University of Beirut Institutional Research Board (Identifier: IM.HC.07), and all participants provided informed consent.

Study Procedures

All measurements were obtained at the clinical research unit of the American University of Beirut Medical Center in a quiet temperature-controlled room set between 20 and 23 °C during the morning hours after an overnight fast and after 15 min of rest. Measurements were obtained before and repeated immediately after outdoor WPS or outdoor exposure. Participants in the water-pipe use group used a standard charcoal heated water pipe loaded with approximately 10 g of Two Apples flavored tobacco (Mazaya) covered with aluminum foil and topped with two charcoals for 30 min on a shaded outdoor balcony adjacent to the measurement room. To control for outdoor environment exposure, control participants sat in the same outdoor environment for 30 min without using tobacco. Participants were requested to abstain from WPS for 24 h before the experiment and for 6 h from caffeine, alcohol, and exercise. Abstinence from tobacco use was confirmed by measuring expired breath CO before initiating study procedures.

Demographics and Health Assessment

Age, sex, and race were recorded. Participants were surveyed for personal and family history of health disorders, intake of medications, and alcohol consumption using an investigator-administered questionnaire. Height and weight were measured in light clothes. BP was measured three times from the left arm using a calibrated sphygmomanometer (W.A. Baum Co., Inc.) while participants were seated after resting for 15 min, and the results were averaged.

WPS Assessment

History of WPS including duration, frequency, session length, number of water pipes used per session, and the type of tobacco was assessed using a validated investigator-administered questionnaire.²⁶ Intensity of WPS during the session was assessed using a home-built device at the American University of Beirut that attaches to the water-pipe smoke hose mouthpiece and records the number of puffs exhaled and puff duration. The device consists of a 5-cm hollow cylinder fitted with a pressure switch that becomes triggered by the negative pressure generated by each puff. Exhaled CO levels in parts per million and percentage were measured using a micro Smokerlyzer (Bedfont) before and after WPS.

Tonometry

Central hemodynamics were measured in the supine position during the morning in a quiet, temperature-controlled room (18-22 °C) before and after WPS or outdoor exposure using the AtCor SphygmoCor system (AtCor Medical). The arterial pulse waves were recorded on the carotid and femoral arteries using the tonometer probe (SPT-301; Millar Instruments) while acquiring the cardiac electrical QRS complex using three ECG leads attached to the chest

wall. The distance from the suprasternal notch to the carotid and femoral pulse points was measured manually. Thereafter, CFPWV, the gold standard measure of arterial stiffness, was calculated using built-in mathematical equations.^{27,28} Applanation tonometry at the radial artery recorded the peripheral arterial pressure waveforms, and the central aortic waveforms then were derived using a built-in mathematical function. Systolic BP, diastolic BP, PP, augmentation pressure, AI, and AI adjusted to an HR of 75 beats/min (AI@75) was calculated from these waveforms.²⁹ Augmentation pressure is the difference between the second and the first systolic aortic pulse wave peaks, expressed in millimeters of mercury. AI is the ratio of augmentation pressure and PP expressed as a percentage. AI is adjusted to an HR of 75 beats/min to obtain AI@75. The SphygmoCor system is equipped with built-in quality control measures, demonstrates low intraoperator and interoperator variability, and is validated against invasive measures of arterial stiffness.³⁰⁻³³

Statistical Analysis

The main dependent or outcome variables were measures of wave reflection of AI@75 and vascular stiffness of CFPWV, treated as continuous variables. Other measures of central (aortic systolic BP, diastolic BP, and AI) and peripheral hemodynamics (brachial systolic BP, diastolic BP, and HR) were evaluated as secondary dependent or outcome variables. The independent or exposure variable for the cross-sectional analysis was the tobacco use status treated as a dichotomous variable (water-pipe use or nonuse). The extent of WPS in water-pipe-years (the product of WPS duration in years with the number of water pipes used per day) also was evaluated as a secondary independent or exposure variable. In the experimental exposure analysis, the acute exposure also was quantified in secondary analyses using exhaled CO (parts per million), carboxyhemoglobin (percentage), the number of water-pipe puffs, and water-pipe puff duration during the session of WPS.

