Longitudinal Effects of Cigarette Smoking and Smoking Cessation on Aortic Wave Reflections, Pulse Wave Velocity, and Carotid Artery Distensibility

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Background—We evaluated the effects of smoking and smoking cessation on aortic wave reflections (augmentation index), aortic pulse wave velocity, and carotid artery distensibility and stiffness (distensibility coefficient, Young’s elastic modulus).

Methods and Results—Current smokers underwent carotid, radial, and femoral artery tonometry and carotid ultrasound at baseline and 3 years after a quit attempt. Baseline associations of smoking heaviness markers (exhaled carbon monoxide and cigarettes smoked/d) and effects of smoking cessation at year 3 on changes in arterial measures were assessed using multivariable linear regression models. The 1417 smokers (54% female) were mean (SD) 49.3 (11.6) years old and smoked 17.2 (8.3) cigarettes/d (exhaled carbon monoxide 14.7 [8.2] parts per million). Arterial measures were associated more strongly with age, blood pressure (BP), and waist circumference than with smoking heaviness markers. Augmentation index was associated independently with carbon monoxide (P=0.004). Pulse wave velocity, distensibility coefficient, and Young’s elastic modulus had small, inconsistent associations with smoking heaviness markers. At year 3, augmentation index improved with smoking cessation (P=0.006) despite more weight gain (2.54 vs 0.36 kg, P<0.001) and insulin resistance (P=0.001) among abstainers, but distensibility coefficient decreased (P=0.004). Changes in arterial measures were related more strongly to changes in BP than smoking cessation.

Conclusions—Arterial wave reflection and stiffness measures were associated more strongly with age, BP, and waist circumference than smoking heaviness. Smoking cessation was associated with weight gain and increased insulin resistance. Changes in arterial measures were predicted by changes in BP, highlighting the need to address weight gain and BP changes during a quit attempt. (J Am Heart Assoc. 2019;8:e013939. DOI: 10.1161/JAHA.119.013939.)

Key Words: arterial stiffness • blood pressure • smoking
Clinical Perspective

What Is New?

- Among current smokers, aortic wave reflections were associated independently with exhaled carbon monoxide, but these reflections and stiffness measures were associated more strongly with age, blood pressure, and waist circumference than smoking heaviness markers.
- After 3 years, aortic wave reflections improved with smoking cessation, despite more weight gain and insulin resistance; however, carotid artery distensibility worsened.

What Are the Clinical Implications?

- Changes in arterial measures with smoking cessation were predicted by changes in blood pressure, highlighting the need to address weight gain and blood pressure changes among smokers making a quit attempt.

Study Procedures

All participants were screened for eligibility and provided written informed consent. At the baseline and year 3 visits, various health markers were recorded including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight (to calculate body mass index), waist circumference, height, and current medication use. Fasting laboratory tests at both visits included a lipid panel, blood glucose, and hemoglobin A1C. Homeostasis model of insulin-resistance (HOMA-IR) was calculated. Smoking burden was measured by patient-reported cpd and confirmed via exhaled CO. Smoking abstinence was defined as patient-reported point-prevalence abstinence for the 7 days before the year 3 visit, which was biochemically confirmed via exhaled CO ($\geq$5 parts per million). Arterial measures were obtained at baseline and at the year 3 visit after an 8-hour fast as below.

Aortic Wave Reflections

After a 10-minute supine rest period, brachial artery blood pressures were obtained by oscillometric sphygmomanometry using a Dinamap Pro-400 (DINAMAP, GE Medical Systems, Milwaukee, WI). Radial artery tonometry was performed using the SphymoCor Px System (AtCor Medical Inc., Itasca, IL). After generation of 11 s of quality radial artery waveforms, this software used a transfer function to estimate the central aortic pressure from the radial pressure. Derived aortic waveforms were calibrated using the peripheral diastolic and mean blood pressures. Alx, which measures the amplitude of pulse wave reflection with greater pulse wave augmentation in stiffer arteries, was calculated. In our laboratory, reproducibility of blinded repeated Alx measurements was excellent (interclass correlation coefficient $= 0.90$ [95% CI 0.85–0.93]).

Material and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

We analyzed baseline and year 3 follow-up data from the WSWS-2 (Wisconsin Smokers Health Study 2), a longitudinal study with 2 components: a randomized, open-label comparative effectiveness trial that evaluated the efficacy of 3 different pharmacotherapies for smoking cessation, and a long-term health study of the effects of smoking and smoking cessation on CVD risk. Participants were smokers recruited from the Madison and Milwaukee areas. Some participants had previously participated in the WSWS-1 and others were newly recruited. Primary inclusion criteria for the WSWS-2 effectiveness trial were as follows: age $\geq 18$ years old, smoking $\geq 5$ cigarettes per day (cpd), exhaled carbon monoxide (CO) value $\geq 5$ parts per million, and desire to quit smoking. Relevant exclusion criteria were as follows: end-stage renal disease; untreated hypertension, heart attack, congestive heart failure or diabetes mellitus hospitalization within the last year; using other forms of tobacco more than twice in the past week; and exclusionary incidental findings from baseline health assessments such as carotid stenosis, advanced heart block, or stress-induced ischemia. This study was approved by the institutional review board at the University of Wisconsin School of Medicine and Public Health.

may accompany smoking cessation. Furthermore, these studies may have yielded different results because they used several different arterial measures that reflect different arterial beds and different manifestations of arterial distensibility and stiffening, including aortic wave reflections and velocity. Characterizing the effects of smoking cessation on aortic wave reflections, pulse wave velocity, and carotid artery distensibility and stiffness measures is an important step for elucidating the mechanisms of cardiovascular risk reduction related to smoking cessation.

