GLOBAL HEART

VOL. 7, NO. 2, 2012
ISSN 2211-8160/$36.00
DOI: 10.1016/j.gheart.2012.06.004

REVIEW

Tobacco, Metabolic and Inflammatory Pathways, and CVD Risk

Momoko Kitami [†,‡], Mohammed K. Ali [†]
Atlanta, GA, USA

Cardiovascular diseases account for 25% of all deaths worldwide; 64% of all deaths are due to chronic noncommunicable diseases, and 39% of these are due to cardiovascular diseases [1]. As demonstrated in the INTERHEART, a study of risk factors for first myocardial infarction in 52 countries and over 27,000 subjects [2], and INTERSTROKE, a study of the importance of conventional and emerging risk factors of stroke in different regions and ethnic groups of the world [3], multicountry case–control studies, tobacco use is a potent risk factor for myocardial infarctions and strokes, and these associations are consistent across countries. It is estimated that there are 1 billion tobacco users worldwide, and tobacco is a leading cause of global mortality, responsible for 6 million deaths annually [4].

In addition to the growing body of literature regarding the epidemiology of tobacco use, there have been extensive studies investigating the biochemical pathways that link smoking with cardiovascular disease pathophysiology and the evolution of atherothrombotic plaque. However, this literature is wide-ranging and complex as tobacco products such as cigarettes contain over 4,720 chemical compounds and 10^{15} to 10^{17} free radicals, and this is in addition to the well-known compounds such as carbon monoxide and nicotine [5]. Also, each pathway is neither mutually exclusive nor linear, and there are a vast number of interactions between chemicals, and interconnectivity between the inflammatory and biochemical pathways that they induce. The purpose of this review, therefore, is to distill this literature and provide a comprehensive but concise overview of the pathways that connect tobacco use, and particularly smoking, with the development of cardiovascular disease. We use a framework (Fig. 1) as an overview of the topic to orientate readers and describe the cardiac, vascular, and metabolic changes individually.

SYSTEMIC

Cardiac output. Smoking leads to increased blood volume being ejected from the left ventricle, and nicotine is one of the key triggers. Nicotine stimulates the release of epinephrine and norepinephrine from the adrenal medulla and this activation of the sympathetic nervous system causes an increase in heart rate, ventricular contractility, and blood pressure in smokers [6–8]. In response to this rise in cardiac output and the reduced oxygen availability due to the presence of carbon monoxide in smoke, the coronary arteries dilate to increase blood flow by up to 40% [4,9]. However, this increased coronary blood flow is still lower than what is required (and much lower than the coronary blood flow response observed in nonsmokers) to contend with the increased demand for oxygen. Thus, smokers are exposed to a chronic state of cardiac ischemia and this is consistent with the findings that cigarette smokers have lower thresholds for angina onset caused by this reduced myocardial oxygen delivery [10].

Vasomotor function. Smokers also have deficient vasomotor function (reduced ability to expand and contract when required) of their vessels, and this is related to a combination of morphological and molecular changes induced by smoking. Morphological studies of the coronary arteries, carotid arteries, and the aorta show that indices of atherosclerosis, such as arterial wall thickening, intima-media thickness, and arterial stenosis are all increased among smokers [11,12]. As a result, func-

From the [†]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA; ‡Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA. Correspondence: M. Kitami (mkali@emory.edu).