Characteristics of participants who use and participants who do not use water pipes are presented as percentage for categorical variables and mean \pm SD for continuous variables and were compared using the Fisher exact and *t* test, respectively. The sustained long-term impact of WPS on vascular parameters was assessed by comparing baseline measurements (before WPS or outdoors exposure) between participants in the water-pipe use group and control participants using the *t* test. The association of parameters associated with WPS and its extent in water-pipe-years (water pipes used per day \times years of WPS) was assessed using linear regression adjusting for possible confounding characteristics that were imbalanced between participants who use and participants who do not use water pipes.

The acute impact of WPS on vascular parameters was evaluated by comparing these parameters before vs after WPS in participants in the water-pipe use group or outdoors exposure in control participants using the paired *t* test. Vascular parameters also were compared between the two exposure groups over time using a mixed linear model that included WPS group and time (before and after exposure) as fixed covariates and a WPS group \times time interaction term in a variance component structure. The associations between changes in hemodynamic measures before and after WPS with (1) exhaled CO (parts per million), (2) the number of water-pipe puffs, and (3) water-pipe puff duration was assessed using Pearson's correlation coefficient. We assessed the impact of outdoor temperature on vascular measurements by evaluating the correlation between outdoor temperature and those measurements using Pearson's correlation coefficient. A *P* value of < .05 was considered statistically significant. All analyses were conducted using SPSS software (SPSS, Inc.).

TABLE 1] Participant Characteristics

Characteristic	Nonuse Group (n = 34)	Water-Pipe Use Group (n = 62)	P Value ^a
Age, y	22.4 ± 3.12	22.6 ± 2.74	.7
Female sex	16 (47.1)	30 (48.4)	1.0
Height, cm	169.4 ± 9.16	170.1 ± 9.28	.7
Weight, kg	71.2 ± 17.37	77.9 ± 20.29	.1
BMI, kg/m ²	24.7 ± 5.3	26.7 ± 5.8	.09
Highest level of education			1.0
Elementary school	2 (5.9)	5 (8.1)	
High school	31 (91.2)	54 (87.1)	
College	1 (2.9)	3 (4.8)	
Yearly income, \$.08
< 60,000	8 (57.1)	42 (85.7)	
60,000-100,000	3 (21.4)	4 (8.17)	
> 100,000	3 (21.4)	3 (6.13)	
Alcohol consumption	5 (14.7)	18 (29.0)	.1
Health characteristics			
Breathing problems ^b	0 (0.0)	1 (1.6)	.5
Malignancy	0 (0.0)	0 (0.0)	...
Cardiovascular disease ^c	0 (0.0)	0 (0.0)	...
Medications	0 (0.0)	0 (0.0)	...
Family history			
Cardiovascular disease	9 (26.5)	28 (45.2)	0.08
Lung disease	4 (11.8)	4 (6.5)	0.4
Malignancy	4 (11.8)	5 (8.1)	0.7
Water-pipe use characteristics			
Age started water-pipe use, y	...	16.6 ± 2.1	...
Tobacco use duration, y	...	6.0 ± 3.4	...
Use water pipe daily	...	35 (56.5)	...
No. of water pipes or heads (10-20 g tobacco) used/d	...	1.1 ± 0.9	...
No. of water pipes used/d over tobacco use duration, water-pipe-y	...	4.9 ± 6.0	...
No. of puffs during 30-min water-pipe use session	...	206.7 ± 167.7	...
Cumulative puff duration during 30-min water-pipe use session, s	...	499.3 ± 456.4	...

Data are presented as No. (%) or mean ± SD, unless otherwise indicated.

^aCategorical variables were compared using the Fisher exact test.

^bIncludes dyspnea, cough, asthma, emphysema, and COPD. One participant reported dyspnea.

