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Vascular Aging is Accelerated in Flight Attendants with Occupational Secondhand Smoke Exposure

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Abstract

Objective: To determine whether early vascular aging may be present in flight attendants with remote in-cabin secondhand smoke (SHS) exposure.

Methods: Twenty-six flight attendants with a history of in-cabin SHS exposure prior to the airline smoking bans were recruited. Pulse wave analysis, peripheral arterial tonometry, and brachial artery reactivity testing evaluated their arterial compliance and endothelial function.

Results: Flight attendants with remote in-cabin SHS exposure have normal blood pressure, pulse wave velocity, and reactive hyperemia index, but abnormal pulse pressure, augmentation index, flow-mediated dilation, and hyperemic mean flow ratio.

Conclusion: These preliminary findings suggest that flight attendants with remote in-cabin SHS exposure have pre-clinical signs of accelerated vascular aging and raise new questions about the relationship between remote SHS exposure and vascular health.

Keywords

secondhand smoke; endothelial dysfunction; arterial stiffness

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Conflicts of Interest: Dr. Neal Benowitz has served as an expert witness in litigation against tobacco companies.

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Introduction:

Compared to the general population, female flight attendants (FAs) have a 3.5-fold increase in cardiovascular disease, as demonstrated by a survey of domestic flight attendants in 2007[1] but this increased risk was no longer seen in a contemporary cohort of active flight attendants in 2014.[2] The reasons for this increased cardiovascular risk in FAs who were working in the early 2000s are not well understood but point to a temporal relationship. FAs generally have a lower prevalence of cardiovascular risk factors including hypertension, diabetes, and high cholesterol when compared to an age- and smoking history- matched population from NHANES[3], which suggests that mechanisms beyond traditional cardiovascular risk factors may be involved in the increased cardiovascular risk of FAs. Prior to the institution of smoking bans on domestic and international flights from 1988 to 1995, FAs were exposed to a significant amount of SHS, approximately 14-fold the SHS of an average person.[4] Although active secondhand smoke (SHS) exposure is known to be associated with increased risk of myocardial infarctions and cardiovascular death by 25–30%[5–7], there is limited data linking remote SHS exposure to future cardiovascular events.

Active SHS exposure has previously been found to have deleterious effects on cardiovascular predictors such as blood pressure, arterial compliance and endothelial function.[8–11] Active smoking leads to an acutely increased arterial stiffness and higher aortic systolic blood pressure, due to smoking-induced reduced pulse pressure amplification and increased arterial wave reflection[12], and a prior investigation of FAs found an association between occupational SHS exposure and systemic hypertension[13]. In addition, active SHS exposure acutely impairs endothelial function in young healthy nonsmokers.[14–16] However, whether remote occupational SHS leads to chronic abnormalities in vascular compliance and endothelial function (25 years later) is unknown.

To assess the effects of remote occupational SHS exposure on vascular aging, we tested arterial stiffness and endothelial dysfunction in a group of FA’s with history of remote, in-cabin SHS exposure.

Materials and Methods:

This study was conducted at Cedars-Sinai Medical Center, Los Angeles, and the Flight Attendant Medical Research Institute (FAMRI) Bland Lane Center at UCSF, San Francisco. Current or prior FAs who previously enrolled in the FAMRI “Cardiopulmonary Effects of Second Hand Smoke on Flight Attendants” study were contacted for the vascular study. Inclusion criteria were age 40 years or older and SHS exposure for at least one year while working on the aircrafts. Exclusion criteria were prior history of Raynaud’s syndrome, mastectomy or arm/hand abnormality which precludes from blood pressure measurement. Participants with personal history of smoking, defined as smoking more than 100 cigarettes in their lifetime, as well as active smokers were excluded from the study. The IRB approved this study, and written consent was obtained from each participant.

All participants also completed a questionnaire (employment, medical, SHS exposure history), clinical examination, spirometry testing, and electrocardiogram as part of the study.