GLOBAL HEART, VOL. 7, NO. 2, 2012
July 2012: 121–128

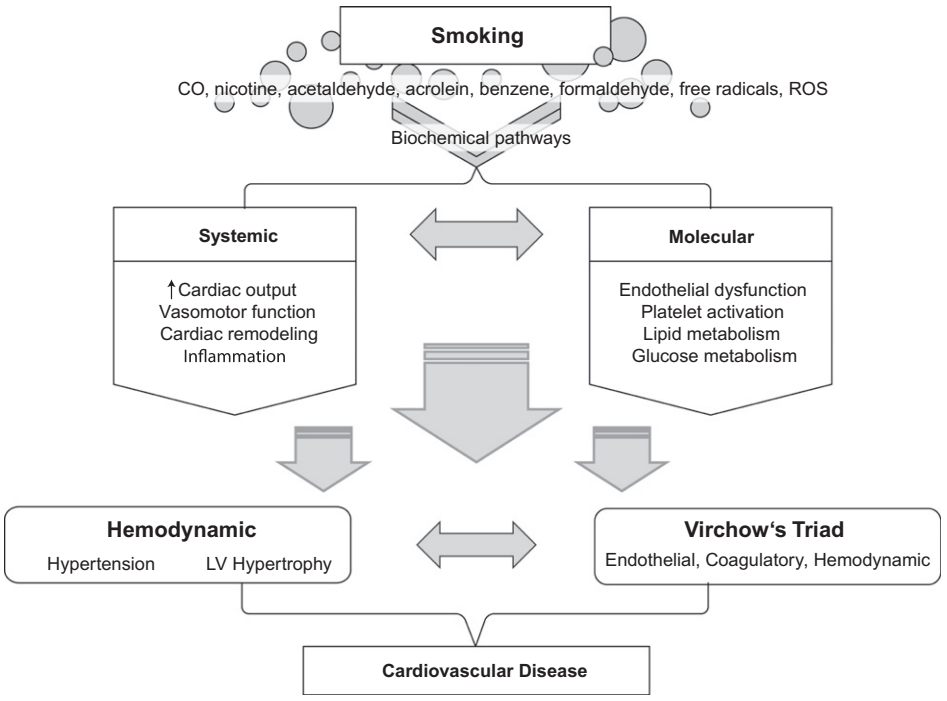

Figure 1. Overview of the pathways that link tobacco use with cardiovascular disease pathophysiology. CO, carbon monoxide; LV, left ventricle; ROS, reactive oxygen species; ↑, increased.

tionally, compared to nonsmokers, smokers' arteries can be characterized as having significantly poorer distensibility and increased stiffness [13].

On a molecular level, compounds in smoke cause a decrease in the bioavailability of a major vasodilator, nitric oxide (NO), and enhance the secretion of vasoconstrictors, such as endothelin-1. Endothelin-1 is constantly secreted at low levels in chronic smokers, which can desensitize the endothelium-dependent vasodilator response mechanism [12]. Imbalanced levels of prostacyclin-I2 and thromboxane-A2 also create a vasoconstrictive tendency among smokers [12,14,15]. Meanwhile, catecholamines induced by nicotine have vasoconstrictor effects in pulmonary and systemic arteries through binding to and activating alpha receptors. These mechanisms all occur in parallel to the increasing blood viscosity, which is related to an increased hematocrit observed in smokers, which reflects exposure to carbon monoxide [16]. Together, vasoconstriction and viscosity contribute to coronary vascular resistance and perpetuate myocardial ischemia [8].

Cardiac remodeling. Cardiac remodeling is another morphological change that is observed among smokers [8]. Both animal and human studies have demonstrated left ventricular hypertrophy and left atrial enlargement as a result of tobacco exposure [17–19]. Atrial fibrosis has also been described among patients that smoke and was noticed during cardiac bypass surgery. Although a definitive causal relationship has not been documented, the literature posits that this atrial morphological change is significantly associated with post-operative atrial fibrillation and is commonly seen in smokers [20]. This observation is supported by other cohort studies showing increased risk for atrial fibrillation among smokers [21]. Atrial fibrillation contributes to the risk of stroke.

In terms of pathology, the myocardium in smokers has been observed to be more hypertrophic and exhibits increased interstitial fibrosis plus signs of myocardial cell apoptosis. Reactive oxygen species (ROS) are centrally involved, damaging myocardial cells, stimulating fibroblasts to proliferate, and activating matrix metalloproteinases [22]. Matrix metalloproteinases are enzymes that degrade elastin and collagen in the extracellular matrix, making the endothelial wall vulnerable [23]. Activation of mitogen-activated protein kinases has also been implicated in left

ventricular remodeling [5,24,25]. As a consequence of these changes, the myocardium becomes enlarged, but the proportion of functioning, contractile myocytes is decreased, leading to suboptimal contractile function. Several studies have documented this reduced left ventricular function among smokers [26]. In vitro studies on cultured human endothelial cells show that nicotine increases the expression and activity of angiotensin-converting enzyme and possibly increases angiotensin-II production [27,28]. Stimulation of the renin–angiotensin system results in vasoconstrictive effects, which may exasperate cardiac remodeling in smokers [22].

