JACC Vol. 22, No. 3
September 1993:642–7

Acute Effect of Cigarette Smoking on the Coronary Circulation: Constriction of Epicardial and Resistance Vessels

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Objectives. **This study was performed to determine the acute effect of cigarette smoking on proximal and distal epicardial conduit and coronary resistance vessels.**

Background. **Cigarette smoking causes constriction of epicardial arteries and a decrease in coronary blood flow in patients with coronary artery disease, despite an increase in myocardial oxygen demand. The role of changes in resistance vessel tone in the acute coronary hemodynamic effect of smoking has not been examined.**

Methods. **Twenty-four long-term smokers were studied during cardiac catheterization after vasoactive medications had been discontinued. The effect of smoking one cigarette 10 to 15 mm long on proximal and distal conduit vessel segments was assessed before and immediately after smoking and at 5, 15 and 30 min after smoking (n = 8). To determine the effect of smoking on resistance vessels, coronary flow velocity was measured in a nonobstructed artery with a 3F intracoronary Doppler catheter before and for 5 min after smoking (n = 8). Eight patients were studied without smoking to control for spontaneous changes in conduit arterial diameter (n = 5) and resistance vessel tone (n = 3).**

Results. **The average diameter of proximal coronary artery segments decreased from 2.56 ± 0.12 mm (mean ± SEM) before smoking to 2.41 ± 0.09 mm 5 min after smoking (−5 ± 2%, $p < 0.05$). Distal coronary diameter decreased from 1.51 ± 0.07 to 1.39 ± 0.06 mm (−8 ± 2%, $p < 0.01$). Marked focal vasoconstriction after smoking was observed in two patients. Coronary diameter returned to baseline by 30 min after smoking. There was no change in vessel diameter in control patients. Despite a significant increase in the heart rate–mean arterial pressure product, coronary flow velocity decreased by 7 ± 4% ($p < 0.05$) and coronary vascular resistance increased by 21 ± 4% ($p < 0.01$) 5 min after smoking. There was no change in these variables in the control subjects.**

Conclusions. **Smoking causes immediate constriction of proximal and distal epicardial coronary arteries and an increase in coronary resistance vessel tone, despite an increase in myocardial oxygen demand. These acute coronary hemodynamic effects may contribute to the adverse cardiovascular consequences of cigarette smoking.**

(J Am Coll Cardiol 1993;22:642–7)

The association between long-term cigarette smoking and atherosclerotic coronary artery disease is well established (1,2). Smoking also has immediate effects on systemic and coronary hemodynamics. Smoking produces an increase in blood pressure, heart rate and contractility, with a resultant increase in myocardial oxygen demand (3–6). Despite this increase in oxygen demand, coronary blood flow (as assessed by coronary sinus thermodilution technique) remains unchanged or may decrease in patients with coronary artery disease (4,7,8). Given the limited spatial resolution of the thermodilution technique, it is impossible to determine from these studies whether smoking-induced reductions in coronary blood flow are due to increases in coronary arteriolar tone or to decreases in epicardial coronary diameter. In addition, smoking may also cause changes in coronary venous drainage that could affect coronary sinus blood flow measurements.

Intracoronary Doppler catheter systems for the assessment of changes in coronary blood flow have been extensively validated and widely used (9). Blood flow responses measured using Doppler and thermodilution techniques may differ substantially (10). Superior spatial resolution and lack of dependence on the pattern of coronary venous drainage make the Doppler catheter technique better suited for assessing the effect of smoking on regional coronary blood flow (11). The major goal of this study was to assess more completely the immediate effects of smoking on coronary flow using Doppler techniques.

Previous angiographic studies (12,13) examining the effect of smoking on epicardial coronary arteries utilized visual assessment of vessel responses or caliper measurements limited to proximal or midcoronary segments (12,13). Accordingly, an additional goal was to characterize the immediate effects of smoking on both proximal and distal

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Manuscript received October 10, 1992; revised manuscript received February 22, 1993, accepted March 8, 1993.

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0735-1097/93/$6.00

epicardial coronary arteries using computerized quantitative angiography.