^cIncludes history of hypertension, angina, coronary heart disease, infarction, peripheral vascular disease, and stroke.

Results

The baseline characteristics of study participants stratified by WPS status are presented in [Table 1](#). Participants in the water-pipe use group and control participants had similar characteristics including age and proportion of female participants. Compared with those who do not use water pipes, the participants who do use water pipes showed a trend that did not reach

statistical significance for a higher BMI and prevalence of a family history of cardiovascular disease. Participants in the water-pipe use group on average used 1.1 ± 0.9 water pipe/d (or head, which typically contains 10-20 g of tobacco) over an average duration of 6.0 ± 3.4 years, and 56% used tobacco via water pipe daily. Among participants who have never used a water pipe, 61.8% reported exposure to second hand tobacco use.

TABLE 2] Baseline CO, Carboxyhemoglobin Peripheral, and Central Hemodynamic Measurements in the Water-Pipe Use Group and Control Group

Baseline Measurement	Nonuse Group (n = 34)	Water-Pipe Use Group (n = 62)	P Value ^a
Exhaled CO, ppm	2.1 ± 1.4	6.3 ± 5.6	< .001
Carboxyhemoglobin, %	0.9 ± 0.5	1.5 ± 1.0	< .001
Brachial BP, mm Hg			
Systolic	112.1 ± 9.2	116.4 ± 13.9	.1
Diastolic	72.2 ± 9.8	72.1 ± 10.7	.9
HR, beats/min	66.9 ± 8.6	69.3 ± 11.2	.3
Tonometry			
Aortic BP, mm Hg			
Systolic	98.8 ± 8.7	102.0 ± 10.9	.1
Diastolic	73.1 ± 10.0	73.5 ± 11.1	.8
AI, %	6.7 ± 14.2	12.4 ± 13.1	.05
HR-adjusted AI, %	3.1 ± 13.9	9.0 ± 12.0	.03
CFPWV, m/s	6.0 ± 1.2	6.2 ± 1.1	.3

Data are presented as mean ± SD, unless otherwise indicated. Boldface indicates $P < .05$. AI = augmentation index; CFPWV = carotid femoral pulse wave velocity; CO = carbon monoxide; HR = heart rate; ppm = parts per million.

^at test.

Compared with those who do not use water pipes, participants in the water-pipe use group showed higher baseline exhaled CO levels, percentage of carboxyhemoglobin, and AI@75 measured before the session of WPS. However, the control group and the participants who do use water pipes showed similar baseline HR, CFPWV, and central and peripheral systolic and diastolic BP (Table 2). After adjusting for BMI and family history of cardiovascular disease, baseline AI@75 remained associated significantly with WPS ($\beta = 6.12$; 95% CI, 0.55-11.69; $P = .03$) and with the extent of WPS (water pipes used/d × WPS duration) expressed in water-pipe-years ($\beta = 2.51$; 95% CI, 0.10-4.92; $P = .04$).

Exhaled CO, carboxyhemoglobin, and hemodynamic variables before and after WPS or sitting outdoors without using tobacco are presented in Table 3. On average, the participants in the water-pipe use group inhaled 206.7 ± 167.7 water-pipe smoke puffs during the 30-min session of WPS. Exhaled CO and carboxyhemoglobin increased markedly after WPS and negligibly in control participants after outdoor exposure. HR and both brachial and aortic systolic BP and brachial and aortic diastolic BP increased significantly after WPS in participants in the water-pipe use group, but not in control participants. The increase in HR after WPS was accompanied by a significant decrease in AI that was not observed in control participants; however, the HR-adjusted AI@75 did not change significantly after WPS in participants who use water pipes

or in control participants. Similarly, no significant change in CFPWV was observed after WPS in those who use water pipes or in control participants. Participants in the water pipe use group showed a significant increase in exhaled CO, carboxyhemoglobin, HR, and brachial and aortic systolic BP after acute WPS as compared with control participants using the mixed linear model (Fig 1, Table 4). The change in HR after WPS correlated with the number of puffs and puff duration, but not with exhaled CO (e-Table 1, e-Figs 1, 2). However, the change in central and peripheral BP did not correlate with any of these measures of WPS intensity nor with ambient outdoor temperature (e-Table 2). In participants who have never used a water pipe, no association between ambient outdoor temperature or exhaled CO after outdoor exposure and the change in any hemodynamic parameter from baseline to after exposure to the outdoor environment was found (e-Table 3).