There are smoking-related modifications in the vasculature as well. For example, matrix metalloproteinases are likely to be involved in weakening the vascular walls (by permitting degradation of extracellular elastin and collagen), pre-disposing them to the development of aneurysms and plaque rupture [29]. Smoking has also been associated with higher risk for coronary artery spasms [30].

Lastly, although the link between smoking and arrhythmia has not been established clearly, the underlying hypoxia and cardiac remodeling seen in smokers may be associated with arrhythmias and coronary spasms and may be a determinant of sudden death among smokers [31].

Inflammation. Systemic and local vascular inflammation have become integral components in our understanding of the processes involved in atherothrombosis [32]. Smoking results in high levels of systemic oxygen free radical circulation, and this oxidative stress plays a critical role in inducing systemic inflammatory pathways [33]. Blood samples of smokers show elevated levels of peripheral leukocytes, [34] C-reactive protein [35], and fibrinogen [36] compared with levels for nonsmokers. Other systemic proinflammatory cytokines are also raised in smokers and include interleukin-6 and tumor necrosis factor alpha. Chronic elevation of these inflammatory markers provide strong evidence that smokers are exposed to a state of chronic systemic inflammation [37].

At the local level of the vascular bed, endothelial cells in smokers express high levels of cell-adhesion molecules for leukocyte recruitment. Examples of these molecules include soluble vascular cell adhesion protein-1, soluble intercellular adhesion molecule-1, and E-selectin. These molecules stimulate the recruitment of inflammatory cells to the endothelial wall and contribute to atherosclerotic plaque development [38].

MOLECULAR

Endothelial dysfunction

Oxidative stress. As we have already described, smoking impairs flow-mediated vasodilation, or endothelium-dependent vasodilation, in both animal and human arteries [4]. This defect in vascular tone is primarily caused by the decrease in bioavailability of NO [39]. Endothelial cells routinely produce NO in response to shear stress. In turn, NO has several positive effects: it increases blood flow and decreases blood pressure; it suppresses the expression of cell adhesion molecules in the endothelium; and it inhibits the adhesion and aggregation of platelets, leukocytes, and proteins. Through these effects, NO has an overarching role in protecting against atherosclerotic plaque formation [40].. The biochemical mechanism behind smoke-induced impairment in NO bioavailability is complex. However, researchers agree that the primary mechanism involves suppression of endothelial nitric oxide synthase (eNOS) expression and NO production, which are predominantly driven by free radicals, reactive oxygen and nitrogen species, and reactive aldehydes in tobacco smoke [41]. These free radicals deplete tetrahydroxybiopterin, the cofactor of eNOS, which leads to the uncoupling of eNOS and the subsequent reduction in NO synthesis [42]. Free radicals also impair the activity of an enzyme that degrades the endogenous inhibitor of eNOS, called asymmetric dimethylarginine. This causes an accumulation of asymmetric dimethylarginine and continuous inhibition of the NOS pathway [43,44].

Furthermore, free radicals in smoke perpetuate the cycle of oxidative stress by inducing the endogenous production of ROS. Free radicals increase the activity of reduced nicotinamide adenine dinucleotide phosphate oxidase (NADPH) and xanthine oxidase through the cyclooxygenase-2 pathway, which are also ROS-producing enzymes [33,45]. Free radicals also raise the level of ROS by inhibiting the activities of ROS-clearing enzymes (e.g., catalase, superoxide dismutase, and glutathione peroxidase) that would otherwise protect cells from oxidative stress [5]. Through these mechanisms, free radicals in smoke work both directly and indirectly to decrease the bioavailability of NO, causing endothelial dysfunction.

GLOBAL HEART, VOL. 7, NO. 2, 2012
July 2012: 121–128

Endothelial progenitor cells. The effects of smoking on endothelial progenitor cells (EPCs) may also explain the impairment of endothelial function. First introduced by Asahara et al. in 1995, EPCs are thought to be bone marrow-derived cells that protect against the effects of an aging endothelium by migrating, differentiating, and proliferating at sites of ischemia and endothelial injury, thereby regenerating injured endothelial walls and restoring vasodilator function [46–48]. Although there is conflicting evidence regarding the role EPCs play in the development of cardiovascular diseases [49], a number of studies show statistically significant inverse associations where decreases in circulating EPC levels are related to increased risks for cardiovascular, cerebrovascular, and other atherosclerotic diseases [50–52]. Smoking has been identified as a major independent factor for the reduction of circulating EPCs and EPC function [53,54]. The current understanding is that: (1) EPCs play an integral role in endothelial regeneration and homeostasis; (2) a decrease in EPCs is predictive for future cardiovascular events; and (3) EPCs are reduced among smokers [48].

