Cigarette Smoking and Coronary Blood Flow

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Cigarette smoking is associated with an increased risk for vascular disease. The effects of smoking and nicotine on coronary and peripheral arterial function have been probed with various invasive and noninvasive techniques. The current review provides a brief summary of the available techniques for measuring coronary or peripheral arterial function and discusses the determinants of myocardial blood flow at rest and during stress. Finally, it summarizes research addressing the effects of smoking on coronary and peripheral arterial function. Acute and chronic smoking does not appear to alter substantially endothelium independent coronary vasodilatory capacity. In contrast, active and passive smoking alters coronary and peripheral arterial vasomotion in patients with and individuals without coronary artery disease (CAD). Therefore, the site of the damaging effects of smoking appears to be the coronary endothelium. The smoking history is correlated with the degree of vasomotor abnormalities. Further, the degree of smoking-induced endothelial dysfunction appears to increase with the severity of CAD. Finally, the coronary endothelial and peripheral arterial vasomotor dysfunction observed in active and passive healthy smokers appear to be to some degree reversible.

Cigarette smoking is a major risk factor resulting in a 2-fold increased risk for peripheral vascular[1] and coronary artery disease (CAD).[2] Cigarette smoking accounts for one fifth of all cardiac deaths and doubles the risk for heart failure.[3] Vascular effects of smoking also include an increased risk for stroke and impotence in young men.[4] Thus, epidemiologic evidence has clearly linked cigarette smoking to vascular disease.

Despite the overwhelming epidemiologic association between smoking and vascular disease, the mechanisms by which smoking exerts its deleterious effects are still incompletely understood. Complicating the understanding of its noxious effects is the fact that cigarette smoke contains thousands of toxic compounds, the 2 most prominent ones being nicotine and carbon monoxide.

Recent research suggests that the main site of toxic effects on the vascular system is the endothelium, and, specifically with regards to the coronary system, the coronary endothelium. Nicotine alters the shape of endothelial cells and reduces prostacycline production.[5] Increased endothelial cell proliferation and intimal hyperplasia as a result of nicotine exposure also have been observed in animal experimental studies.[6] Serum carbon monoxide levels are increased in smokers and this is associated with increased numbers of damaged endothelial cells circulating in human blood.[7] Interestingly, tobacco smoke had a much greater effect than nontobacco smoke on circulating endothelial cells and platelets, suggesting specifically harmful components of tobacco smoke. Nicotine alone can cause acute endothelial dysfunction, although to a significantly smaller extent than cigarette smoke.[8] Free radicals contained in the tar and the gas phase of cigarette smoke can damage the vascular endothelium.[5]

Quantitative electron microscopy was used to determine the effects of nicotine on the ultrastruc-

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ture of aortic endothelial cells in mice[9] that were exposed to extremely high nicotine levels, comparable with humans smoking 50 to 100 cigarettes/day. Nicotine resulted in cytoplasmic vacuoles, mitochondrial swelling, and edema. In fact, the vacuole volume fraction from aortic endothelium was twice as high in nicotine-exposed mice than in the control group. Overall, the study showed significant endothelial injury as a result of nicotine exposure.

Thus, cigarette smoke appears to damage the coronary endothelium that plays a pivotal role in controlling coronary function. Release of nitric oxide from the endothelium is important for adapting the coronary vasomotor tone to changes in myocardial oxygen demand and impairments in this system result in coronary endothelial dysfunction.[10,11]

The effects of smoking and nicotine on coronary and peripheral arterial function have been probed with various invasive and noninvasive techniques. The current review provides a brief summary of the available techniques for measuring coronary or peripheral arterial function and discusses the determinants of myocardial blood flow at rest and during stress. Finally, it summarizes the research addressing the effects of smoking on coronary and peripheral arterial function.

Measurements of Myocardial and Coronary Blood Flow

Single photon emission tomography or stress echocardiography is used clinically to determine presence, location, and extent of CAD. These techniques, however, are not quantitative and rely on regional differences in the myocardial uptake of radiotracers, as is the case for single photon emission tomography, or wall motion heterogeneities for echocardiography to identify abnormalities in coronary blood flow. They can only uncover hemodynamically significant disease once the coronary lumen is obstructed by at least 50%.[12] Such obstructive coronary disease is frequently not present, especially in younger smokers. Moreover, even in patients with known CAD, the effects of smoking on coronary blood flow cannot be quantified with these techniques. These qualitative or semiquantitative imaging tests therefore are not useful to evaluate sometimes-subtle smoking-induced alterations on myocardial blood flow or coronary function.