Discussion

To our knowledge, this is the first study that evaluated both the acute and sustained effects of WPS on arterial function in young, otherwise healthy individuals from the community. In this study, we found that HR and brachial and aortic systolic BP and diastolic BP acutely increased after a 30-min outdoor WPS session, but not in control participants exposed to the same outdoor environment for the same duration. In contrast, HR-adjusted AI was higher at baseline in participants who habitually use water pipes compared with participants

TABLE 3] Exhaled CO and Hemodynamic Measurements Before and After Outdoor Water-Pipe Use in the Use Group and Outdoor Environment Exposure in Control Participants

Variable	Nonuse Group (Control Participants; n = 30)				Water-Pipe Use Group (n = 60)			
	Before Exposure	After Exposure	Mean Change (95% CI)	P Value for Change	Before Exposure	After Exposure	Mean Change (95% CI)	P Value for Change
Exhaled CO, ppm ^a	2.0 ± 1.4	2.5 ± 1.6	0.5 (0.0 to 1.0)	.05	6.4 ± 5.7	36.0 ± 29.5	29.6 (22.4 to 36.9)	< .001
Carboxyhemoglobin, % ^a	0.8 ± 0.5	1.0 ± 0.4	0.1 (-0.01 to 0.3)	.051	1.6 ± 1.0	6.3 ± 4.8	4.8 (3.6 to 6.0)	< .001
Brachial BP, mm Hg								
Systolic	112.6 ± 9.6	109.9 ± 9.8	-2.7 (-5.1 to 0.3)	.03	116.3 ± 13.8	120.4 ± 12.9	4.1 (1.9 to 6.4)	< .001
Diastolic	73.3 ± 9.6	75.1 ± 10.4	1.8 (-1.0 to 4.7)	.2	72.2 ± 10.6	75.8 ± 12.5	3.7 (1.6 to 5.8)	< .001
HR, beats/min	66.1 ± 8.7	65.1 ± 9.2	-1.0 (-3.4 to 1.4)	.4	68.7 ± 10.8	76.4 ± 12.2	7.8 (5.5 to 10.0)	< .001
Aortic BP, mm Hg								
Systolic ^b	99.1 ± 8.7	98.7 ± 8.4	-0.4 (-2.3 to 1.5)	.7	102.0 ± 10.8	104.3 ± 10.5	2.3 (0.3 to 4.3)	.03
Diastolic	73.8 ± 9.8	75.6 ± 10.3	1.8 (-0.9 to 4.5)	.2	73.5 ± 11.0	76.5 ± 12.3	3.0 (0.7 to 5.3)	.01
AI, %	7.5 ± 14.4	9.4 ± 13.2	2.0 (-1.9 to 5.9)	.3	12.1 ± 12.3	5.9 ± 11.6	-6.2 (-9.0 to -3.4)	< .001
HR-adjusted AI, %	3.5 ± 14.4	4.5 ± 12.8	1.0 (-3.0 to 5.0)	.6	8.4 ± 11.1	6.8 ± 10.4	-1.6 (-4.6 to 1.4)	.3
CFPWV, m/s	6.1 ± 0.9	6.0 ± 1.0	-0.1 (-0.4 to 0.1)	.3	6.2 ± 1.1	6.3 ± 1.1	0.1 (-0.1 to 0.3)	.2

Data are presented as mean ± SD, unless otherwise indicated. Boldface indicates $P < .05$. AI = augmentation index; CFPWV = carotid femoral pulse wave velocity; CO = carbon monoxide; HR = heart rate; ppm = parts per million.