Lipid metabolism. Numerous epidemiologic studies demonstrate altered lipid profiles among smokers. This includes significantly increased levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDLc), as well as lower levels of the antioxidant high-density lipoprotein cholesterol (HDLc) and apolipoprotein A-1 in smokers compared with nonsmokers [55–58]. The low HDL/LDL ratio among smokers indicate a state of high atherogenicity among smokers, and various pathological mechanisms for smoking-induced lipid abnormalities have been postulated [59].

In addition to this, nicotine-stimulated sympathetic up-regulation promotes lipolysis and catabolism, leading to the release of free fatty acids in plasma. Smoking also reduces the activity of lipoprotein lipase in adipose tissue, which works to break down and clear triglycerides from the blood [60,61]. As a result, the excess triglycerides in circulation promote very low-density lipoprotein cholesterol formation and small, dense LDLc synthesis, both of which are more prone to perpetuate the development of atherosclerotic plaque [62]. Smoking is also associated with increased hepatic lipase activity and this has 2 important effects: (1) it produces atherogenic small, dense LDLc, which is both toxic to the endothelium and releases even more free radicals and (2) it produces small, dense HDLc, which actually diminishes the protective antiatherogenic abilities of circulating HDLc [63,64]. Additionally, free radicals in cigarette smoke cause the oxidation of LDLc and lipoproteins, making it easier for these to be deposited in the subendothelial space. These lipids are all highly atherogenic and are avidly engulfed by macrophages through endocytosis, causing an accumulation of foam cells and fibrous plaque formation [65,66].

Studies have also shown how smoking affects lipid transfer enzymes. Smoking reduces the enzymatic activity of lecithin cholesterol acyltransferase, an enzyme that transports esterified cholesterol into the HDL core. Without this mechanism, less cholesterol is transported to the liver for catabolism [67].

Glucose metabolism. In addition to altered lipid profiles, smokers also experience abnormalities in glucose metabolism. Multiple cohort studies have demonstrated that smoking is associated with an increased risk for type 2 diabetes [68–70]. These same studies have shown that there is a positive dose-dependent relationship between the number of cigarettes smoked and risk for type 2 diabetes [71,72]. Studies have linked smoking with insulin resistance in both diabetic and nondiabetic patients [73–75], and it has been postulated that this mechanism drives diabetes risk.

Smoking cessation is particularly important in people with diabetes, as smoking makes glucose control more difficult. Studies have shown that larger insulin dose is required to achieve the same level of glucose control in smokers on insulin therapy compared with glucose control in nonsmokers [76]. Smoking also significantly increases the risks for macrovascular and microvascular complications; in particular, the risk for coronary artery disease, stroke, and peripheral vascular disease in people with diabetes is further amplified by smoking [77,78]. Smoking cessation can help slow down the progression of diabetic nephropathy [79] and microalbuminuria [80] in patients with diabetes. It is not clear, however, how smoking interacts with diabetes-related retinopathy and neuropathy risk, but it is likely that smoking perpetuates the risks of developing these microvascular complications [70].

It is still unclear which pathophysiological mechanisms are involved in terms of how smoking relates to insulin resistance. Several theories have been proposed and debated. Nicotine may have a

central role through inducing catecholamine release and stimulating the sympathetic nervous system (which has an insulin-antagonistic effect). Smoking has also been found to cause a reduction in glucose uptake in peripheral tissues and, in effect, reducing insulin sensitivity. Chemical toxicity from cigarette smoke may be a culprit, impairing pancreatic beta cells (decreasing insulin secretion) and desensitizing insulin receptors (decreasing insulin sensitivity). Dysfunctional lipid metabolism and elevated free fatty acids may also contribute to insulin insensitivity. Other less well-established theories include the effects of chronic and systemic inflammation caused by smoking on insulin resistance [4,81,82].