Several invasive and noninvasive techniques have been used to quantify the effects of smoking on coronary or myocardial blood flow. Foremost among the invasive techniques are the coronary sinus thermodilution method, inert gas clearance techniques, and intracoronary Doppler velocity probes.[13] However, because of their invasiveness these approaches are associated with significant morbidity and therefore only can be applied in small groups of research subjects. In contrast, positron emission tomography (PET) provides quantitative measurements of myocardial blood flow noninvasively. Several PET tracers to quantify myocardial blood flow include the generator-produced isotope rubidium-82,[14-16] and the cyclotron-produced N-13 ammonia,[17,18] and O-15 water[19-27] have been used in humans.

Recent tomographs permit the simultaneous acquisition of more than 60 cross-sectional images of the left ventricular myocardium.[28,29] Images can be obtained serially to determine the arterial input function and myocardial time activity curves.[26,30] By using validated tracer kinetic models, myocardial blood flow can be quantified for the entire left ventricle or for vascular territories, or for even smaller myocardial regions. Estimates of myocardial blood flow obtained in $mL \cdot min^{-1} \cdot g^{-1}$ are reproducible within[27] and across institutions[25] and have been used successfully to evaluate the effects of smoking on myocardial blood flow.

Before interpreting such quantitative measurements the determinants of myocardial blood flow at rest and during various stress tests need to be understood. The following section briefly addresses this issue.

Determinants of Myocardial Blood Flow at Rest

Myocardial blood flow at rest correlates with myocardial oxygen consumption,[31] which depends on left ventricular wall stress, contractility, pressure work, volume work, and heart rate. Autoregulatory mechanisms that involve the coronary endothelium, vascular smooth muscles, or myocytes modulate the balance between myocardial oxygen supply and demand. In isolated heart preparations myocardial blood flow remains relatively constant

for perfusion pressures ranging from 80 to 150 mm Hg[32] for any given level of cardiac work. Different from these findings in the isolated heart preparation, myocardial blood flow in humans is related linearly to cardiac work.[33] A significant relationship between resting rate pressure product and myocardial blood flow was shown noninvasively with PET in vivo.[34-37]

Thus, myocardial blood flow in humans at rest varies between individuals as a function of differences in cardiac work or oxygen consumption. It can be modulated by physiologic processes such as aging or interventions such as cardiovascular conditioning.[37,38] Pharmacologic interventions such as β-receptor blockade[39] reduce resting blood flow by reducing cardiac work.

For instance, a blood flow level of 0.4 mL · min^{-1} · g^{-1} might be entirely normal for a hypotensive patient with a low resting heart rate but might also be found in an area of nontransmural myocardial infarction.

Myocardial Blood Flow During Stress

Physical Stress

The coronary system is unique in its ability to respond to increases in myocardial oxygen demand with appropriate and proportional increases in myocardial blood flow. This ability has been termed the *coronary vasodilatory capacity* or *flow reserve*. Animal experimental data as well as studies in humans showed that coronary blood flow could increase 3- to 5-fold in response to physiologic or pharmacologic stimuli. Physical exercise increases myocardial oxygen consumption, which needs to be accommodated for by appropriate increases in coronary blood flow. Holmberg et al[33] established a close correlation between coronary blood flow and cardiac work for a wide range of rate pressure products during exercise.

Pharmacologic Stress

Because physical stress is not feasible during cardiac catheterization and also not possible during PET imaging, the coronary vasodilatory capacity is most frequently probed by using pharmacologic stressors. These stressors include dipyridamole, adenosine,[40,41] papaverine, and nitroglycerine, all of which induce coronary vasodilation in a largely endothelial-independent fashion.[42,43] Dipyridamole, adenosine, and papaverine induce 3- to 4-fold increases in myocardial blood flow as established by intracoronary flow velocity measurements[44] and subsequently by PET.[45] However, increases in blood flow during near-maximal arteriolar vasodilation exert a secondary vasodilatory effect on the proximal circulation if normal endothelial function is maintained. This phenomenon, termed *flow-mediated coronary* or *peripheral arterial vasodilation* has been shown to be endothelial dependent.[46] Nevertheless, for the current article we will assume that pharmacologic stress with adenosine, dipyridamole, papaverine, or nitroglycerine induces coronary vasodilation in a largely endothelial-independent fashion.