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Twenty-six FAs were enrolled to undergo vascular testing, including pulse wave analysis, peripheral arterial tonometry (PAT), and brachial artery reactivity testing (BART). To confirm current non-smoking status of participants and to confirm the absence of active/recent SHS exposure, urine cotinine and urine 4- (Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) were obtained.

Measurement of SHS Exposure:

Published FAMRI definitions were used to characterize SHS exposure[3]. A detailed assessment of in-cabin exposure was collected. FAs recorded the starting and ending month and year of airline service and report whether the majority of their flight routes were domestic or international or combined. For FAs who flew predominantly domestic routes, 1988 was defined as the ban year date, since this was the year smoking bans went into effect for the majority of US domestic routes. For FAs who flew mostly flew international routes, 1995 was used as ban year date, since this was the year US airlines began to ban smoking on international flights. Consideration was not made for cabin chamber worked (i.e., first class, coach), as this has not been demonstrated to have a significant effect on SHS exposure amongst flight attendants[17]. Total years and hours of flying (pre+ post smoking ban) were calculated. Non- aircraft related SHS exposure were ascertained by asking about childhood exposures, exposure in the home, exposure outside of the home, and exposure in other workplaces. Assessment of smoke exposure includes years of exposure and average hours per day that the participant had seen or smelled smoke in each environment. Cumulative SHS exposure was expressed as years and hours of SHS exposure for both pre- and post-ban SHS exposure (including non-aircraft related SHS exposure). Significant SHS exposure was defined as >1 hour a day.

To confirm current non-smoking status of participants and to confirm the absence of active/recent SHS exposure, urine cotinine and urine 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) were measured.[18, 19] The purpose of these measures was to confirm that the participants did not have acute or recent SHS exposure, as the half-life of cotinine is 16 hours while the half-life of NNAL is 10–16 days. Urine cotinine level greater than 0.25 ng/ml was considered significant for SHS exposure and greater than 31.5 ng/ml for active smoking (sensitivity 97.1%, specificity 93.9%).[20] Urine NNAL level greater than 1.25 pg/mL was considered significant for SHS exposure, while optimal cutoff points of urine NNAL to discriminate SHS exposure versus active smoking was 47.3 pg/mL (sensitivity 87.4%, specificity 96.5%)[20] or 64 pg/mg creatinine[21]. All cotinine and NNAL levels were measured at the FAMRI core lab at UCSF.

Vascular Testing:

All participants underwent pulse wave analysis and PAT at rest, and a subset of 10 participants underwent BART. In preparation for the vascular studies, FA's were asked to fast for 8 hours prior to testing, not consume caffeine, tobacco, or stimulants for 12 hours, no vasoactive medications 12 hours before testing, arrive with clipped nails, wear accessible clothing in order to have access to the arm, and to not engage in strenuous exercise before testing. Vascular testing protocols are detailed below.

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Pulse Wave Analysis: Pulse wave analysis using the SphygmoCor system (AtCor Medical, Australia) was performed to measure aortic pulse wave velocity (PWV) and augmentation index (AIx), as they have previously been shown to predict hard cardiovascular adverse events[22–24] and are reproducible[22]. PWV was assessed by recording the pulse waves of the carotid and femoral arteries using applanation tonometry as previously published[25]. Brachial waveforms were used to generate central aortic pressure waveforms (Figure 1), which was then used to determine AIx, defined as the ratio of wave reflection amplitude to central pulse pressure. AIx was also normalized for heart rate of 75 bpm (AIx75), as there is a linear relationship between heart rate and AIx. Normal reference values for PWV are 8.4 ± 1.7 (age 50–59 years), 9.7 ± 2.0 (age 60–69 years), and 11.7 ± 2.9 (age ≥ 70 years)[26]. Reference AIx is 15±13 for men and women (mean age 63 years) in the Framingham study[27]. Reference values for AIx75 are not available for the age range of this study. All pulse wave analysis data were reviewed by the Vascular Core Lab at CSMC.