Methods

Study patients. The study group consisted of 24 patients (16 men, 8 women, aged 53 ± 3 years [mean ± SEM]) referred for cardiac catheterization for the evaluation of chest pain. All patients were current and long-term smokers (≥1 pack/day for ≥1 year) and none had congestive heart failure, recent (<2 weeks) myocardial infarction or prior coronary bypass surgery. Vasoactive medications, including beta-adrenergic blocking agents, calcium channel antagonists and long-acting nitrates, were withheld for ≥18 h before the study. Patients refrained from smoking for ≥12 h the study. Premedication consisted of diphenhydramine (50 mg) and diazepam (5 mg) orally approximately 1 h before the procedure. The research study was performed ≥15 min after completion of diagnostic catheterization. Patients were allowed to smoke their usual brand of cigarette, provided the nicotine content was >0.8 mg. The research protocol was approved by the University of Iowa Institutional Review Board, and written informed consent for the research protocol was obtained from each subject before cardiac catheterization.

Branches of the left coronary system were studied in all cases. Coronary angiography was performed with nonionic contrast medium delivered by power injector, using the same flow rate and volume for each injection (9 ml at a rate of 3 to 4 ml/s) and recorded on 35-mm cine film. X-ray positioner, image intensifier and table settings were held constant during the study. Coronary artery diameters were measured using a computerized quantitative coronary angiography system with automatic vessel edge detection (CAAS, Pie Medical) (14). The variability of coronary diameter measurements with this system in our laboratory is similar to that reported previously by others (14).

Effect of smoking on conduit vessels. The effect of smoking on epicardial coronary vessels was assessed in eight patients (five men, three women, age 48 ± 3 years). There were six patients with normal-appearing smooth arteries and two with mild atherosclerosis or single-vessel coronary artery disease involving the right coronary artery. No patient had a >50% diameter stenosis in the left coronary artery. Three of the eight patients were receiving calcium channel blockers before the study, none were receiving beta-adrenergic blockers and five were taking aspirin. Control angiography was performed in a right anterior oblique view that best demonstrated segments of the proximal and distal left anterior descending and left circumflex coronary arteries that were suitable for quantitative analysis. Each patient smoked one cigarette over 5 to 8 min and coronary angiography was repeated immediately after smoking (time 0) and at 5, 15 and 30 min after smoking. Heart rate and systemic arterial pressure were monitored continuously and recorded before each angiogram. A control group of five additional patients (four men, one woman, aged 63 ± 5 years) completed the protocol but did not smoke.

The presmoking angiogram was used to select one proximal and one distal arterial segment 10 to 15 mm in length in both the left anterior descending and left circumflex arteries for analysis. The average diameter of each segment was determined using the known diameter of the angiographic catheter to correct for magnification. Using branch vessels for orientation, the identical arterial segments were analyzed on each of the angiograms obtained after smoking. Thus, the effect of smoking on the diameter of two proximal and two distal epicardial coronary segments was assessed in each patient.

Effect of smoking on resistance vessels. The effect of smoking on vascular resistance in a nonstenotic coronary artery was assessed in eight patients (five men, four women, aged 51 ± 4 years). Two patients had smooth coronary arteries and six had angiographic evidence of coronary atherosclerosis. Two of the patients were taking calcium channel blockers before study, two were receiving beta-adrenergic blockers and one was taking both drugs. Seven of the eight patients were taking aspirin. Intracoronary nitroglycerin (200 μg) was administered before placement of the Doppler catheter to prevent changes in coronary diameter that might alter the relation between coronary flow velocity and volumetric coronary blood flow. A 3F 20-MHz Doppler catheter (NuMed Inc.) was advanced over a 0.014-in. (0.036 cm) angioplasty guide wire into the midportion of the vessel and positioned to obtain a high quality phasic flow velocity signal. The pulsed Doppler velocimeter with a zero-crossing counter (Bioengineering Department, University of Iowa Hospitals and Clinics) was range gated to maximize the amplitude of the mean coronary blood flow velocity signal. Phasic and mean coronary blood flow velocity (kHz shift), mean arterial pressure (mm Hg) and heart rate (beats/min) were continuously monitored and recorded before (control), immediately after (time 0) and 2.5 min and 5 min after smoking one cigarette. Three additional control patients underwent the identical protocol but did not smoke. To assess for any changes in coronary caliber that might affect the relation between flow velocity and volumetric flow, coronary angiography in a view best demonstrating the site of Doppler crystal placement was performed before smoking and at 5 min after smoking.