Physiologic processes and pharmacologic interventions can affect maximally achievable blood flows during exercise or pharmacologic interventions. Using intracoronary Doppler flow velocity measurements, Egashira et al[47] found no significant age-dependent decline in maximally achievable coronary flow. These findings were confirmed by Schelbert's group[34] but disputed by others.[37] In addition, impairments in coronary vasodilatory capacity can be reversed to some degree by lifestyle modifications.[38] Therapeutic drugs also can affect coronary blood flow. For instance, β-receptor blockade might enhance coronary vasodilatory capacity by reducing extravascular resistive forces during the diastolic coronary flow phase.[39]

In summary, both resting and hyperemic myocardial blood flow can be altered by a variety of physiologic processes and pharmacologic interventions. These factors need to be considered before quantitative blood flow measurements can be interpreted in a meaningful fashion.

Probing Coronary Endothelial Function

Zeiher et al[48] observed in 1991 that endothelial dysfunction precedes angiographically detectable CAD. Their study included 11 patients with smooth coronary artery disease and no risk factors for CAD, 9 patients with smooth coronary artery disease but risk factors for CAD, 9 patients with smooth coronary artery segments but other areas of disease, and 9 patients with diffuse intimal irregularities. All patients underwent quantitative

angiography and Doppler flow velocity measurements during intracoronary acetylcholine for probing endothelial-dependent coronary function and nitroglycerine and papaverine for evaluating endothelial-independent vasomotion. The investigators showed increasingly abnormal flow velocity responses dependent on the stage of underlying early coronary artery disease or risk for disease. Importantly, they also showed that abnormal flow velocity responses to acetylcholine were paralleled by abnormal responses to cold pressor testing.

Lending support to the notion that endothelial dysfunction represents a very early disease stage, Vita et al[49] reported an abnormal coronary vasomotor response to acetylcholine in patients with minimal coronary artery disease. Interestingly, they also observed an increased sensitivity of the endothelium to adrenergic stimulation with phenylephrine, which might contribute to ischemic events.

As mentioned earlier, the coronary flow velocity response to acetylcholine is correlated with that of cold pressor testing.[48] In 1988, Nabel et al[50] evaluated the response of the coronary system to sympathetic stimuli as induced by cold pressor testing. This study included 8 patients with normal coronary arteries, 9 patients with mild disease, and 13 patients with atherosclerotic lesions with greater than 50% diameter narrowing. Cold pressor testing, during which the patient's hands were submersed in ice water, was used to activate the sympathetic system. Quantitative angiography and Doppler flow velocity measurements were used to determine the vascular and flow velocity response to cold. Exposure to cold induced coronary vasodilation by 12% $\pm$ 1% in patients with normal coronary arteries whereas the diameter decreased by 9% $\pm$ 1% and 24% $\pm$ 6% in irregular and stenotic segments, respectively. Thus, the degree of atherosclerosis was associated with the degree of impairment in vasomotor response to cold. Meeder et al[51] also showed a significant relationship between coronary flow velocity and the myocardial blood flow response to cold pressor testing.

Cold pressor testing evokes a mixed neuronal response, with releases of catecholamines from terminal nerve endings and the adrenal medulla[52] that leads to modest increases in blood pressure and heart rate by about 30%.[53] Catecholamines stimulate myocardial β_1 receptors with corresponding increases in cardiac work and coronary blood flow in healthy individuals. Stimulation of vascular smooth muscle α_1—adreno-receptors promotes coronary vasoconstriction whereas coronary β_2-receptor stimulation promotes coronary vasodilation. Further vasodilation results from stimulation of endothelial α_2 receptors, leading to release of nitric oxide from the endothelium.[54] Increased shear stresses owing to higher flow velocities lead to further increases in nitric oxide release.[52,55] Thus, these regulatory mechanisms depend on a preserved endothelial function and are dysfunctional in individuals at risk for and those with CAD.

The degree of abnormal blood flow responses to cold stimulation can be quantified noninvasively with PET. Blood flow measurements during cold pressor testing are therefore increasingly accepted for probing endothelial-dependent coronary vasomotion in humans.