Peripheral Artery Tonometry (PAT): PAT using EndoPAT2000 (Itamar Medical, Israel) was performed to assess endothelial dysfunction, as previously published[28]. Endothelium-dependent flow mediated dilation (Figure 2) causes an increase in the PAT signal amplitude and is analyzed by a computerized, automated algorithm (Itamar Medical), with calculation of the reactive hyperemia index (RHI) as the post-occlusion to pre-occlusion ratio. RHI, which predicts cardiovascular adverse events[11], is reproducible and has been accepted as a reliable noninvasive measure for large community cohorts[28, 29]. Normal RHI is considered to be ≥1.67[30]. PAT images were reviewed by the Vascular Core Lab at CSMC.

Brachial artery reactivity testing (BART): After a supine ten-minute rest, the subject's brachial artery baseline diameter (BAD), flow mediated dilation (FMD), and hyperemic mean flow ratio as previously described[31]. Reactive Hyperemic velocity-time integral (RH VTI) was measured after cuff release averaging the first three full cardiac cycles (Figure 3). FMD (% change) was calculated as diameter change from baseline. The hyperemic mean flow ratio was calculated by dividing mean flow during hyperemia by mean flow at baseline. Brachial FMD of 4.4±2.8 % was the mean reference value for men and women (mean age 61 years) who were free of clinical cardiovascular disease in the Multi- Ethnic Study of Atherosclerosis (MESA).[32] In the Framingham Heart Study (mean age 61 years, 13% had cardiovascular disease), FMD was 3.3±3.0% in women and 2.3±2.4% in men, while hyperemic mean flow ratio was 9.1±5.5 in women and 7.2±4.9 in men[31]. RH VTI references values were not reported in the MESA or Framingham cohorts. Ultrasound images were measured by the Core Lab at UCSF.

Statistical Analysis:

Values are expressed as mean ± standard deviation or percentages as indicated. Pearson correlation coefficients (p-values) were used to report associations among these measures.

Results:

Baseline characteristics are described in Table 1. FAs had a mean age of 62 years and were predominantly female (85%). Majority of the FAs had no known cardiovascular risk factors.

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Mean hours of in-cabin SHS exposure pre-ban was 13,668 hours over a mean of 14 years. Vascular measures show that FAs with pre-ban SHS exposure have a normal group mean blood pressure, pulse wave velocity, and reactive hyperemia index, but abnormal pulse pressure, augmentation index, flow-mediated dilation and hyperemic mean flow ratio (Table 2).

In-cabin SHS exposure correlated with age (r=0.40, p=0.045) and trended with total flight years (r=0.34, p=0.086) but did not correlate with blood pressure, pulse pressure, PWV, FMD % change, or RHI. Age did not correlate with pulse pressure, AIx, AIx75, or PWV in this study. Systolic blood pressure had a significant correlation with PWV (r=0.45, p=0.021) but did not correlate with AIx or AIx75. There was a trend between AIx and PWV (r= 0.35, p=0.081). In the small subgroup of 10 participants who underwent BART, FMD % change was inversely related to RHI (r= −0.64, p=0.047).

Discussion:

We found evidence of accelerated vascular aging in flight attendants exposed to in-cabin SHS prior to the smoking ban, as represented by a high AIx, high systolic blood pressure, high pulse pressure, low FMD % change, and low hyperemic flow ratio. Active SHS exposure has previously been linked to increases in arterial blood pressure and arterial stiffness and impairment of endothelial function in healthy young men[14, 33], and we now report that nonsmoking FAs with remote in-cabin SHS exposure have abnormal measures of vascular health even 25 years after the airline smoking ban. Our population was predominantly female and middle aged, with no significant cardiovascular risk factors other than a long duration of remote in-cabin SHS exposure. We found large vessel dysfunction (abnormal AIx, pulse pressure, FMD % change, and hyperemic mean flow ratio) among these participants, while their small vessel function (RHI) was within normal limits. Our lack of correlation between vascular variables was likely related to our small sample size, as we were also not able to correlate age with any of our vascular marker. Thus, these results should be viewed as preliminary, and should be confirmed in a larger study.