We performed the first large, comprehensive, longitudinal study to evaluate the effects of smoking and smoking cessation on aortic wave reflections (aortic augmentation index [Alx]), aortic pulse wave velocity (PWV), and carotid artery distensibility and stiffness measures (distensibility coefficient and Young's elastic modulus [YEM]) in a large, longitudinal cohort of smokers making a quit attempt who were followed for 3 years.
Carotid-Femoral PWV

Carotid and femoral artery tonometry were used to calculate PWV. PWV measures the speed at which a pulse wave travels through the circulatory system, with higher values indicating stiffer arteries.\(^{32}\) While subjects were supine, 3 electrodes were placed to obtain an electrocardiographic signal with a high-amplitude R-wave. The location of a strong right carotid pulse was palpated and the distance between the suprasternal notch and the palpated carotid pulse was recorded. The location of a strong right femoral pulse was palpated and the measured distance to the suprasternal notch was recorded. Applanation tonometry of the carotid artery followed by the femoral artery was performed using the SphymoCor Px System (AtCor Medical Inc., Itasca, IL). Only waveforms with ≥80% detectable upstrokes and SD of ≤10% of the derived PWV were saved. PWV was calculated from the average of 2 high-quality measurements. In our laboratory, reproducibility of blinded repeated PWV measurements was excellent (interclass correlation coefficient=0.91 [95% CI 0.70–0.98]).\(^ {41}\)

Common Carotid Artery Distensibility

Longitudinal B-mode ultrasound images were obtained of the distal segment of the right common carotid artery using a high-resolution linear array transducer (L10-5) with a cardiovascular ultrasound system (CV70; Siemens Medical Solutions, Mountain View, CA). Simultaneous ECG was used to capture 3-beat loops. Systolic and diastolic artery diameter measurements of the distal 1 cm of the common carotid artery were made manually from 3 consecutive cardiac cycles using Access Point Web (version 8.0, Freeland Systems, Alpharetta, GA).

The carotid artery distensibility coefficient (DC, mm Hg\(^{-1}\times 10^3\)) was calculated as:

\[
DC = \frac{(Ds^2 - Dd^2)}{\Delta p \cdot Dd^2}
\]

Ds represents the internal arterial diameter at peak systole, Dd represents the internal diameter at end-diastole, and \(\Delta p\) represents the difference between the systolic and diastolic measurements (pulse pressure). DC represents a change in artery diameter throughout the cardiac cycle for a given change in blood pressure, with higher values in more distensible and lower values in stiffer arteries.\(^ {43,44}\)

YEM (mm Hg) of the carotid artery was calculated as:

\[
YEM = \left( \frac{Dd}{h} \right) \cdot \frac{1}{DC}
\]

Dd is the arterial diameter at end-diastole, h is the arterial wall thickness at end-diastole (external carotid artery diameter minus internal carotid artery diameter). YEM describes artery stiffness per centimeter of wall thickness, with higher values indicating stiffer arteries.\(^ {43–45}\) YEM and DC are inversely related; thus increased arterial stiffness corresponds to a lower DC and a higher YEM.\(^ {42,44}\) For reproducibility analyses, we blindly remeasured DC and YEM from 24 WSHS-2 participants. Reproducibility was excellent: for DC, interclass correlation coefficient=0.88 (95% CI 0.77–0.94); for YEM, interclass correlation coefficient=0.89 (95% CI 0.76–0.95).

Statistical Analysis

Analyses were performed using SPSS software (version 25.0; IBM Corp, Armonk, NY). Descriptive statistics were used to evaluate baseline participant characteristics. We expected smoking heaviness (cpd, CO) to adversely influence arterial measures (higher Alx, higher PWV, lower DC, higher YEM) and evaluated those relations and the relations between arterial measures and traditional cardiovascular disease risk factors (age, sex, race, body mass index, waist circumference, heart rate, SBP, DBP, lipids, HOMA-IR) using Pearson and point-biserial correlations. We used the Benjamini-Hochberg procedure to evaluate the 21 predictors for each outcome. To characterize the independent associations of these factors, we created separate hierarchical linear regression models to determine the influence of smoking heaviness on each arterial measure (Alx, PWV, DC, YEM) after adjustment for traditional CVD risk factors and use of antihypertensive, lipid-lowering, and antiglycemic medications. Pack-years of smoking was not considered as a marker of smoking heaviness for this analysis because it is so strongly correlated with cigarettes smoked per day (r=0.80, \(P<0.0001\)) and age (r=0.56, \(P<0.0001\)). Models of Alx also controlled for heart rate.\(^ {46}\)

Independent samples \(t\) tests and \(\chi^2\) tests were used to evaluate differences between continuing smokers and successful abstainers at year 3, as well as year 3 returners and nonreturners. We expected that smoking cessation would lead to improvements in arterial measures, independently of changes in CVD risk factors that may have occurred over 3 years. Separate hierarchical linear regression models were used to evaluate changes in arterial measures based on smoking status, with each year 3 arterial measure as the outcome and the baseline arterial measure as a predictor. The regression models were then adjusted for age, sex, race, and changes in waist circumference, total cholesterol, high-density lipoprotein cholesterol, SBP, DBP, and HOMA-IR in order to examine the relative importance of these variables in predicting changes in arterial measures after a quit attempt. The sensitivity of these models to the effects of antihypertensive, lipid-lowering, and antiglycemic medications at baseline and in year 3 also was evaluated. To further explore the
possibility of differential effects by key participant characteristics, we used regression models to determine whether baseline smoking heaviness (cpd, CO), age (median split), sex, and race (white/nonwhite) moderated the effect of year 3 status on each year 3 arterial measure using a moderator*year 3 smoking status term.