As a measure of the change in coronary vascular resistance after smoking, a coronary vascular resistance index was calculated as the quotient of (Mean aortic pressure [mm Hg]/Blood flow velocity [kHz shift]) after smoking and (Mean aortic pressure/Blood flow velocity) at control.

Data analysis. Results are shown as mean value ± SEM. For each patient group, values at control and after smoking were compared using a repeated measures analysis of variance. The Bonferroni procedure was used to correct for multiple comparisons. A p value ≤ 0.05 was considered significant.

Table 1. Effect of Smoking on Hemodynamics and Coronary Artery Diameter

		Time After Smoking (min)			
	Baseline	0	5	15	30
Hemodynamics (8 patients)					
Heart rate (beats/min)	73 ± 3	81 ± 5*	83 ± 6*	78 ± 5	74 ± 5
Mean arterial pressure (mm Hg)	95 ± 3	97 ± 3	98 ± 3	93 ± 1	92 ± 1
Heart rate–mean arterial pressure product (beats/min × mm Hg)	6,979 ± 322	7,915 ± 430	7,988 ± 392	7,613 ± 578	6,819 ± 498
Coronary diameter (mm Hg) (16 segments)					
Proximal	2.56 ± 0.12	2.47 ± 0.10	2.41 ± 0.09*	2.49 ± 0.09	2.52 ± 0.10
Distal	1.51 ± 0.07	1.45 ± 0.07	1.39 ± 0.06†	1.47 ± 0.06	1.48 ± 0.07

*$p < 0.05$ versus baseline. †$p < 0.01$ versus baseline. Values are expressed as mean value ± SEM.

Results

Conduit vessel studies (Table 1). Before smoking, the heart rate averaged 73 ± 3 beats/min, mean arterial pressure was 95 ± 3 mm Hg and heart rate–mean arterial pressure product averaged 6,979 ± 322 beats/min × mm Hg (n = 8). Smoking resulted in an increase in heart rate to a maximum of 83 ± 6 beats/min ($p < 0.05$) at 5 min. The peak mean arterial pressure was 98 ± 3 mm Hg after smoking (p = NS). The heart rate–mean arterial pressure product increased to a maximum of 7,988 ± 392 beats/min × mm Hg at 5 min after smoking (p = 0.06).

Cigarette smoking caused diffuse constriction of the left anterior descending and left circumflex coronary arteries, with the peak effect observed 5 min after completion of smoking (Table 1). The diameter of proximal coronary artery segments decreased from 2.56 ± 0.12 to 2.41 ± 0.09 mm (−5 ± 2%, $p < 0.05$). Distal coronary artery diameter decreased from 1.51 ± 0.07 to 1.39 ± 0.06 mm (−8 ± 2%, $p < 0.01$). The difference in percent reduction in coronary diameter in proximal and distal segments was not statistically significant. If a circular cross section is assumed, the diameter changes represent a reduction in cross-sectional area of 9 ± 4% and 14 ± 3% for the proximal and distal segments, respectively. There was no significant difference in the extent of coronary vasoconstriction in left anterior descending and left circumflex arteries. In five smokers who underwent identical angiographic study but did not smoke, there was no change in heart rate, arterial blood pressure or coronary artery diameter (proximal 2.59 ± 0.16 mm control vs. 2.60 ± 0.16 mm at 5 min; distal 1.53 ± 0.08 mm control vs. 1.54 ± 0.08 mm at 5 min).

The effect of smoking on epicardial vessels in individual patients was variable. The average diameter of at least one proximal or distal coronary segment decreased by >5% in all eight patients and by >10% in five of the eight patients. In two patients, smoking caused marked *focal* vasoconstriction that was easily detected by visual inspection. In a 40-year old man with minor coronary lumen irregularities, the minimal diameter of a proximal left anterior descending artery segment decreased from 2.61 mm before smoking to 1.60 mm 5 min after smoking (39% reduction) (Fig. 1). In a 43-year old man with smooth coronary arteries, there was a 26% decrease in the minimal lumen diameter of a proximal left circumflex artery segment (3.01 mm before smoking to 2.24 mm at 5 min). No patient developed chest pain or electrocardiographic changes after smoking. The coronary response to smoking was unrelated to the patient's previous antianginal therapy or aspirin use.