Another noninvasive approach for probing vascular endothelial function uses brachial artery ultrasound. The release of a pneumatic arm cuff after inflation is followed by flow-medicated arterial vasodilation, the degree of which depends on endothelial function.[56] This is based on the notion that increases in blood flow during near-maximal vasodilation result in secondary flow increases termed *flow-mediated vasodilation*. This second wind is an endothelium-dependent process and can be determined by using brachial artery ultrasound. As an advantage, this technique is widely available, inexpensive, and noninvasive. As a disadvantage, measurements of brachial artery vasoreactivity might not necessarily be translatable into coronary vasomotor function. However, this technique has been used as a surrogate measure of overall vascular endothelial function.

Hemodynamic Effects of Smoking

Cigarette smoking induces the release of catecholamines from the adrenal medulla and terminal nerve endings. This is evidenced by an early increase of serum norepinephrine levels followed by an increase in serum epinephrine levels.[57] Cryer et al[58] observed prompt increases in blood pressure and heart rate within 2.5 minutes after the start of smoking, with a peak hemodynamic response after 5 minutes.

These catecholamines stimulate myocardial $\beta 1$ receptors, resulting in increases in heart rate, contractility, and systolic blood pressure. Thus, acute smoking results in increases in cardiac work. Consistently, Nicod et al[59] observed a smoking-induced increase in rate pressure product in 38 long-term smokers. This was owing to increases in both heart rate and systolic blood pressure by about 10%. Regan et al[60] reported similar hemodynamic effects in 8 smokers with CAD, and others confirmed these findings more recently.[61] A comparable magnitude of hemodynamic changes occurred after 4 mg of nicotine administered in a chewing gum.[62] In addition, nicotine increased myocardial oxygen consumption by 6% to 18% at any rate pressure product level at rest or during pacing. The investigators speculated that the increased myocardial oxygen consumption was caused by nicotine-induced increases in myocardial contractility.

Effects of Smoking and Nicotine on Myocardial Blood Flow, Vasomotion, and Flow Reserve

Acute Smoking

Schelbert's group[61] at UCLA studied systematically the effects of acute and long-term smoking on myocardial blood flow and flow reserve. PET blood flow measurements were obtained at rest and during dipyridamole-induced hyperemia under baseline conditions and then again during smoking of one cigarette. The baseline measurements were used to determine the effects of chronic long-term smoking while the smoking during the blood flow measurements was performed to evaluate the acute effects of cigarette smoking on myocardial blood flow. The expected increases in systolic blood pressure and heart rate during acute smoking were associated with significant increases in myocardial blood flow from 0.70 ± 0.17 mL $\cdot$ min^{-1} $\cdot$ g^{-1} to 0.88 ± 0.17 mL $\cdot$ min^{-1} $\cdot$ g^{-1}. Smoking during dipyridamole hyperemia reduced the hyperemic flows by 10%. Thus, acute smoking resulted in a significant decline in the myocardial flow reserve from 3.36 ± 0.83 to 2.28 ± 028.[61] Importantly, the flow reserve under baseline conditions (reflecting chronic smoking) did not differ significantly between healthy controls and smokers although a tendency toward a lower flow reserve in smokers was observed (3.82 ± 0.71 *v* 3.36 ± 0.83; $P = .16$). In contrast, acute smoking reduced the myocardial flow reserve from 3.36 ± 0.83 to 2.28 ± 0.28; $P < .0001$). This decline was attributed to both reductions in hyperemic blood flows and increases in resting blood flow during smoking. The increases in resting blood flow were owing to increases in cardiac work during smoking and the investigators speculated that the attenuated hyperemic flow response during acute smoking was explained by smoking induced $\alpha 2$-receptor mediated coronary vasoconstriction.

Smoking of 2 cigarettes failed to increase coronary sinus blood flow in the majority of patients with proximal left anterior descending coronary artery or left circumflex disease.[59] In contrast, sinus blood flow increased during smoking in all 10 patients without proximal lesions. Further, smoking during pacing increased coronary blood flow by 45 ± 21 mL $\cdot$ min^{-1} in patients without proximal coronary artery disease, whereas patients with proximal disease responded to pacing and smoking with an increase of only 36 ± 16 mL $\cdot$ min^{-1}. The findings suggested an abnormally increased coronary vasomotor tone at the site of proximal atherosclerotic lesions during smoking. Alternatively, more severe endothelial dysfunction in patients with proximal than in those with distal disease might have accounted for this finding.