Results

Baseline Participant Characteristics

Baseline characteristics of all participants are shown in Table 1. There were 1417 smokers in this study. They were 54.0% female, 66.5% white, and were mean (SD) 49.3 (11.6) years old with a smoking heaviness of 17.2 (8.3) cpd and an exhaled CO of 14.7 (8.2) parts per million.

Table 1. Baseline Participant Characteristics (N=1417)

| Characteristic                  | Mean (SD) | Range |
|--------------------------------|-----------|-------|
| Age, y                         | 49.3 (11.6) | 18–90 |
| Sex (% female)                 | 54.0      |       |
| Race                           |           |       |
| White, %                       | 66.5      |       |
| Nonwhite, %                    | 33.5      |       |
| Cigarettes smoked/d            | 17.2 (8.3) | 5–75  |
| Exhaled carbon monoxide, ppm   | 14.7 (8.2) | 4–67  |
| Weight, kg                     | 85.7 (20.6) | 42–181 |
| Body mass index, kg/m²         | 29.4 (6.5) | 16–56 |
| Waist circumference, cm        | 98.3 (15.9) | 48–153 |
| Heart rate, bpm                | 65.5 (10.3) | 41–106 |
| Systolic blood pressure, mm Hg | 126.5 (17.1) | 79–197 |
| Diastolic blood pressure, mm Hg| 76.0 (10.1) | 53–117 |
| Pulse pressure, mm Hg          | 50.5 (15.4) | 12.5–115 |
| Total cholesterol, mg/dL       | 192.7 (41.0) | 84–452 |
| High-density lipoprotein cholesterol, mg/dL | 50.3 (17.4) | 19–149 |
| Low-density lipoprotein cholesterol, mg/dL | 114.4 (34.7) | 17–302 |
| Triglycerides, mg/dL           | 142.1 (130.4) | 30–2774 |
| Hemoglobin A1C, %              | 5.9 (1.0) | 4–14.4 |
| HOMA-IR                        | 3.1 (3.5) | 0–39.1 |
| Medication use, %              |           |       |
| Antihypertensive               | 28.8      |       |
| Lipid-lowering                 | 17.5      |       |
| Antiglycemic medications       | 7.8       |       |

HOMA-IR indicates homeostasis model of insulin resistance.

Baseline Associations of CVD Risk Factors and Smoking Heaviness with Arterial Measures

Alx correlated significantly with age (r=−0.52, P<0.001), sex (female=0, male=1; r=−0.31, P<0.001), race (white=1, nonwhite=2; r=−0.09, P=0.001), SBP (r=0.24, P<0.001), and DBP (r=0.23, P<0.001), but no other traditional CVD risk factors. Alx did not correlate significantly with cpd or CO; however, in models that adjusted for age and other CVD risk factors, Alx was independently associated with CO (standardized beta=0.054 [SE 0.027], P=0.004). PWV correlated significantly with age (r=−0.48, P<0.001), sex (r=0.07, P<0.001), race (r=0.08, P=0.005), SBP (r=0.50, P<0.001), DBP (r=0.38, P<0.001), and waist circumference (r=0.28, P<0.001). PWV correlated weakly with cpd (r=0.06, P=0.03) and inversely with exhaled CO (r=−0.06, P=0.03), but these associations no longer were significant using the Benjamini-Hochberg correction or after adjusting for age.

DC correlated significantly and inversely with age (r=−0.42, P<0.001), sex (r=−0.15, P<0.001), race (r=−0.17, P<0.001), SBP (r=−0.49, P<0.001), DBP (r=−0.34, P<0.001), and waist circumference (r=−0.27, P<0.001). DC had a weak correlation with CO (r=0.11, P<0.001); however, this association no longer was significant after adjusting for blood pressure (P=0.290). DC was not significantly correlated with cpd. YEM correlated significantly with age (r=0.19, P<0.001), sex (r=0.11, P<0.001), race (r=0.08, P=0.003), SBP (r=0.37, P<0.001), DBP (r=0.27, P<0.001), and waist circumference (r=0.13, P<0.001). YEM also had a weak, inverse correlation with CO (r=−0.08, P=0.002) that no longer was statistically significant after adjusting for blood pressure. The unexpected directionality of the weak correlations between DC and YEM with CO levels likely was related to their stronger inverse relationships with waist circumference and HOMA-IR, which were more strongly associated with DC and YEM than CO (data not shown).

Characteristics of Participants at Year 3

The 848 participants who completed year 3 follow-up are described in Table 2, including mean changes from baseline. There were some differences among people who attended the year 3 visit, compared with those who did not; they were older (mean age 50.0 [11.3] vs 48.2 [11.9] years old; P=0.003), had lower SBPs (125.6 [16.9] mm Hg, P=0.018), lower heart rate (64.8 [10.1] vs 66.5 [10.4] bpm, P=0.002), and were more commonly on lipid-lowering medication (19.3% vs. 14.8%) at baseline. No other significant differences in predictor variables were identified (Table S1).

