CLINICAL STUDY

Is Acute High-Dose Secondhand Smoke Exposure Always Harmful to Microvascular Function in Healthy Adults?

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Long-term exposure to secondhand smoke (SHS) is associated with impaired vascular function. The authors investigated the vascular and blood pressure (BP) reactions to acute SHS exposure. Twenty-five healthy nonsmoking adults underwent a 1-hour exposure to SHS (mean fine particulate matter <2.5 μm level=315±116 μg/m^3). Microvascular endothelial-dependent vasodilatation (EDV) (EndoPAT, Itamar Medical, Caesarea, Israel) and aortic hemodynamics/compliance (SphygmoCor, AtCor Medical, West Ryde, Australia) were measured before and after the SHS exposure with BP measured every 15 minutes during and for a 24-hour period before and after the exposure. SHS exposure did not change EDV, aortic hemodynamics, arterial compliance, or 24-hour BP. However, diastolic BP significantly increased during the SHS exposure period by 3.4±5.6 mm Hg. Our brief SHS exposure did not impair microvascular endothelial function or arterial compliance in healthy nonsmoking adults, but brachial diastolic BP increased.
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Exposure to secondhand smoke (SHS) increases cardiovascular (CV) risk.[1,2] Several studies have shown that a ban on indoor smoking in public venues reduces CV events within only months.[3,4] Thus, it is possible that even short-term exposure (or repeated brief contacts with) SHS can rapidly impart clinically meaningful health risks.[2]

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Among several potential biologic mechanisms explaining this association, the most recent Surgeon General's Report states that the evidence is sufficient to infer a causal relationship between SHS and endothelial cell dysfunction.[5] Although long-term exposure is consistently linked to impaired vascular function,[1] the few studies reporting the effects of brief exposure are inconsistent.[2] In addition, the acute effect of SHS on systemic hemodynamics also remains controversial.[2] Avoidance of SHS is proven to reduce CV risk and should be recommended to all high-risk patients.[3,4] Nonetheless, many individuals may be involuntarily exposed.

The aims of this study were therefore to specifically determine whether short-term SHS exposure impairs vascular function and/or alters systemic hemodynamics. Since most previous reports have focused on only one vascular territory (thereby missing the entirety of potentially discordant CV responses),[1,2] we investigated the effect of SHS on both microvascular endothelial-dependent vasodilatation (EDV) and large arterial compliance and central aortic hemodynamics.

METHODS

The study protocol was approved by the University of Michigan institutional review board. We recruited 25 healthy nonsmoking adults aged 18 to 50 years who lived in a nonsmoking household and were not exposed to SHS on a routine basis. All participants were free of known CV disease or risk factors (fasting glucose <126 mg/dL, low-density lipoprotein cholesterol <160 mg/dL, blood pressure [BP] <140/90 mm Hg) and taking no medications known to alter vascular function. All female participants had a negative urine pregnancy test result upon enrollment.

Participants were fasting >8 hours prior to each study visit. They underwent a 1-hour exposure to SHS in a smoking research laboratory between 8 and 9 am. All vascular studies and systemic hemodynamic measurements were done on-site before and after each exposure by the same technician using the same equipment. Participants wore an ambulatory BP

monitor (90207 ABP Monitor; Spacelabs Healthcare, Inc., Issaquah, WA) for 24 hours before and after the exposure.