Acute smoking results in constriction of the proximal and distal coronary arteries in CAD patients.[63] In this study, 24 long-term smokers with CAD were asked to smoke a cigarette during cardiac catheterization. Coronary flow velocity was measured at baseline and serially during cigarette smoking. Both proximal and distal coronary artery diameter decreased by 5% to 8% in response to smoking. In addition, despite smoking-induced increases in rate pressure product, coronary flow velocity decreased by $7\% \pm 4\%$, whereas coronary vascular resistance increased by $21\% \pm 4\%$. Thus, the physiologic relationship between cardiac work and blood flow velocity was abolished during acute smoking in patients with CAD.

In summary, acute smoking might increase coronary or myocardial blood flow in otherwise healthy subjects. In contrast, patients at risk for or with documented CAD respond to smoking with

increases in coronary vascular resistance or decreases in coronary blood flow.

Chronic Smoking

By using quantitative coronary angiography, Zeiher et al[64] measured the diameter of the epicardial coronary arteries at baseline, after intracoronary papaverine, and nitroglycerine in 96 smokers or nonsmokers with CAD. Measurements were limited to the left anterior descending coronary artery and only patients with left anterior descending stenosis of less than 30% were included. In this population, the dilation of proximal epicardial coronary arteries in response to papaverine (as an index of endothelial dependent flow–mediated coronary vasodilation) was significantly blunted in smokers when compared with nonsmokers. The response to nitroglycerine (as a marker of endothelial-independent coronary vasodilation) was also significantly attenuated yet to a smaller degree than the flow-mediated epicardial coronary artery vasodilation. Importantly, this impairment was present regardless of the presence of coronary artery sclerotic lesions as determined by intravascular ultrasound. Thus, smokers with coronary artery disease exhibited abnormal endothelium-dependent and -independent coronary vasomotion.

In healthy individuals, long-term smoking primarily affects coronary and peripheral arterial endothelial function.[56,61,65] Schelbert's group[65] systematically investigated the effects of long-term smoking on coronary vasomotion and vasodilator capacity. The investigators included 16 long-term smokers and 17 nonsmokers in their study of myocardial blood flow at rest, during cold pressor testing, and during dipyridamole-induced hyperemia. The hemodynamic response to cold exposure was similar in smokers and nonsmokers with increases of the rate pressure product by 20% to 30%. However, myocardial blood flow as determined with N-13 ammonia PET increased significantly only in nonsmokers but not in smokers in response to cold. In fact, when normalized to the rate pressure product as an index of cardiac work, blood flow decreased in smokers but remained unchanged in nonsmokers in response to cold. As another important finding, the degree in impairment of flow in response to cold pressor testing was correlated with the number of years of smoking. The investigators concluded that the abnormal blood flow response to cold was likely explained by coronary endothelial dysfunction.[65]

To further elucidate the role of the coronary endothelium the same group subsequently measured myocardial blood flow at rest and during cold pressor testing under baseline conditions and then again during L-arginine infusion.[66] This approach was chosen because L-arginine is the substrate for NO synthase,[10] which might be useful for restoring coronary endothelial function. Eleven healthy smokers and 12 age-matched controls were included in this study. The endothelium-independent flow response to dipyridamole was fully preserved. L-arginine, the precursor of NO, was administered intravenously in smokers at baseline and during cold pressor testing. At baseline, myocardial blood flow increased by only 11% $\pm$ 14% in smokers during cold pressor testing (*v* 44% $\pm$ 25% in nonsmokers), but increased normally by 48% $\pm$ 28% during cold pressor testing after intravenous L-arginine. Thus, the abnormal coronary vasomotion in long-term smokers in response to cold pressor testing appears to be related to endothelial dysfunction that can be restored by intravenous L-arginine.[66]

Several other studies also provided support to the notion that smoking induces endothelial dysfunction. Barua et al[67] showed an abnormal flow mediated brachial artery vasodilation in 15 healthy smokers. This impairment was present in heavy and light cigarette smokers.[68] The same group also determined the dose-dependent effects of cigarette smoking on brachial artery endothelial-dependent and -independent blood flow.[68] Brachial artery ultrasonography was used to measure the brachial artery diameter at rest, during reactive hyperemia, as a surrogate marker for arterial endothelial function, and after sublingual nitroglycerine as a marker of endothelial-independent vasodilation. The results suggested that light and heavy smoking had comparable adverse effects on brachial artery endothelial function. Interestingly, both heavy and light smokers also had abnormal basal and stimulated NO production and endothelial nitric oxide synthase levels as measured in human umbilical endothelial cell cultures.