^aNonuse group: n = 29; use group: n = 58.

^bUse group: n = 59.

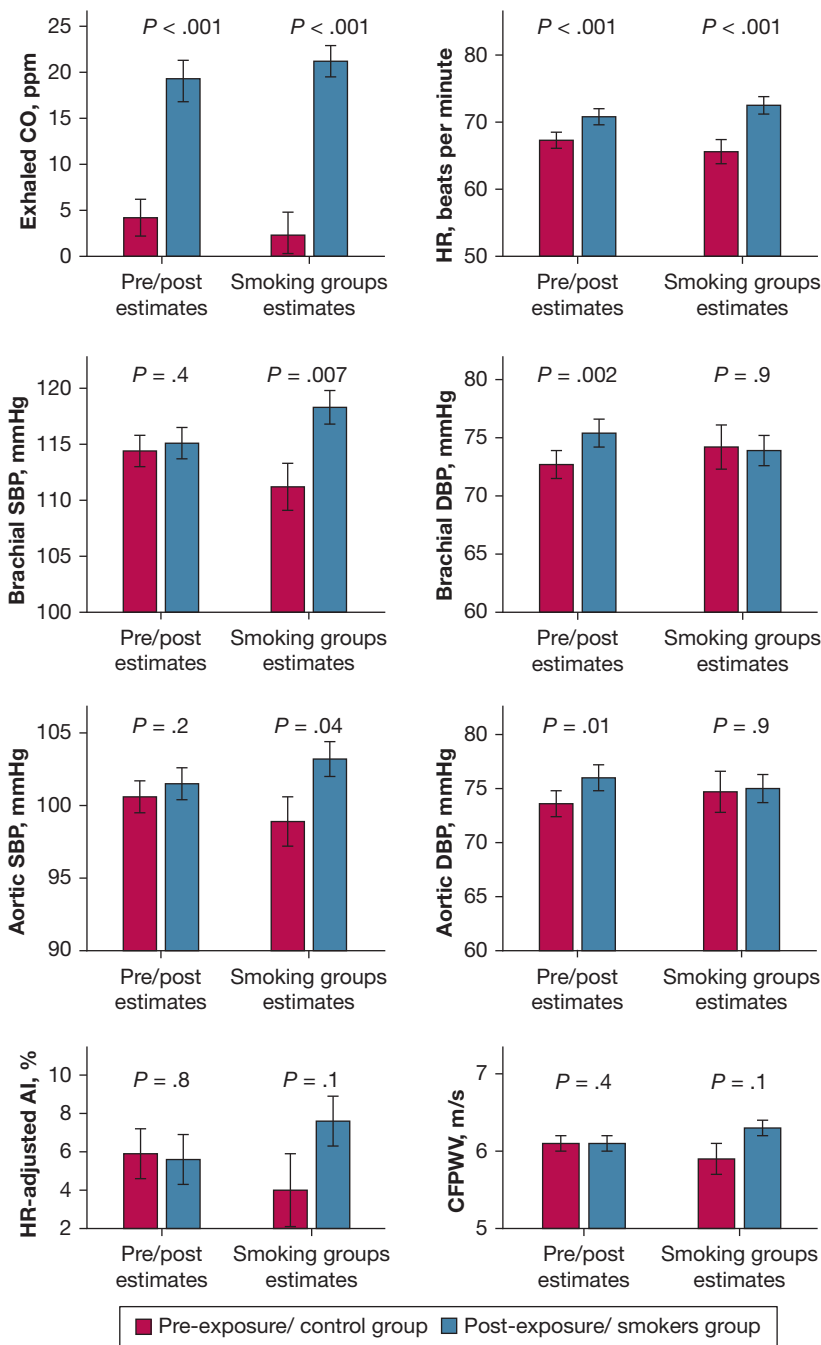


Figure 1 – A-H, Bar graphs showing exhaled CO and hemodynamic measurement estimates before and after exposure and among water-pipe tobacco use groups: exhaled CO (A), HR (B), brachial SBP (C), brachial DBP (D), aortic SBP (E), aortic DBP (F), HR-adjusted AI (G), and CFPWV (H). AI = augmentation index; CFPWV = carotid-femora pulse wave velocity; CO = carbon monoxide; DBP = diastolic BP; HR = heart rate; SBP = systolic BP.

who have never used a water pipe and did not change acutely significantly after a session of WPS. These results suggest that WPS has both immediate and chronic effects on arterial function.