Vascular dysfunction induced by smoking exposure is related to reduced nitric oxide production, proatherogenic alterations in the vascular wall, endothelial damage, and inflammation[34]. SHS may thus lead to early vascular aging even in the absence of significant traditional cardiovascular risk factors such as hypertension, diabetes, and hypercholesterolemia.

Based on our preliminary study, a comparison of the vascular markers of FAs with remote in- cabin SHS exposure to FAs without remote in-cabin SHS exposure should be performed in a larger sample with matching for age, total flight hours, and cardiovascular risk factors. Other FA-related factors such as sleep patterns[35], altitude[36], and cosmic radiation[37] are potential confounders for vascular health. We were not surprised at the lack of correlation between age and vascular markers given the small sample size and the narrow age range of our FAs (age 51–75). A prior analysis by the Anglo- Cardiff Collaborative Trial demonstrated that while both AIx and PWV positively correlate with age, the age-related changes in AIx and PWV are non-linear[38]. PAT RHI has also been shown to correlate with

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cardiometabolic factors (cholesterol, diabetes, smoking, blood pressure) but not with age[39]. Although we expected a positive relationship between FMD and RHI, prior studies have demonstrated no correlation between PAT RHI and brachial artery FMD[39–41], suggesting that PAT RHI and brachial artery FMD evaluate two different vascular phenotypes (large conduit arteries vs smaller digital vessels). Further investigation is needed to determine whether there is heterogeneity in the impact of SHS exposure on different-sized vessels. Nevertheless, both PAT RHI and brachial artery FMD significantly predict cardiovascular events, and recently the prognostic values of these tests were found to be similar[42].

Limitations:

Limitations of this study include the small sample size and reliance on the reference values of historical published controls.

Conclusions:

Flight attendants with in-cabin SHS prior to the airline smoking ban have a group mean normal blood pressure, pulse wave velocity, and reactive hyperemia index, however have evidence of vascular aging by three concurrent tests including abnormal pulse pressure, augmentation index and flow- mediated dilation. These preliminary findings suggest that flight attendants with in-cabin SHS prior to the airline smoking ban have pre-clinical accelerated vascular aging. Given that CVD remains the leading cause of mortality in the US, further investigation should be conducted in a larger cohort to evaluate the relationship between chronic SHS exposure duration and vascular health, with controlling of traditional cardiovascular risk factors and potential confounders such as sleep patterns, altitude, and cosmic radiation.