Compared with continuing smokers (N=636), successful abstainers (N=212) were more likely to be white (82.1% vs 59.0%, P<0.001) with a similar percent female (56% vs 54%, P=0.58). Baseline SBPs and DBPs and pulse pressures were
similar. Of those abstinent at year 3, 69% also had been abstinent at year 1; of those who smoked at year 3, 95% were smoking at year 1. Successful abstainers gained more weight (5.6 [8.9] vs 0.8 [7.9] kg, \( P < 0.001 \)), had a significantly larger change (year 3-baseline) in waist circumference (6.4 [7.4] vs 1.9 [8.6] cm; \( P = 0.001 \)), high-density lipoprotein cholesterol (5.9 [10.5] vs 3.2 [12.4] mg/dL; \( P = 0.005 \)), and HOMA-IR (1.6 [3.2] vs 0.5 [3.8] mg/dL; \( P < 0.001 \)) compared with continuing smokers. Abstainers had a greater increase in SBP (5.9 [13.5] vs 3.3 [15.6] mm Hg; \( P = 0.084 \)) and pulse pressure (4.4 [12.4] vs 1.9 [14.1] mm Hg, \( P = 0.03 \)), but not DBP. After year 3, the percentage of continuing smokers on antihypertensive medications increased to 39%, but decreased to 36% among successful abstainers. Also, use of antihypertensive medication increased, especially among continuously smokers (74 new users vs 28 new users) so SBP, DBP, and pulse pressure were similar among continuing smokers and eventual abstainers. However, weight gain correlated significantly with increases in HOMA-IR \( (r=0.29, P<0.001) \) and SBP \( (r=0.08, P=0.022) \) in all participants at year 3. Among continual smokers, weight gain also correlated inversely with DBP \( (r=-0.10, P=0.017) \).

### Changes in Arterial Measures at Year 3 Related to Smoking Cessation Group

Changes in arterial measures among abstainers and continuing smokers at year 3 are shown in Table 3. In hierarchical linear regression models of year 3 arterial measures adjusted for the baseline arterial measure (but not other covariates), year 3 AIx was less in abstainers \( (P=0.006) \) than in continuing smokers. Year 3 DC was lower in abstainers than in smokers \( (P=0.004) \). Neither year 3 PWV nor YEM were significantly impacted by smoking status.

To better understand the factors that influenced changes in arterial measures 3 years after the quit attempt, we examined the impact of year 3 smoking status on year 3 arterial stiffness measures after accounting for baseline arterial measures, age, sex, race, and changes in CVD risk factors (waist circumference, BMI, etc.).

#### Table 2. Participant Characteristics at Year 3 and Changes from Baseline

|                          | All (N=848) | Smokers (N=636) | Abstainers (N=212) |
|--------------------------|------------|-----------------|-------------------|
|                          | Year 3 Mean (SD) | Mean Change From Baseline (SD) | Year 3 Mean (SD) | Mean Change From Baseline (SD) | Year 3 Mean (SD) | Mean Change From Baseline (SD) |
| Age, y                   | 53.2 (11.3) | 3.1 (0.4)       | 53.0 (11.0)       | 3.1 (0.4)                    | 53.9 (12.0)       | 3.2 (0.4)                       |
| Sex (% female)           | 54.2       |                 | 53.6              |                             | 56.1              |                                 |
| Race (% white)           | 64.7       |                 | 59.0              |                             | 82.1              |                                 |
| Cigarettes/d             | 10.9 (8.0) | -6.2 (8.8)      | 10.8 (8.0)        | -6.2 (8.8)                  | 0                 | -16.8 (7.2)                     |
| Carbon monoxide, ppm     | 9.8 (8.6)  | -4.6 (9.6)      | 12.5 (8.5)        | -1.9 (8.5)                  | 2.0 (0.9)         | -12.7 (7.9)                     |
| Weight, kg               | 87.2 (21.2)| 2.0 (8.4)       | 85.7 (20.3)       | 0.8 (7.9)                   | 91.5 (23.3)       | 5.6 (8.9)                       |
| Body mass index, kg/m²   | 30.0 (7.0) | 0.7 (2.9)       | 29.5 (6.7)        | 0.3 (2.8)                   | 31.2 (7.5)        | 1.9 (3.2)                       |
| Waist circumference, cm  | 101.6 (16.1)| 3.1 (8.5)     | 100.9 (15.6)      | 1.9 (8.6)                   | 103.6 (17.5)      | 6.4 (7.4)                       |
| Heart rate, bpm          | 66.2 (11.2)| 1.7 (9.1)       | 66.5 (11.1)       | 2.0 (9.3)                   | 65.5 (11.4)       | 0.8 (8.4)                       |
| Systolic blood pressure, mm Hg | 129.3 (17.4) | 4.0 (15.1)   | 129.0 (17.8)      | 3.4 (15.6)                  | 130.0 (16.3)      | 5.9 (13.5)                      |
| Diastolic blood pressure, mm Hg | 77.0 (10.0) | 1.5 (8.3)     | 77.2 (10.3)       | 1.5 (8.3)                   | 76.2 (9.0)        | 1.4 (8.3)                       |
| Pulse pressure, mm Hg    | 52.3 (15.1)| 2.5 (13.7)      | 51.8 (14.9)       | 1.9 (14.1)                  | 53.8 (15.6)       | 4.4 (12.4)                      |
| Total cholesterol, mg/dL | 190.8 (41.5)| -1.6 (38.5)  | 188.8 (41.0)      | -2.9 (39.1)                 | 196.6 (42.5)      | 2.4 (36.7)                      |
| High-density lipoprotein cholesterol, mg/dL | 54.1 (18.5) | 3.9 (12.0)    | 53.9 (18.3)       | 3.2 (12.4)                  | 54.6 (19.0)       | 5.9 (10.5)                      |
| Low-density lipoprotein cholesterol, mg/dL | 109.1 (37.0) | -4.9 (33.1)  | 108.0 (36.9)      | -5.2 (33.6)                 | 112.5 (37.0)      | -3.9 (31.7)                     |
| Triglycerides, mg/dL     | 142.9 (129.5)| 0.7 (135.2)  | 137.8 (109.0)     | -3.9 (125.8)                | 157.6 (176.2)     | 14.2 (159.2)                    |
| Hemoglobin A1C, %        | 6.0 (1.0)  | 0.1 (0.7)       | 6.0 (1.0)         | 0.1 (0.7)                   | 6.0 (0.8)         | 0.1 (0.5)                       |
| HOMA-IR                  | 3.9 (4.4)  | 0.7 (3.6)       | 3.6 (4.1)         | 0.5 (3.8)                   | 4.8 (5.2)         | 1.6 (3.2)                       |