The finding of increased arterial pulse wave reflection in young, seemingly healthy asymptomatic individuals who use water pipes is important because increased AI is a predictor of cardiovascular risk and the presence of coronary artery disease in asymptomatic individuals.¹⁴ This study extends the findings of increased AI in older

individuals who use water pipes (mean age, 51.5 ± 9.2 years) with a long history of WPS (mean, 25.4 ± 11.2 years)¹³ to younger individuals (mean age, 22.6 ± 2.74 years) with a shorter duration of WPS (mean, 6.0 ± 3.4 years). Similar to our findings, cigarette use also has been associated with higher AI, but not CFPWV, in multiple studies.³⁴⁻³⁶

The lack of acute change in HR-adjusted AI@75 after WPS in this experiment suggests that the elevated AI in individuals who use water pipes is sustained rather

TABLE 4] Estimated Mean Exhaled CO and Hemodynamic Measurement Differences Between Time Points and User Group^a

Variable	Time Comparison				Group Comparison			
	Before Exposure	After Exposure	Mean Change (95% CI)	P Value for Change	Nonuse Group	Water-Pipe Use Group ^b	Mean Change (95% CI)	P Value for Change
Exhaled CO, ppm ^c	4.2 ± 2.0 (0.3-8.1)	19.3 ± 2.0 (15.4-23.2)	15.1 (10.0-20.1)	< .001	2.3 ± 2.5 (-2.6 to 7.2)	21.2 ± 1.7 (17.7-24.7)	18.9 (12.9-24.9)	< .001
Carboxyhemoglobin, % ^c	1.2 ± 0.3 (0.5-1.8)	3.7 ± 0.3 (3.0-4.3)	2.5 (1.6-3.3)	< .001	0.9 ± 0.1 (0.1-1.7)	3.9 ± 0.3 (3.3-4.5)	3.0 (2.1-4.0)	< .001
Brachial BP, mm Hg								
Systolic	114.4 ± 1.4 (111.7-117.1)	115.1 ± 1.4 (112.4-117.9)	0.7 (-1.0 to 2.5)	.4	111.2 ± 2.1 (107.0-115.4)	118.3 ± 1.5 (115.3-121.3)	7.1 (1.9-12.3)	.007
Diastolic	72.7 ± 1.2 (70.2-75.1)	75.4 ± 1.2 (73.0-77.9)	2.8 (1.0-4.5)	.002	74.2 ± 1.9 (70.5-78.0)	73.9 ± 1.3 (71.3-76.6)	-0.3 (-4.9 to 4.3)	.9
HR, beats/min	67.3 ± 1.2 (65.0-70.0)	70.8 ± 1.2 (68.4-73.1)	3.4 (1.6-5.2)	< .001	65.6 ± 1.8 (62.0-69.2)	72.5 ± 1.3 (70.0-75.1)	7.0 (2.5-11.4)	.002
Aortic BP, mm Hg								
Systolic ^d	100.6 ± 1.1 (98.3-102.8)	101.5 ± 1.1 (99.3-103.7)	1.0 (-0.6 to 2.5)	.2	98.9 ± 1.7 (95.5-102.3)	103.2 ± 1.2 (100.7-105.6)	4.2 (0.04-8.4)	.04
Diastolic	73.6 ± 1.2 (71.1-76.1)	76.0 ± 1.2 (73.5-78.5)	2.4 (0.5-4.3)	.01	74.7 ± 1.9 (70.9-78.4)	75.0 ± 1.3 (72.3-77.7)	0.3 (-4.3 to 4.9)	.9
AI, %	9.8 ± 1.4 (7.0-12.6)	7.7 ± 1.4 (4.9-10.5)	-2.1 (-4.5-0.3)	.08	8.5 ± 2.1 (4.3-12.6)	9.0 ± 1.5 (6.0-12.0)	0.6 (-4.5 to 5.6)	.8
HR-adjusted AI, %	5.9 ± 1.3 (3.3-8.5)	5.6 ± 1.3 (3.0-8.2)	-0.3 (-2.8 to 2.2)	.8	4.0 ± 1.9 (0.2-7.7)	7.6 ± 1.3 (4.9-10.3)	3.6 (-1.0 to 8.2)	.1
CFPWV, m/s	6.1 ± 0.1 (5.8-6.3)	6.1 ± 0.1 (5.9-6.4)	-0.1 (-0.1 to 2.4)	.4	5.9 ± 0.2 (5.5-6.3)	6.3 ± 0.1 (6.0-6.6)	0.4 (-0.1 to 0.8)	.1