Exposures occurred in a ventilated room where participants remained resting in a seated position throughout the study. We generated mainstream and sidestream SHS because both are toxicologically important.[1,2] One cigarette was actively smoked within 2 m of the participant, while we left a second cigarette lit on an ashtray within 1 m of the participant. Our smoker smoked at a rate of 1 cigarette every 15 minutes, and the cigarette in the ashtray was replaced every 15 minutes. Carbon monoxide (CO) levels were continuously monitored (Thermo Environmental Franklin, MA), which always remained <10 PPM to assure CV effects were not attributed to CO. Fine particulate matter <2.5 μm ($PM_{2.5}$) levels were continuously measured during exposures by a laser-based light scattering instrument (nephelometer, MIE Inc, Bedford, MA) that was placed at the level of the head within 1 m of the participant. Each participant had his or her dominant arm brachial BP measured in triplicate at the start and every 15 minutes throughout the exposure. The BP results were blinded to the participants and recorded in the memory of the automated oscillometric device (Omron HEM-712C, Omron, Schaumburg, IL). The mean of the second and third BP and heart rate were recorded for analyses.

Vascular Studies

Participants lay supine for 10 minutes prior to all vascular studies. First, central aortic BP waveform and hemodynamic analyses were performed by right arm radial artery tonometer. Second, arterial compliance was measured by determining pulse wave velocity (carotid and femoral artery tonometer positions). Both methods were performed using the SphygmoCor system (AtCor Medical, West Ryde, Australia), as we have previously described.[6] Third, participants remained supine for 5 minutes, and then finger EDV was measured by determining the reactive hyperemia index (RHI) using the EndoPAT2000 system.[7] Last, endothelial-independent vasodilatation was determined by the finger nitroglycerin index, as previously described.[7]

Statistical Methods

Data were collected and analyzed using SPSS 15.0 for Windows. All pre-exposure vs post-exposure parameters were compared by 2-tailed paired *t* tests. The slopes of the changes of the intra-exposure BP and heart rate were compared vs a slope of zero by a linear mixed model analysis. The 5 time points for BP and heart rate were compared by a mixed model analysis. Significance was defined as a $P<.05$.

RESULTS

All participants were healthy and without CV risk factors (Table I). $PM_{2.5}$ levels during exposure were high (315±116 μg/m^3; range 158–565 μg/m^3), yet at environmentally relevant concentrations, as found in public smoking areas in restaurants and bars.[8] SHS exposure did not significantly impair EDV (RHI), arterial compliance (pulse wave velocity), or central aortic or 24-hour ambulatory brachial BP (Table II).

Table I. Participant Characteristics

	Entire Cohort (N=25)
Demographics	
Age, y	32±9
Sex	
Female	16
Male	9
BMI, kg/m^2	25.5±3.8
Blood laboratory values	
Total cholesterol, mg/dL	178±31
LDL-C, mg/dL	110±30
HDL-C, mg/dL	52±13
Triglycerides, mg/dL	85±51

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. All values are presented as mean±SD.

Table III shows the exposure BP and heart rate responses; systolic BP and heart rate did not change. However, diastolic BP significantly increased ($P<.05$) during the SHS exposure (Figure), and it increased in 19 participants (76%).

DISCUSSION

Unlike the adverse effects of chronic exposure,[1] the acute effect of SHS on the vasculature remains controversial.[1,2] Contrary to our hypothesis, we did not confirm any detrimental effect of a single hour of exposure to high levels of SHS on microvascular endothelial function or arterial compliance in healthy nonsmoking adults. However, we believe there was a vascular response to the exposure because there was a rapid increase in diastolic BP in most participants during the period of smoke inhalation. Although SHS exposure did not impair vascular function in our study, CV events may be triggered by the prohypertensive reaction following a brief SHS exposure.

Vascular Responses to SHS

There have been surprisingly few and inconsistent study results regarding the acute effect of SHS on vascular function among healthy nonsmokers.[2] In 2 previous studies, forearm microvascular endothelial function did not change after only 15 minutes of exposure.[9,10] In contrast, coronary flow reserve to adenosine infusion (myocardial resistance arterial vascular function) was impaired after 30 minutes.[11]

Table II. Vascular and Hemodynamic Responses Before and After Secondhand Smoke Exposure