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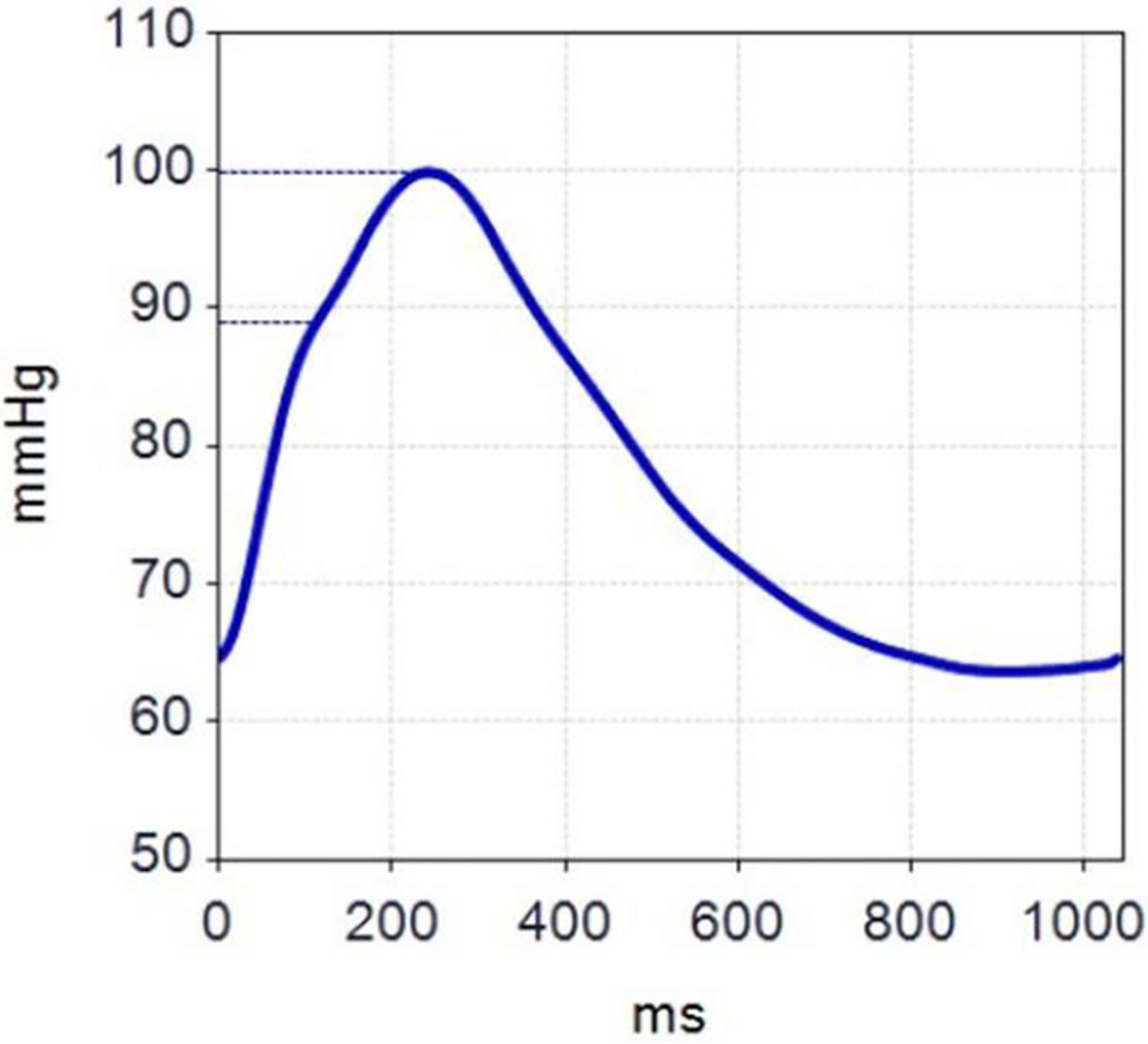

Figure 1: Pulse Wave Analysis.

Example of pulse wave analysis in a 54-year-old female healthy flight attendant with 10,800 hours of SHS prior to the airline smoking ban. Aortic blood pressure was 100/65, pulse pressure 35 mmHg, and augmentation index (AIx) was 43%, which is above average for her age. Higher AIx is associated with stiff arteries.

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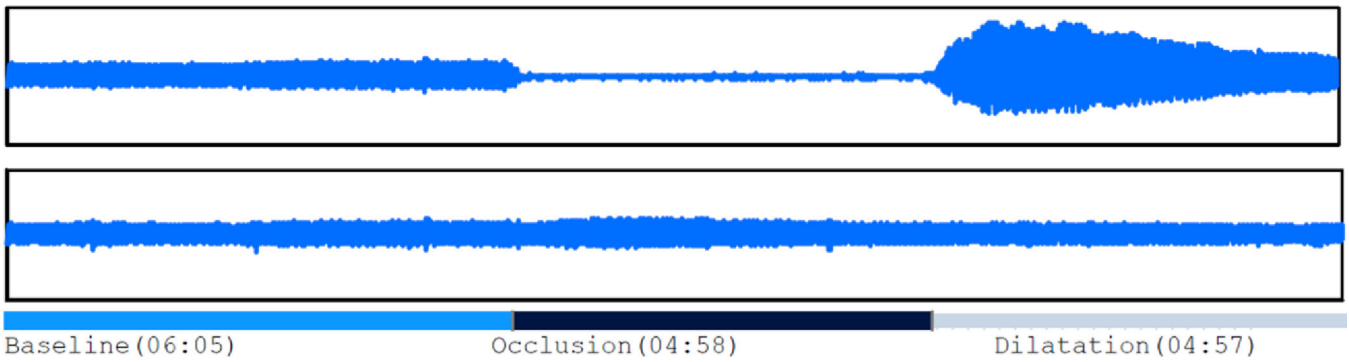