Resistance vessel studies (Table 2, Fig. 2 and 3). After smoking, the heart rate increased from 79 ± 6 beats/min to a maximum of 90 ± 4 beats/min at 2.5 min ($p < 0.01$). Mean arterial pressure increased from 102 ± 6 to 113 ± 5 mm Hg at 5 min ($p < 0.01$). The heart rate–mean arterial pressure

Table 2. Effect of Smoking on Coronary Resistance Vessels in Eight Patients

		Time After Smoking (min)		
	Baseline	0	2.5	5
Heart rate (beats/min)	79 ± 6	87 ± 5*	90 ± 4†	85 ± 5
Mean arterial pressure (mm Hg)	102 ± 6	112 ± 5†	113 ± 5†	113 ± 5†
Heart rate–mean arterial pressure product (beats/min × mm Hg)	8,160 ± 703	9,795 ± 746†	10,174 ± 787†	9,640 ± 719†
Coronary flow velocity (% of control)	100	104 ± 3	102 ± 3	93 ± 4*
Coronary vascular resistance index	1	1.07 ± 0.03	1.11 ± 0.03†	1.21 ± 0.04†

*$p < 0.05$ versus baseline. †$p < 0.01$ versus baseline. Values are expressed as baseline value or mean value ± SEM.

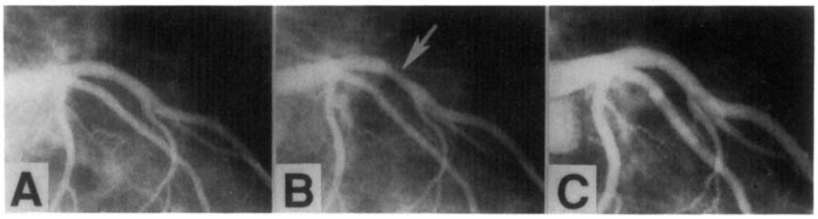


Figure 1. Before smoking (A), there is minor lumen narrowing in the proximal left anterior descending artery. Five minutes after smoking one cigarette (B), there is marked focal vasoconstriction (arrow) with a 39% reduction in minimal lumen diameter. Panel C shows the vessel after intracoronary nitroglycerin.

product increased from 8,160 ± 703 to 10,174 ± 787 beats/min × mm Hg at 2.5 min ($p < 0.01$) (Fig. 2).

After smoking there was a reduction in coronary flow velocity and a progressive increase in coronary vascular resistance, despite a concomitant 26 ± 6% increase in myocardial oxygen demand as assessed by the heart rate–mean arterial pressure product (Table 2, Fig. 3). Coronary blood flow velocity decreased by 7 ± 4% from control and coronary vascular resistance index increased to a maximum of 1.21 ± 0.04 at 5 min. The resistance vessel response was unrelated to the patient's previous antianginal therapy. Coronary artery diameter at the site of the Doppler catheter crystal was unchanged (3.40 ± 0.19 mm control vs. 3.40 ± 0.21 mm at 5 min) in this group pretreated with nitroglycerin. In three smokers who underwent coronary flow velocity measurements under identical conditions but did not smoke, there was no change in the heart rate–mean arterial pressure product (7,486 ± 974 beats/min × mm Hg control vs. 7,337 ± 1,120 beats/min × mm Hg at 5 min), coronary vascular resistance index (1.03 ± 3 at 5 min) or other study variables.

Discussion

Previous studies. The acute *systemic* hemodynamic effects of cigarette smoking have been well described (3–6). Smoking causes a prompt increase in heart rate, myocardial contractility and systemic vascular resistance. The effects of smoking on the coronary circulation have been less well studied. In proximal epicardial vessels, smoking can cause diffuse vasoconstriction and may precipitate coronary artery vasospasm (12,13). The effect of smoking on coronary blood flow has been examined primarily by investigators using the coronary sinus thermodilution technique (4,7,8). In patients with obstructive coronary artery disease, coronary sinus blood flow may remain unchanged or decrease despite an increase in myocardial oxygen demand. This effect of smoking on coronary sinus flow could be due to 1) epicardial vasoconstriction, 2) an increase in resistance vessel tone, or 3) smoking-induced redistribution of coronary venous drainage.