Data are presented as estimated mean ± SE (95% CI), unless otherwise indicated. Boldface indicates $P < .05$. AI = augmentation index; CFPWV = carotid femoral pulse wave velocity; CO = carbon monoxide; HR = heart rate; ppm = parts per million.

^aHemodynamic measurements were estimated and compared between different time points and the two exposure groups using a longitudinal mixed linear model that included user group (water-pipe use or nonuse) and time (before and after exposure) and water-pipe use group × time interaction.

^bData are presented as mean ± SD (95% CI).

^cNonuse group: n = 29; use group: n = 58.

^dUse group: n = 59.

than a carryover acute effect. Although AI and CFPWV were reported to increase acutely after indoor WPS in young, healthy individuals who habitually use water pipes,¹² HR-adjusted AI was not reported in that study and control participants were not evaluated. In this experiment, AI decreased acutely after WPS, accompanied by increased HR. Because increased HR is associated with a decrease in AI, the change in HR-adjusted AI@75 was not significant after accounting for the increase in HR. Control participants showed no significant increase in HR and no change in AI or HR-adjusted AI@75 after outdoor exposure. However, CFPWV did not change acutely significantly after WPS or outdoor exposure. Thus, outdoor WPS is not associated with further acute changes in large-vessel function in individuals who use water pipes, who have sustained impairment in AI compared with those who do not.

Possible reasons for the differences in findings between the two studies include differences in the experimental conditions. In this experiment, WPS occurred on a shaded outdoor balcony (a common setting for WPS), whereas in the experiment by Rezk-Hanna et al,¹² WPS occurred in an air-tight chamber, which may have resulted in different intensities of WPS exposure in the two experiments. Indeed, in a previous study, acute changes in cardiopulmonary parameters were more accentuated with indoor vs outdoor WPS.³⁷ Furthermore, although measurements were obtained in a temperature-controlled room, exposure to outdoor temperature or urban pollution could have impacted our measurements. Nevertheless, aside from a decrease in systolic BP, which is likely related to prolonged inactivity, hemodynamic parameters did not change significantly in control participants exposed to the outdoor environment without using tobacco. Furthermore, the ambient outdoor temperature in Beirut is mild and varied between 18 and 31 °C at the time of the experiment. Additionally, we found no correlation between change in hemodynamic parameters and outdoor temperature or exhaled CO in control participants. The duration of WPS and the amount of flavored tobacco used otherwise were similar in both experiments; however, in the latter study, 12.5 g of three different tobacco flavors (Starbust brand) were used (containing the same nicotine level, 0.05%), whereas we used 10 g of apple-flavored (Mazaya brand; 0.05% nicotine) tobacco. Although the resulting change in exhaled CO after WPS in both experiments was similar, it is possible that different tobacco flavoring could result in different inhaled toxicants and possibly different

effects on hemodynamic parameters. Finally, participants in both studies were of similar age and included both male and female participants, and the sample size was larger in our study (60 individuals who use water pipes vs 48); therefore, it is unlikely that the different results can be attributed to differences in sample characteristics.