Figure 2: Peripheral Arterial Tonometry.

Example of PAT in a 58-year-old female flight attendant with a history of hyperlipidemia and 10,920 hours of SHS prior to the airline smoking ban. The top row demonstrates the digital pulse amplitude of the index finger from the non-dominant hand, while the bottom row demonstrates the digital pulse amplitude of the control index finger from the dominant hand. Her reactive hyperemia index (RHI) was 3.3, which is above average for her age. Lower RHI represents endothelial dysfunction of the microvascular system.

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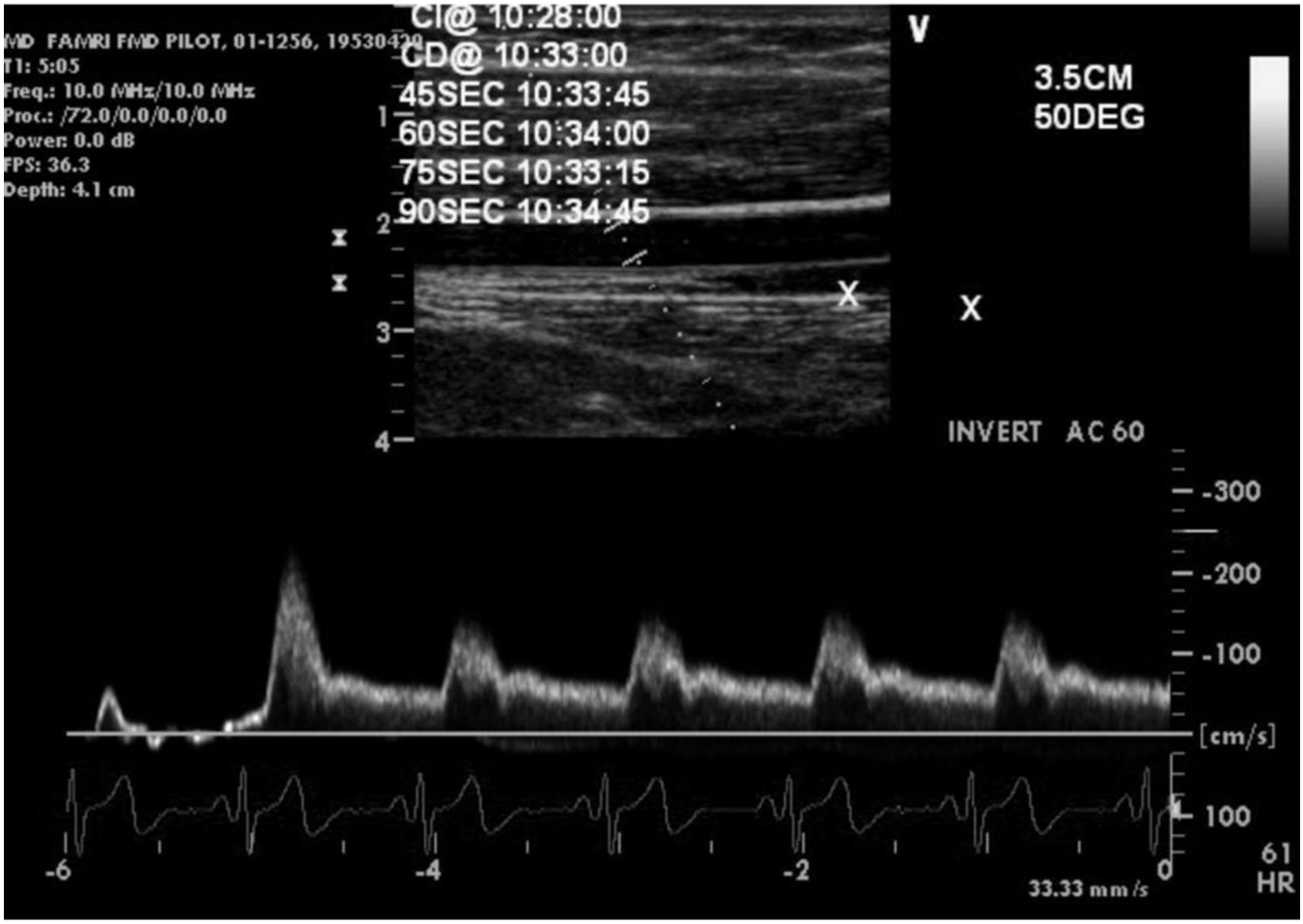