Present study. In the present study, we directly examined the effect of smoking on coronary resistance vessels using the intracoronary Doppler technique (9). By measuring coronary flow velocity in nonobstructed vessels pretreated with nitroglycerin to prevent changes in epicardial artery diameter, the effect of smoking on coronary resistance vessels can be determined. Five minutes after smoking one cigarette, coronary blood flow velocity decreased by 7% and coronary vascular resistance increased by 21% despite a significant increase in heart rate–mean arterial pressure product, an index of myocardial oxygen demand. In epicardial arteries, smoking caused diffuse constriction of proximal and distal vascular segments. In two patients, smoking caused marked *focal* vasoconstriction in an angiographically normal proximal coronary artery. These findings are in agreement with previous studies (12,13) on the effect of smoking on epicardial vessels. Epicardial coronary vasoconstriction resolved within 30 min after smoking.

Figure 2. Effect of smoking on heart rate (HR)–mean arterial pressure (MAP) product and coronary flow velocity (CFV). Coronary flow velocity decreased by 7 ± 4% 5 min after smoking despite an increase in the heart rate–mean arterial pressure product. *$p <$ 0.05 versus baseline. †$p < 0.01$ versus baseline. bpm = beats per minute.

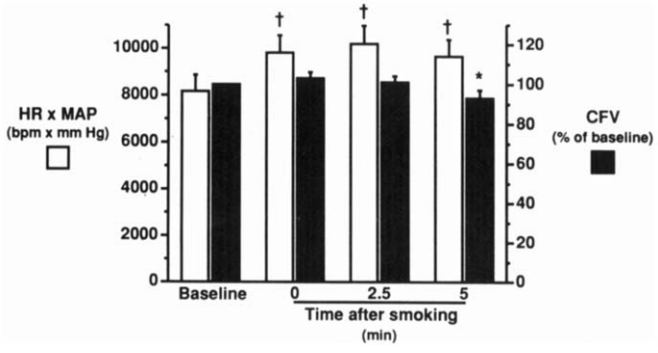
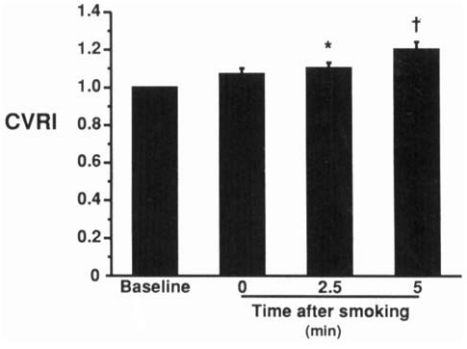


Figure 3. Effect of smoking on the coronary vascular resistance index (CVRI). *$p < 0.05$ versus baseline. †$p < 0.01$ versus baseline.



The degree of epicardial vasoconstriction we observed was less than the 12% reduction in coronary diameter reported by Moreyra et al. (13). This difference may be due to differences in the study groups and the method used to measure coronary diameter. Angiographic evidence of coronary atherosclerosis was present in nearly 60% of their study group and in only 25% of the patients in the conduit vessel protocol in our study. Atherosclerosis has been shown to potentiate the coronary response to other vasoconstrictor stimuli (15–17). We used an automated edge detection system to assess the effect of smoking on the average diameter of an arterial segment ≥10 mm long. Moreyra et al. (13) used an electronic caliper device that measures coronary diameter at a single user-defined point and may have been more likely to detect focal vasoconstriction caused by smoking.

Intracoronary injection of radiographic contrast medium produces transient vasodilation of both conduit and resistance vessels. These contrast-induced hemodynamic changes may influence the results of an angiographic assessment of the coronary vascular effects of smoking. The use of a nonionic contrast agent reduces but does not eliminate these vasoactive changes (18,19). In the conduit vessel protocol, the influence of contrast medium on coronary vessel diameter was minimized by waiting ≥5 min between each coronary injection. In the resistance vessel protocol, baseline coronary flow velocity measurements were obtained ≥5 min after coronary angiography at a time when flow velocity was stable. No additional contrast injections were performed until the completion of the study. Finally, control subjects who did not smoke completed each of the two protocols and thus received the same dose of contrast medium at the same time intervals. There was no change in either coronary diameter or coronary flow velocity in these subjects.