	Pre-Exposure	Post-Exposure	24 Hours Post
Microvascular function			
Reactive hyperemia index	1.76±0.57	1.76±0.42	–
Nitroglycerin index	1.44±0.75	1.40±0.51	–
Arterial compliance and hemodynamics			
Central systolic blood pressure, mm Hg	105±10	101±8	–
Pulse pressure, mm Hg	33±6	27±5	–
Augmentation pressure, mm Hg	4±5	4±5	–
Augmentation index, % @ HR 75	7±13	5±19	–
Ejection duration, %	35±5	33±5	–
Subendocardial viability ratio, %	166±41	184±36	–
Pulse wave velocity, m/s	7±1	7±1	–
Ambulatory blood pressure monitoring			
Systolic blood pressure, mm Hg	112±8	–	112±8
Diastolic blood pressure, mm Hg	67±6	–	68±7
Heart rate, beats/min	72±12	–	73±15

All data are presented as mean±SD, n=25.

Table III. Blood Pressure and Heart Rate During Secondhand Smoke Exposures

Time, min	Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg	Heart Rate, beats/min
0 (start)	112±8	70±5	66±13
15	110±8	71±6	64±13
30	110±8	71±7	64±12
45	111±8	74±6	65±13
60 (end)	112±8	74±7[a]	66±11

All data are presented as mean±SD, n=25. [a]$P<.05$ as compared to baseline, time 0.

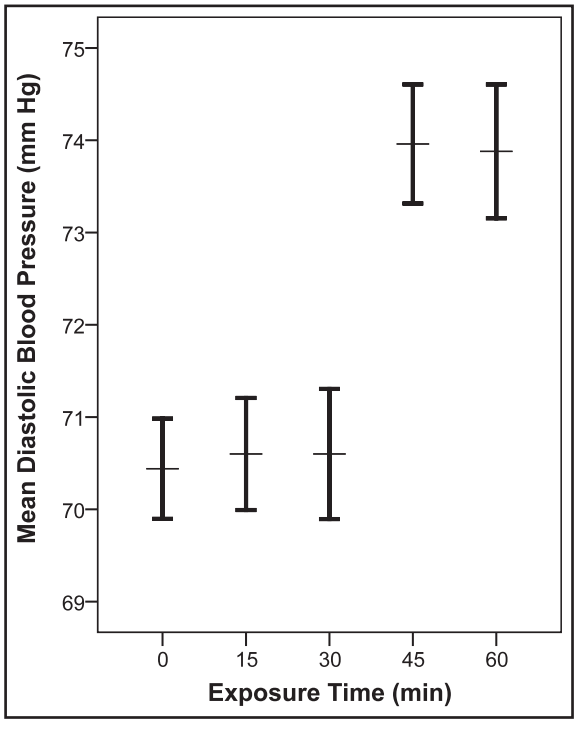

Figure. Diastolic blood pressure responses during secondhand smoke exposures.

SHS has also been shown to cause conduit brachial artery endothelial dysfunction following 20 and 30 minutes of inhalation.[12,13] The effect on arterial compliance has also been discordant with reductions reported in some[14] but not all studies.[15] Finally, the most recent publications have corroborated that conduit brachial[16] and skin microvascular[17] EDV are indeed blunted and aortic augmentation index is increased[17] after 30 to 60 minutes of SHS exposure.

The explanation for the lack of impairment in vascular function in the current study remains unclear. Given the long duration of exposure (1 hour), high $PM_{2.5}$ levels (315±116 μg/m^3), and our relatively large sample size (n=25) comparable with previous experiments, it is unlikely that our null findings simply represent a type 2 error or an inadequate exposure concentration/duration. The published results suggest that the arterial territory under scrutiny may be a critically important factor. The microvasculature (such as the present experiment) appears to be inconsistently adversely affected,[9,10,17] and conduit arterial EDV does seem to be more typically impaired following exposures.[12,13,16,17] Therefore, larger arteries may be acutely susceptible to SHS, or perhaps the methodology we employed—use of the validated EndoPAT device—was not sensitive enough to detect any potential effect. It is also plausible that differences

may exist between presumably homogeneous populations of "healthy" participants. For example, the effect of $PM_{2.5}$ on heart rate variability is critically determined by variations in antioxidant genes in healthy adults (eg, glutathione S-transferase).[18]