HOMA-IR indicates homeostasis model of insulin resistance.
Table 3. Changes in Arterial Measures From Baseline to Year 3

|                  | Baseline (N=1417) | Year 3 (N=848) | Year 3 Smokers (N=636) | Year 3 Abstainers (N=212) |
|------------------|-------------------|----------------|------------------------|---------------------------|
|                  |                   |                | Baseline | Year 3 | Δ | Baseline | Year 3 | Δ | P Value* |
| Aix, %           |                   |                |          |       |    |          |       |    |         |
|                  | 27.5 (12.3)       | 28.9 (10.8)    | 28.4 (11.9) | 29.4 (10.5) | 1.0 (7.9) | 26.8 (11.5) | 27.3 (11.4) | 0.2 (6.9) | 0.006 |
| PWV, m/s         | 7.2 (1.7)         | 7.4 (1.0)      | 7.2 (1.6)  | 7.5 (2.0)  | 0.3 (1.5)  | 7.1 (1.5)  | 7.2 (1.5)  | 0.2 (1.2) | 0.239 |
| DC, mm Hg−1×103 | 4.2 (1.9)         | 3.6 (1.6)      | 3.6 (1.6)  | 4.3 (2.0)  | 0.7 (1.7)  | −0.6 (1.7) | 4.3 (1.8)  | 3.4 (1.6) | 1.0 (1.6) | 0.004 |
| YEM, mm Hg       | 1339.1 (823.6)    | 1458.7 (1022.9)| 1312.2 (848.9)| 1430.4 (945.6)| 120.7 (908.8)| 1296.4 (700.2)| 1545.2 (1228.3)| 270.6 (1304.1)| 0.074 |

All values are means (SDs). Aix indicates aortic augmentation index; DC, carotid distensibility coefficient; PWV, carotid-femoral pulse wave velocity; YEM, carotid Young’s elastic modulus. *P value for group effect in hierarchical linear regression model of year 3 arterial measures, adjusted for baseline arterial measure.

Table 4. Predictors of Arterial Measures at Year 3: Augmentation Index

|                  | Standardized β | SE     | P Value |
|------------------|----------------|--------|---------|
| A Heart rate     | −0.32          | 0.043  | <0.001  |
| Sex              | −0.17          | 0.979  | 0.001   |
| Δ Systolic blood pressure | −0.12        | 0.034  | 0.022   |
| Δ Diastolic blood pressure | 0.12         | 0.063  | 0.016   |
| Year 3 smoking status | 0.03         | 1.026  | 0.484   |

All data are from hierarchical linear regression models, adjusted for baseline augmentation index, where sex was coded as female=0, male=1, and year 3 smoking status was coded as abstainers=0, continuing smokers=1. Δ—year 3—baseline value.

Table 5. Predictors of Arterial Measures at Year 3: Pulse Wave Velocity

|                  | Standardized β | SE | P Value |
|------------------|----------------|----|---------|
| Age              | 0.31           | 0.02| <0.001  |
| Δ Diastolic blood pressure | 0.16         | 0.02 | 0.028   |
| Smoking status   | 0.13           | 0.30| 0.053   |

All data are from hierarchical linear regression models, adjusted for baseline pulse wave velocity, where year 3 smoking status was coded as abstainers=0, continuing smokers=1. Δ—year 3—baseline value.

The harmful effects of smoking and the numerous benefits of smoking cessation are well-established. However, the effects of smoking cessation on arterial distensibility, stiffness, and wave reflections are unclear. Prior studies evaluating the longitudinal effects of smoking cessation on arterial stiffness and wave reflections were limited by small sample size, short-term follow-up, cross-sectional study designs, and incomplete arterial stiffness assessment, yielding widely varying effect sizes and conclusions.12–14,17,20–22,26,29,30,33–36 This is the first large, comprehensive, longitudinal study to evaluate the effects of smoking and smoking cessation on aortic wave reflections (which reflect global arterial stiffness), aortic PWV (which reflects regional arterial stiffness), and carotid artery distensibility and stiffness (which reflect local arterial stiffness) in a contemporary cohort of smokers making a quit attempt.