Figure 3: Brachial Artery Reactivity Testing.

Example of BART in a 62-year-old male flight attendant with history of hyperlipidemia and 12,960 hours of SHS prior to the airline smoking ban. Brachial artery diameter was measured as 4.2 mm at baseline, and flow-mediated dilation (FMD) was 3.3%, which is considered low for age. Lower FMD represents endothelial dysfunction of the large arteries. Vascular velocity tracings are recorded after cuff release for measurement of the reactive hyperemic velocity time integral (RH VTI).

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Table 1.

Baseline Characteristics

Characteristic	Mean (SD), Median (Range) or N (%)
Age (years)	61.6 (6.3)
	61 (51 – 75)
Sex	
Male	4 (15%)
Female	22 (85%)
Ethnicity	
Caucasian	17 (65%)
Black	6 (23%)
Asian	3 (12%)
Other	0
Cardiovascular Risk Factors	
Hypertension	2 (8%)
Hyperlipidemia	5 (19%)
Diabetes	0
Prior history of Cardiovascular Disease	0
SHS Exposure (pre-ban)	
Years	14.2 (5.9)
	13 (4 – 27)
Hours	13,668 (5,989)
	11,940 (3,360 – 28,080)
Urine Cotinine (ng/mL)	0.04 (0.01)
Urine NNAL (pg/mL)	0.31 (0.19)
Normalized NNAL/Creatinine (pg/mg)	0.40 (0.42)

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Table 2.

Vascular Measures

Measurement	Mean (SD)	Reference Values
Pulse Wave Velocity (PWV, m/s)	8.7 (1.5) (all)	
	8.8 (1.0) (50≤ age <60, n=12)	8.4 (1.7)[43]
	8.5 (2.0) (60≤ age <70, n=11)	9.7 (2.0)[43]
	8.5 (1.8) (70≤ age, n=3)	11.7 (2.9)[43]
Augmentation Index (AIx, %)	**33.9 (8.3)**	**15.0 (13.0)**[27]
Heart-rate corrected AIx (%)	25.6 (9.9)	not available *
Reactive Hyperemia Index	2.4 (0.6)	1.78 (0.08)[30]
Brachial SBP (mmHg)	**125 (17)**	**90–120**
Brachial DBP (mmHg)	74 (8)	60–80
Brachial Pulse Pressure (mmHg)	**51 (13)**	**30–40**
Flow-Mediated Dilation (%change)	**2.7 (1.9)**	**4.4 (2.8)**[32]
Reactive Hyperemic VTI (cm)	72 (15)	not available *
Hyperemic Mean Flow Ratio	**6.0 (1.4)**	**9.1 (5.5)**[31]

DBP=diastolic BP, SBP=systolic BP, VTI= velocity time integral

*no published reference controls available to match age range of flight attendants. Shaded rows indicate that the measurement in the flight attendants was outside the reference values derived from a similar population.