Potential mechanisms. As in the systemic circulation, the acute coronary vasoconstrictor effect of smoking may be due in part to activation of the sympathetic nervous system. Cryer et al. (3) demonstrated that plasma epinephrine and norepinephrine levels begin to increase within 5 min after the start of smoking and reach a peak concentration within 10 to 12 min. Stimulation of epicardial and resistance vessel alpha-adrenergic receptors by circulating or locally released catecholamines could lead to epicardial vasoconstriction and an increase in coronary vascular resistance. Other interventions, including mental stress (16), isometric handgrip (20,21), and cold pressor testing (15), have also been shown to produce adrenergically mediated coronary vasoconstriction. Alpha-adrenergic blockade can reverse the smoking-induced decrease in coronary sinus blood flow in patients with coronary artery disease (22). The specific effect of alpha-adrenergic blockade on epicardial and resistance vessel responses to smoking has not been examined.

The integrity of vascular endothelial cell function may play an important role in determining the coronary vascular response to cigarette smoking (23,24). Endothelial dysfunction can precede angiographic evidence of coronary atherosclerosis (25,26). There is little known about the effect of long-term cigarette smoking on vascular endothelial cell function. Repeated exposure to carbon monoxide and nicotine may lead to endothelial cell damage (27) and impaired endothelial-mediated vasodilation. Thus, although 8 of the 16 patients who smoked in our study had angiographically smooth coronary arteries, it cannot be assumed that they had normal vascular endothelial function.

Smoking produces other pharmacologic effects that influence the mechanisms of vascular control, including 1) inhibition of prostacyclin production by vascular endothelial cells (28,29), 2) activation of platelets (30–32), 3) release of vasopressin, growth hormone, adrenocorticotropic hormone and cortisol, and 4) increase in circulating levels of free fatty acids, glycerol and lactate (33). The contribution of these factors to the immediate effects of smoking on coronary conduit and resistance vessels is unknown.

Study limitations. The present study has several limitations. 1) All patients enrolled in this study were long-term smokers. The effect of active smoking or environmental tobacco smoke exposure on the coronary circulation in nonsmokers cannot be determined. 2) The dose of cigarette smoke in each patient was not controlled or assessed. Differences in the amount and composition of cigarette smoke inhaled may account in part for the heterogeneous coronary vascular response to smoking. 3) Assessment of changes in Doppler coronary flow velocity accurately reflect changes in volumetric coronary blood flow only if there is no change in the cross-sectional area of the vessel at the site of the Doppler crystal. Pretreatment with intracoronary nitroglycerin prevented a smoking-induced change in coronary artery caliber. 4) We did not examine the effect of smoking at the site of flow-limiting coronary stenoses. Adrenergic stimulation may be enhanced at the site of atherosclerotic stenoses (21,34) and could result in a significant decrease in coronary blood flow. 5) We cannot determine the specific components of cigarette smoke responsible for coronary vasoconstriction. The majority of the cardiovascular effects of smoking are probably due to nicotine, but other components, including carbon monoxide, may also play a role. In the study by Moreyra et al. (13), there was a weak correlation between the degree of epicardial vasoconstriction after smoking and the arterial nicotine concentration.

Clinical implications. Among patients with coronary artery disease smokers are at greater risk for myocardial infarction, unstable angina and sudden death than are nonsmokers (1,2). In patients with coronary artery disease, smoking one cigarette can produce myocardial perfusion abnormalities at significantly lower levels of myocardial oxygen demand than occur after exercise (35). Smoking can also lower the anginal threshold (36) and increase the frequency of ischemic events during daily activity (37). Repeated acute episodes of coronary vasoconstriction may play an important role in these ischemic consequences of smoking. Focal constriction of epicardial vessels in patients

with atherosclerotic coronary artery disease could lead to further vascular endothelial damage and plaque rupture. Constriction of coronary stenoses and resistance vessels may limit coronary blood flow and lower ischemic threshold.

Conclusions. The acute coronary hemodynamic effects of cigarette smoking include constriction of large and small epicardial arteries and coronary resistance vessels, with a resultant decrease in coronary blood flow despite an increase in myocardial oxygen demand. These acute effects may contribute to the adverse cardiovascular consequences of smoking.

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