When examining associations among those smoking at baseline, we observed a weak association between exhaled CO levels and Aix. Unlike a previous study that identified a dose-dependent association of Aix with smoking heaviness, as measured by cpd,22 we did not find an association between cpd and Aix. We did not find any associations between smoking heaviness and PWV, DC, or YEM. Aix was associated with other traditional CVD risk factors such as age, SBP, DBP, and heart rate, as described previously.24,40 Similarly, PWV, DC, and YEM were most strongly and consistently associated with increasing age, blood pressures, and waist circumference. Overall, among current smokers, age, blood pressures, and central adiposity were much more strongly associated with arterial measures than was smoking heaviness. These...
Table 6. Predictors of Arterial Measures at Year 3: Distensibility Coefficient

|                          | Standardized $B$ | SE | $P$ Value |
|--------------------------|------------------|----|-----------|
| Δ Systolic blood pressure| −0.31            | <0.001 | <0.001   |
| Smoking status           | 0.11             | <0.001 | 0.067    |

All data are from hierarchical linear regression models, adjusted for baseline distensibility coefficient, where year 3 smoking status was coded as abstainers=0, continuing smokers=1. Δ=year 3—baseline value.

findings emphasize that the effects of smoking cigarettes on arterial injury are multifactorial and may not even be related to arterial stiffness. After 3 years, successful abstainers had significantly greater weight gain and greater increases in waist circumference, insulin resistance, and pulse pressure compared with continuing smokers, consistent with prior studies demonstrating that weight gain after successful smoking cessation can lead to comorbidities such as hypertension and disorders of glucose metabolism. Despite weight gain, abstainers in our study still experienced improvements in AIx but not PWV. Prior studies have described similar findings, with significant improvements in AIx, but not PWV. Changes in AIx after 3 years were influenced more by changes in blood pressure and changes in heart rate than by abstinence, consistent with our cross-sectional observation that nonsmoking risk factors more powerfully influence AIx than smoking heaviness. In this study, more women quit smoking compared with men. Women also experienced less of an increase in AIx over time compared with men, which likely contributed to lower AIx values among abstainers. Heart rate went up in both groups, but less among abstainers compared with continuing smokers, possibly because of a decrease in autonomic activity with smoking cessation. Abstainers tended to have greater increases in SBP compared with continuing smokers; however, this may be because of more use of antihypertensive medication among continuing smokers. The effects of smoking cessation on blood pressure are complicated and seem to be affected by baseline blood pressures, degree of weight gain, and changes in antihypertensive medications.

Successful abstainers had worse measures of carotid DC and YEM than continuing smokers. In a small study, smoking cessation did not improve carotid DC or intima-media thickness. As we have noted previously, this may be because of greater weight gain and its attendant increases in blood pressure and insulin resistance among abstainers. Our multivariable models suggest that worsening DC and YEM are most strongly related to increases in SBP and possibly insulin resistance for YEM. Carotid artery systolic and diastolic diameters did not differ between successful abstainers and continuing smokers and were not related to weight gain (data not shown). Weight gain, insulin resistance, and increases in blood pressure among successful abstainers may mitigate some of the beneficial arterial effects of smoking cessation such as improvements in arterial endothelial function.

**Limitations**

As commonly seen in smoking cessation studies, ≈40% of participants did not return for their year 3 follow-up visits. This is consistent with dropout rates in other recent smoking cessation pharmacotherapy trials. Those who completed the year 3 follow-up visit were more likely to be older and white with higher systolic blood pressures at baseline than those who did not. They also used more antihypertensive medications. We used exhaled CO as a quantitative measure of smoking heaviness. Serum cotinine may be a more accurate marker. We had to use CO levels because it is a biomarker that would not be affected by the nicotine from nicotine replacement therapy during the treatment phase of this study; at year 3 no participants were using nicotine replacement therapy. All of our participants were smokers at baseline, so we do not have a nonsmoking control group with whom to compare the changes. Although the effects of other risk factors on arterial stiffness measures in nonsmokers have been well described in the medical literature, we cannot exclude the influence of unknown confounders, especially changes in diet. Indeed, this study was not designed to evaluate causes of weight gain after smoking cessation; because we did not obtain food records from participants, we could not assess the effects of changes in dietary composition. This was the longest prospective study of the effects of smoking cessation on changes in arterial wave reflection and stiffness measures we are aware of; however, our follow-up duration of 3 years may not have been long enough to detect changes; indeed, a decade or more may be needed. Finally, the generalized transfer function to derive central aortic wave forms for calculating AIx may have differential error between sexes and people with impaired glucose metabolism.

Table 7. Predictors of Arterial Measures at Year 3: Young’s Elastic Modulus

|                          | Standardized $B$ | SE | $P$ Value |
|--------------------------|------------------|----|-----------|
| Δ Systolic blood pressure| 0.19             | 4.0 | 0.012     |
| Δ HOMA-IR                | 0.14             | 10.9 | 0.050     |
| Smoking status           | −0.05            | 120.3 | 0.474     |

All data are from hierarchical linear regression models, adjusted for baseline Young’s Elastic Modulus, where year 3 smoking status was coded as abstainers=0, continuing smokers=1. Δ=year 3—baseline value. HOMA-IR indicates homeostasis model of insulin resistance.
Conclusions
In a large cohort of contemporary smokers, aortic Alx was independently associated with exhaled CO, a measure of smoking heaviness. However, arterial wave reflection and stiffness measures were associated more strongly with age, blood pressure, and waist circumference than smoking heaviness. Smoking cessation was associated with weight gain, increased insulin resistance, and increased pulse pressure. Changes in arterial wave reflections and stiffness were predicted by changes in blood pressure, highlighting the need to address weight gain and blood pressure changes among smokers making a quit attempt.