Platelet activation. Repeated studies have demonstrated thrombogenicity among smokers and have attributed this to high platelet adhesiveness ("stickiness") and aggregation, as well as alterations in the expression of antithrombotic, prothrombotic, and fibrinolytic factors. Spontaneous aggregation of platelets was first observed in smoker's plasma in vitro [83]. This was then corroborated by studies showing in vivo elevations in markers of platelet aggregation. For example, urinary thromboxane A2 (TxA2) metabolites—11-deydro-TxB2, and 2, 3-dinor-TxB2—have all been shown to be more elevated among smokers than among nonsmokers [84,85]. Smoking also causes decreased bioavailability of platelet-derived NO and decreased platelet sensitivity to NO, both of which act to promote platelet activation [86,87]. Compared with nonsmokers, smokers also have higher circulating levels of von Willebrand factor [88], tissue factor [89], and fibrinogen [36], which cumulatively perpetuate a prothrombotic state.

Impaired fibrinolytic activity has also been observed in smokers. Studies on smokers' coronary arteries have shown relatively lower levels of tissue plasminogen activator compared with the increase in plasminogen activator inhibitor-1 [90]. This imbalance in the tissue plasminogen activator/plasminogen activator inhibitor-1 ratio disrupts fibrinolysis, effectively permitting thrombus formation and propagation.

SUMMARY AND IMPLICATIONS

Altogether, tobacco use and particularly cigarette smoking, induce a number of factors, pathways, and mechanisms that predispose, program, or perpetuate atherosclerotic diseases of the vasculature and systemically strain the myocardium. The mechanisms and pathways described overlap and interact a great deal. The majority of the enzymes, hormones, or inflammatory markers described have a primary pathophysiologic role, while also perpetuating other pathways. A case in point is how smoking creates a pre-disposing milieu by impairing the endothelium and increasing expression of cell-adhesion molecules—all of this is attributed to decreased production of endothelium-derived NO. Meanwhile, NO is also known to prevent platelet aggregation and thrombus formation, and so the lack of NO perpetuates plaque formation and atherosclerosis [91]. Additionally, smokers have a raised hematocrit and blood viscosity as a consequence of exposure to high levels of carbon monoxide and carboxyhemoglobin. These further perpetuate the risk of atherothrombogenic diseases among smokers [16,92], and all it takes is time and insults that trigger ischemia (e.g., high oxygen or metabolic demand that can also be attributed to high systemic vascular tone) to tip the individual toward acute vascular events. Endothelial wall injury caused by oxidative stress, arterial stenosis due to atherosclerosis by alternations in the lipid and glucose metabolism, enhanced platelet activation, and the impairment of fibrinolytic activity each interferes with Virchow's triad, promoting a state of thrombogenicity and the development of cardiovascular disease in smokers.

Although this is not an exhaustive review, an overview of this nature at least familiarizes the clinician with the pathways involved in tobacco-related cardiac and vascular abnormalities and provides a broad understanding for how different therapies may address the biochemical and pathophysiological abnormalities that can be attributed to smoking. So, from a clinical standpoint, this concise review identifies the key targets for how to preserve or rehabilitate vascular or cardiac dysfunction through therapies and patient counseling.

From a public health perspective, the addictive and wide-ranging damage caused by smoking reaffirms the need to legislate and/or advocate for preventing and protecting against active and passive exposure to tobacco. The complexity of pathways involved in tobacco-related cardiovascular pathophysiology suggests that single therapies may only have small benefits for patients with tobacco-related disease. A review of this nature also propagates the public health and clinical world's skepticism of substitute tobacco products (e.g., electronic cigarettes) that keep appearing as new

GLOBAL HEART, VOL. 7, NO. 2, 2012
July 2012: 121–128

and "less harmful" alternatives for tobacco users. The complexity of effects that is orchestrated by each compound in a cigarette implies that even these products with only a few hazardous compounds can have substantial harmful effects on cardiac and vascular structure and physiology. As such, the only comprehensive, ethical, and cost-effective methods of avoiding or decreasing tobacco-related harms are to prevent and protect against exposure, or to help those that are already exposed to stop smoking. These tenets of prevention, protection, and cessation are the same 3 themes embodied in the World Health Organization's Framework Convention on Tobacco Control, and it is hoped that all countries adopt and implement the clear mandate set out in this global framework.