Hemodynamic Responses to SHS

The acute effect of SHS on BP is mixed in the literature as well. Some studies have reported that SHS increases brachial BP,[16] while others have not.[9,10,17] Since the prohypertensive response in our present study was modest, was transient in nature, and occurred solely during the actual inhalation of smoke, it could have been overlooked in previous experiments. In addition, the BP increase occurred predominantly during the latter portion of exposure, which may explain why results of shorter-duration experiments (eg, <30 minutes) were negative in this regard. In support of the veracity of our present results, we observed similar elevations in diastolic BP (~4 mm Hg) during exposure to high levels of ambient $PM_{2.5}$ air pollution.[19,20] Thus, the totality of our findings support that the acute inhalation of fine particulate matter, whether from SHS or ambient air pollution origin, is capable of rapidly elevating diastolic BP.

Mechanisms of BP Responses to SHS

SHS can affect the CV system by indirect actions of inflammatory mediators (eg, cytokines) released by pulmonary cells or by actions of soluble smoke constituents capable of entering the circulation and directly interacting with vascular cells.[1] Since exposure did not impair EDV (determined largely by vascular cell nitric oxide bioavailability) or large artery compliance, these pathways are less probable causes of the BP changes. Alternatively, the inhalation of particulate matter within SHS can rapidly alter autonomic reflex pathways via interaction with pulmonary nerves/receptors that produces a relative hyperactivity of the sympathetic nervous system.[1] Indeed, heart rate variability is reduced by SHS in a temporal fashion congruent with our observed rapid prohypertensive response.[21] Moreover, 1 hour of SHS has been shown to increase resting energy expenditure, consistent with sympathetic stimulation.[22] Given the rapid nature of the prohypertensive response, it seems most plausible that autonomic imbalance was the most plausible mechanism. Whether this was mediated by inhaled particulate matter or due to an effect of inhaled vapor phase nicotine as suggested in other studies,[17] requires more investigation. However, since ambient air pollution can trigger similar elevations in BP,[19] it seems unlikely that the response was due entirely to inhaled nicotine.

Limitations

One recognized limitation is a lack of a clean air control limb, but there is no reason to believe that the biologic outcomes (eg, BP, EDV) in this study should spontaneously and consistently change (in either direction) over a 1-hour time period and thus bias our results. It is not biologically sound that diastolic BP should spontaneously increase due to maintaining a seated position for 1 hour. If anything, it is likely that these parameters would trend downward with prolonged resting, as was seen with most other hemodynamic measures (Table II). Indeed, our previous experiments have shown that filtered air exposure (placebo), does not significantly increase diastolic BP during prolonged sitting for up to 2 hours.[19] We therefore did not feel it necessary to include a filtered air limb given our observed lack of a placebo (filtered air) effect upon these outcomes in our previous studies of air pollution.[19,20] Although we cannot entirely rule out the possibility, the hemodynamic responses observed after SHS exposure are not likely to represent random fluctuations. Finally, we did not assess brachial endothelial function, as in previous positive reports.[16,23,24] It is possible that a true impairment in larger conduit artery endothelial function might have gone unobserved. Nonetheless, unlike in most previous SHS exposure studies, we specifically assessed the responses of 2 different and pertinent vascular territories.

CONCLUSIONS

One hour of SHS did not impair microvascular endothelial function or arterial compliance in healthy nonsmoking adults in our study. However, there was a rapid prohypertensive reaction that occurred in most individuals, a finding previously reported in some SHS studies. Therefore, even brief SHS exposure can instigate potentially harmful hemodynamic responses that may raise CV risk in certain individuals.

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