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Disclosures
None.

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SUPPLEMENTAL MATERIAL
Table S1. Comparisons of Baseline Values from Participants that Completed versus Participants that did not Complete the Year 3 Visit.

| Baseline variables                          | Completed Year 3 (N=848) | Did not complete Year 3 (N=569) | Test statistic (t-test or χ²) | p-value |
|--------------------------------------------|--------------------------|---------------------------------|-------------------------------|---------|
| Age (years)                                | 50.0 (11.3)              | 48.2 (11.9)                     | -2.93                         | 0.003   |
| Sex (% female)                             | 54.2                     | 53.6                            | 0.06                          | 0.81    |
| Race (% white)                             | 64.7                     | 69.2                            | 3.10                          | 0.08    |
| Cigarettes per day                         | 16.9 (8.1)               | 17.7 (8.5)                      | 1.75                          | 0.08    |
| Carbon monoxide (ppm)                      | 14.5 (8.2)               | 15.2 (8.3)                      | 1.59                          | 0.11    |
| Weight (kg)                                | 85.5 (20.3)              | 86.1 (21.0)                     | 0.56                          | 0.58    |
| Body-mass index (kg/m²)                    | 29.4 (6.5)               | 29.4 (6.5)                      | -0.11                         | 0.92    |
| Waist circumference (cm)                   | 98.4 (15.6)              | 98.2 (16.2)                     | -0.27                         | 0.79    |
| Systolic blood pressure (mmHg)             | 125.6 (16.9)             | 127.9 (17.5)                    | 2.39                          | 0.02    |
| Diastolic blood pressure (mmHg)            | 75.7 (9.9)               | 76.4 (10.3)                     | 1.28                          | 0.20    |
| Pulse pressure (mmHg)                      | 49.9 (15.1)              | 51.4 (15.8)                     | 1.82                          | 0.07    |
| Heart rate (bpm)                           | 64.8 (10.1)              | 66.5 (10.4)                     | 3.08                          | 0.002   |
| Total cholesterol (mg/dL)                  | 192.4 (40.7)             | 193.1 (41.5)                    | 0.33                          | 0.74    |
| High-density lipoprotein cholesterol (mg/dL)| 50.3 (17.7)             | 50.2 (17.1)                     | -0.11                         | 0.92    |
| Low-density lipoprotein cholesterol (mg/dL)| 114.2 (34.3)            | 114.6 (35.2)                    | 0.24                          | 0.81    |
| Triglycerides (mg/dL)                      | 141.6 (120.1)            | 142.9 (144.6)                   | 0.19                          | 0.85    |
| Hemoglobin A₁C (%)                         | 5.9 (0.9)                | 5.9 (1.1)                       | -0.14                         | 0.89    |
| HOMA-IR                                    | 3.1 (3.8)                | 3.1 (3.2)                       | -0.37                         | 0.71    |
| Medication use (%)                         |                          |                                 |                               |         |
| Antihypertensive                           | 30.4                     | 26.4                            | 2.74                          | 0.10    |
| Lipid-lowering                             | 19.3                     | 14.8                            | 4.94                          | 0.03    |
| Anti-glycemic                              | 8.5                      | 6.9                             | 1.26                          | 0.26    |

SD = standard deviation; HOMA-IR = homeostasis model of insulin resistance
Table S2. Changes in Year 3 Arterial Measures by Smoking Status by Age, Sex, and Race Groups.

Changes in Arterial Measures from Baseline to Year 3 by Age (median split; ≤50 vs ≥51 years old)

|                | Baseline (N=1417) | Year 3 (N=848) | Year 3 Smokers (N=636) | Year 3 Abstainers (N=212) |
|----------------|-------------------|----------------|------------------------|--------------------------|
|                | Baseline | Year 3 | Δ | Baseline | Year 3 | Δ |
| AIx (%)        | Younger   | 22.2 (12.6) | 24.6 (10.7) | 22.9 (12.3) | 25.2 (10.4) | 2.1 (8.3) | 22.3 (12.1) | 22.7 (11.6) | 0.3 (6.2) |
|                | Older     | 32.3 (9.7) | 32.2 (9.6) | 32.7 (9.6) | 32.7 (9.4) | 0.1 (7.5) | 30.2 (9.7) | 30.6 (10.1) | 0.2 (7.5) |
| PWV (m/s)      | Younger   | 6.5 (1.2) | 6.7 (1.4) | 6.5 (1.2) | 6.8 (1.5) | 0.3 (1.2) | 6.4 (1.6) | 6.5 (1.2) | 0.3 (1.1) |
|                | Older     | 7.7 (1.8) | 8.0 (2.0) | 7.7 (1.8) | 8.0 (2.1) | 0.3 (1.7) | 7.6 (1.6) | 7.7 (1.5) | 0.2 (1.3) |
| DC (mmHg⁻¹ x 10³) | Younger | 4.8 (2.0) | 4.1 (1.7) | 4.9 (2.0) | 4.2 (1.7) | -0.7 (1.8) | 5.2 (1.9) | 3.9 (1.8) | -1.3 (1.8) |
|                | Older     | 3.7 (1.7) | 3.2 (1.5) | 3.8 (1.8) | 3.2 (1.6) | -0.6 (1.6) | 3.6 (1.5) | 3.0 (1.2) | -0.7 (1.4) |
| YEM (mmHg)     | Younger   | 1227.6 (659.5) | 1326.6 (1008.2) | 1160.6 (675.5) | 1238.0 (638.0) | 70.7 (625.2) | 1110.9 (545.5) | 1604.0 (1687.3) | 492.8 (1728.1) |
|                | Older     | 1430.5 (902.9) | 1560.3 (1027.7) | 1394.3 (903.7) | 1574.5 (1109.3) | 188.9 (1024.1) | 1442.1 (775.4) | 1518.0 (734.9) | 112.7 (845.1) |