The association of WPS with wave reflection, but not with CFPWV, suggests that WPS is associated with increased peripheral arterial vasoconstriction,³⁴ rather than increased stiffness of central arteries.¹⁴ Water-pipe smoke contains multiple toxicants that could affect tone in peripheral resistance vessels directly or indirectly, including nicotine, tobacco toxicants, and other charcoal combustion products. Nicotine exposure acutely stimulates smooth muscle contraction in arteries and arterioles, which could explain the acute increase in BP we observed after WPS.^{38,39} Moreover, water-pipe smoke inhibits mediators of vasodilation (adenosine monophosphate-activated protein kinase and endothelial nitric oxide synthase) *in vitro*⁴⁰ and increases EF-1, a potent vasoconstrictor in mice.⁴¹

However, the mechanisms that mediate the association of WPS and sustained increased AI are not well understood. Chronic nicotine exposure stimulates vascular endothelial growth factor release and neovascularization in multiple organs, decreases microvascular resistance, and increases blood flow, which is not expected to increase AI.⁴² Nevertheless, tobacco use via WPS-induced lipid metabolism impairment^{43,44} and kidney dysfunction,⁴⁵ increased BP,⁸ systemic inflammation, oxidative stress,⁴⁶ and vascular calcifications⁴⁷ are other possible intermediate mechanisms implicated in the sustained higher AI among individuals who use water pipes.⁴⁸ Furthermore, the acute increase in central BP after WPS increases cardiac afterload could, over time leading to left ventricular remodeling and altered dynamics¹⁶ that in turn can lead to higher AI.⁴⁹

This study is limited by its cross-sectional design, which does not allow firm conclusions on the causality of the association between WPS and HR-adjusted AI noted in the cross-sectional analysis. Although determinants of vascular health were balanced in individuals who did use water pipes and those who did not, family history of cardiovascular disease was more common in the water-pipe use group and BMI was slightly higher compared with control participants. Nevertheless, the association of WPS with HR-adjusted AI remained significant after adjusting for these potential confounders. The higher

proportion of alcohol consumption and lower income among the participants who use water pipes was not statistically significant, but potentially could have influenced vascular measures. Most control participants reported secondhand tobacco smoke exposure, which may have affected vascular measures among this group and biased the results to the null. Because of ethical considerations, we could not evaluate the acute effects of WPS in individuals who do not use water pipes; thus, we can not rule out such effects in this group. Finally, exposure was assessed outdoors in our study; although outdoor WPS is common, our findings cannot be generalized to indoor WPS. Balancing these limitations is the community-based study sample of asymptomatic healthy young individuals selected, independent of cardiovascular disease risk, and the experimental design that controlled for environmental exposure. Furthermore, the evaluation of individuals who exclusively use water pipes and those who have never used a water pipe, and exclusion of individuals with concurrent or prior history of cigarette or other forms of tobacco use, eliminated important confounding. Additionally, the multimodal assessment of WPS including a novel smart mouthpiece device and adjustment for potential confounders further strengthens this study. Finally, the assessment of acute and sustained effects of WPS in the same study confirmed that the higher AI among individuals who use water pipes is sustained rather than a carryover acute effect.

Interpretation

In a group of apparently healthy, young asymptomatic individuals from the community, habitual WPS and its extent (WPS duration \times water pipes used/d) were associated with a sustained increased HR-adjusted AI, and one 30-min session of WPS acutely increased HR and brachial and aortic BP. These findings suggest that WPS is associated with both acute and chronic adverse effects on vascular health even in young, apparently healthy, individuals. These results add to the evidence implicating WPS in cardiovascular diseases and serve as a strong public health warning. Prospective controlled studies that evaluate vascular function among WPS longitudinally are needed to assess the long-term health impact of WPS better.

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