Kugiyama et al[69] used quantitative angiography to evaluate the vasomotor response to acetylcholine and mono-methyl-L-arginine injected into the left main coronary artery. Acetylcholine infu-

sion resulted in normal coronary vasodilation in nonsmokers. In contrast, smokers responded to acetylcholine with coronary vasoconstriction. Mono-methyl-L-arginine, an antagonist of L-arginine, the precursor of nitric oxide, attenuated or abolished the vasodilator response to acetylcholine in nonsmokers but had no effects on coronary diameter in smokers during acetylcholine provocation, suggesting that endothelial dysfunction accounted for the abnormal vasomotor response to acetylcholine in smokers. This dysfunction can be reversed, at least in part, by 4 weeks of treatment with the antioxidant vitamin E.[70]

The degree of endothelial dysfunction might also be modified by ethnicity and dietary differences. Using the brachial artery ultrasound technique Woo et al[71] studied the endothelial dependent flow mediated response of the brachial artery in 72 Chinese and 72 Caucasians. Chinese and non-Chinese nonsmokers had a similar flow mediated brachial artery vasodilation of 7.9 and 8.4%. In contrast, only non-Chinese smokers had an attenuated forearm vasodilation (3.9%) while no such effect was observed in Chinese smokers. The authors speculated that the greater consumption of antioxidant-containing teas and foods by the Chinese population might have exerted a protective effect.

Passive Smoking

Passive smoking is associated with an increased risk for CAD.[72] Raitakari et al[73] showed that the endothelial dysfunction observed in passive smokers is at least partially reversible. In their study of 60 healthy subjects, former passive smokers exhibited a better brachial artery response to reactive hyperemia than current passive smokers (5.1% ± 4.1% *v* 2.3% ± 2.1%; $P < .01$). When compared with nonsmoking controls, the endothelial-dependent brachial artery dilation was, however, still attenuated.

Celermajer et al[74] enrolled 26 healthy subjects who were exposed to environmental smoke, 26 active smokers, and 26 healthy controls to determine the brachial artery response to reactive hyperemia. They reported a similarly attenuated flow-mediated brachial artery vasodilation in active and passive smokers. Importantly, the degree of impairment was related to the intensity of passive smoke exposure. Woo et al[75] studied 20 young casino workers with heavy exposure to environmental smoke. Brachial artery flow mediated vasodilation was significantly lower in passive smokers than in controls (6.6% ± 3.4% *v* 10.6% ± 2.3%; $P < .0001$), whereas nitroglycerine-induced vasodilation, as a marker of endothelial-independent vasodilation, did not differ between the 2 groups. These and other studies suggest that passive smoking can result in endothelial dysfunction that, however, is at least in part reversible.

Effects of Nicotine

Several studies attempted to elucidate the independent effects of nicotine on coronary vasomotion. Animal experimental studies have suggested that these effects are dose dependent.[76]

Kaijser and Berglund[62] studied the effects of a chewing gum containing 4 mg of nicotine on coronary sinus blood flow. Flow measurements were obtained at baseline and during various pacing-induced heart rates with and without nicotine stimulation. Coronary sinus blood flow was higher with nicotine than under baseline conditions at any level of cardiac pacing. The increase in myocardial oxygen consumption, however, was disproportionally high relative to the nicotine- induced increases in coronary sinus blood flow. The investigators suggested that α-adrenergic coronary vasoconstriction might have accounted for this finding.

Summary

Invasive and noninvasive techniques have been used to evaluate and quantify the effects of smoking on coronary and peripheral arterial vasomotion and vasodilatory function. Acute and chronic smoking does not appear to alter substantially endothelium-independent coronary vasodilatory capacity. In contrast, acute and chronic active and passive smoking induces abnormalities in coronary and peripheral arterial vasomotion in patients with and individuals without CAD. The site of the damaging effects of smoking is the coronary endothelium. The smoking history appears to be correlated with the degree of vasomotor abnormalities. Further, the degree of smoking-induced abnormalities in coronary function appears to increase with the severity of CAD. Finally, the coronary endothelial and peripheral arterial vasomo-

tor dysfunction observed in active and passive healthy smokers appear to be, to some degree, reversible.

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