Changes in Arterial Measures from Baseline to Year 3 by Sex

|                | Baseline (N=1417) | Year 3 (N=848) | Year 3 Smokers (N=636) | Year 3 Abstainers (N=212) |
|----------------|-------------------|----------------|------------------------|--------------------------|
|                | Baseline | Year 3 | Δ | Baseline | Year 3 | Δ |
| AIx (%)        | Men      | 23.4 (12.2) | 25.7 (10.4) | 24.7 (11.5) | 26.3 (10.0) | 1.4 (8.3) | 22.6 (10.8) | 23.7 (11.3) | 1.1 (6.9) |
|                | Women    | 31.0 (11.2) | 31.6 (10.3) | 31.6 (11.3) | 32.1 (10.2) | 0.6 (7.6) | 30.2 (10.9) | 30.2 (10.6) | -0.5 (7.0) |
| PWV (m/s)      | Men      | 7.3 (1.7) | 7.5 (1.8) | 7.3 (1.6) | 7.5 (1.8) | 0.3 (1.5) | 7.2 (1.5) | 7.5 (1.5) | 0.5 (1.3) |
|                          | Women | 7.0 (1.6) | 7.4 (1.9) | 7.2 (1.8) | 7.5 (2.1) | 0.4 (1.5) | 7.0 (1.6) | 6.9 (1.4) | 0.04 (1.2) |
|--------------------------|-------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| DC (mmHg ×10³)           | Men   | 3.9 (1.7) | 3.4 (1.5) | 4.0 (1.8) | 3.5 (1.6) | -0.5 (1.6)| 3.9 (1.4) | 3.0 (1.1) | -0.9 (1.2) |
|                          | Women | 4.5 (2.0) | 3.7 (1.7) | 4.5 (2.1) | 3.8 (1.7) | -0.7 (1.8)| 4.6 (2.1) | 3.7 (1.8) | -1.0 (1.9) |
| YEM (mmHg)               | Men   | 1435.9 (870.2) | 1528.9 (998.7) | 1404.5 (900.6) | 1515.8 (1074.8) | 111.1 (1020.5) | 1334.3 (583.2) | 1571.4 (701.1) | 242.1 (746.6) |
|                          | Women | 1256.5 (772.6) | 1399.4 (1040.4) | 1232.1 (794.1) | 1356.6 (812.1) | 129.0 (800.2) | 1266.4 (781.6) | 1524.6 (1520.9) | 293.0 (1616.4) |

### Changes in Arterial Measures from Baseline to Year 3 by Race/Ethnicity (White vs. Non-White)

|                          | Baseline (N=1417) | Year 3 (N=848) | Year 3 Smokers (N=636) | Year 3 Abstainers (N=212) | Δ |
|--------------------------|-------------------|----------------|------------------------|---------------------------|---|
| Alx (%)                  | White 26.7 (12.4) | 28.5 (10.6)    | 27.6 (11.8)            | 29.1 (10.3)               | 1.4 (7.6)   | Baseline 26.3 (11.5) | Year 3 27.1 (11.3) | Δ 0.6 (6.5) |
|                          | Non-white 29.0 (11.9) | 29.6 (11.0)   | 29.6 (11.9)            | 29.9 (10.8)               | 0.3 (8.3)   | Baseline 29.2 (11.3) | Year 3 28.0 (11.9) | Δ -1.4 (8.6) |
| PWV (m/s)                | White 7.1 (1.6)  | 7.3 (1.8)      | 7.1 (1.6)              | 7.4 (1.9)                 | 0.3 (1.4)   | Baseline 7.0 (1.6)  | Year 3 7.1 (1.5)  | Δ 0.2 (1.2) |
|                          | Non-white 7.3 (1.7) | 7.7 (2.0)      | 7.4 (1.8)              | 7.8 (2.1)                 | 0.3 (1.6)   | Baseline 7.5 (1.3)  | Year 3 7.6 (1.4)  | Δ 0.3 (1.5) |
| DC (mmHg ×10³)           | White 4.4 (1.9)  | 3.8 (1.7)      | 4.6 (2.1)              | 4.0 (1.7)                 | -0.6 (1.9)  | Baseline 4.4 (1.8)  | Year 3 3.5 (1.6)  | Δ -0.9 (1.5) |
|                          | Non-white 3.8 (1.7) | 3.1 (1.5)      | 3.8 (1.7)              | 3.1 (1.5)                 | -0.7 (1.5)  | Baseline 3.9 (2.1)  | Year 3 2.8 (1.4)  | Δ -1.2 (2.0) |
| YEM (mmHg)               | White 1292.4 (793.8) | 1336.9 (759.0) | 1252.9 (850.1)        | 1290.4 (768.6)            | 35.5 (886.9)| Baseline 1266.4 (622.3)| Year 3 1439.8 (729.2) | 183.3 (758.7) |
|                          | Non-white 1433.3 (873.7) | 1686.5 (1360.7) | 1399.1 (841.3)        | 1636.7 (1128.7)           | 247.1 (927.8)| Baseline 1438.0 (988.2)| Year 3 2034.1 (2426.3) | 687.1 (2650.9) |