REFERENCES

1. World Health Organization. Global Status Report on Noncommunicable Diseases 2010 [pdf]. April 2011. Available at: http://www.who.int/nmh/publications/ncd_report2010/en/. Accessed December 8, 2011.
2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. Lancet 2004;364:937–52.
3. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case–control study. Lancet 2010;376:112–23.
4. U.S. Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the surgeon general. Atlanta, GA, USA: Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010. Available at: http://www.surgeongeneral.gov/library/reports/tobaccosmoke/index.html. Accessed November 27, 2011.
5. Rafacho BP, Azevedo PS, Polegato BF, et al. Tobacco smoke induces ventricular remodeling associated with an increase in NADPH oxidase activity. Cell Physiol Biochem 2011;27:305–12.
6. Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med 1976;295:573–7.
7. Arcavi L, Jacob 3rd P, Hellerstein M, Benowitz NL. Divergent tolerance to metabolic and cardiovascular effects of nicotine in smokers with low and high levels of cigarette consumption. Clin Pharmacol Ther 1994;56:55–64.
8. Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Prog Cardiovasc Dis 2003;46:91–111.
9. Czernin J, Waldherr C. Cigarette smoking and coronary blood flow. Prog Cardiovasc Dis 2003;45:395–404.
10. Yamada S, Zhang XQ, Kadono T, et al. Direct toxic effects of aqueous extract of cigarette smoke on cardiac myocytes at clinically relevant concentrations. Toxicol Appl Pharmacol 2009;236:71–7.
11. Pittilo RM. Cigarette smoking, endothelial injury and cardiovascular disease. Int J Exp Pathol 2000;81:219–30.
12. Rahman MM, Laher I. Structural and functional alteration of blood vessels caused by cigarette smoking: an overview of molecular mechanisms. Curr Vasc Pharmacol 2007;5:276–92.
13. Doonan RJ, Scheffler P, Yu A, et al. Altered arterial stiffness and subendocardial viability ratio in young healthy light smokers after acute exercise. PLoS One 2011;6:e26151.
14. Vanhoutte PM, Feletou M, Taddei S. Endothelium-dependent contractions in hypertension. Br J Pharmacol 2005;144:449–58.
15. Huang RY, Chen GG. Cigarette smoking, cyclooxygenase-2 pathway and cancer. Biochim Biophys Acta 2011;1815:158–69.
16. Levenson J, Simon AC, Cambien FA, Beretti C. Cigarette smoking and hypertension. Factors independently associated with blood hyperviscosity and arterial rigidity. Arteriosclerosis 1987;7:572–7.
17. Gidding SS, Xie X, Liu K, et al. Cardiac function in smokers and nonsmokers: the CARDIA study. The Coronary Artery Risk Development in Young Adults Study. J Am Coll Cardiol 1995;26:211–6.
18. Meurrens K, Ruf S, Ross G, et al. Smoking accelerates the progression of hypertension-induced myocardial hypertrophy to heart failure in spontaneously hypertensive rats. Cardiovasc Res 2007;76:311–22.
19. Talukder MA, Johnson WM, Varadharaj S, et al. Chronic cigarette smoking causes hypertension, increased oxidative stress, impaired NO bioavailability, endothelial dysfunction, and cardiac remodeling in mice. Am J Physiol Heart Circ Physiol 2011;300:H388–96.
20. Goette A, Lendeckel U, Kuchenbecker A, et al. Cigarette smoking induces atrial fibrosis in humans via nicotine. Heart 2007;93:1056–63.
21. Heeringa J, Kors JA, Hofman A, et al. Cigarette smoking and risk of atrial fibrillation: the Rotterdam Study. Am Heart J 2008;156:1163–9.
22. Varela-Carver A, Parker H, Kleinert C, Rimoldi O. Adverse effects of cigarette smoke and induction of oxidative stress in cardiomyocytes and vascular endothelium. Curr Pharm Des 2010;16:2551–8.
23. Pistoia F, Cipollone F, Ferri C, et al. Cyclooxygenase and atherosclerosis: a smoking area. Curr Pharm Des 2010;16:2567–71.
24. Castardeli E, Duarte DR, Minicucci MF, et al. Tobacco smoke-induced left ventricular remodelling is not associated with metalloproteinase-2 or -9 activation. Eur J Heart Fail 2007;9:1081–5.
25. Gu L, Pandey V, Geenen DL, et al. Cigarette smoke-induced left ventricular remodelling is associated with activation of mitogen-activated protein kinases. Eur J Heart Fail 2008;10:1057–64.
26. Rosen BD, Saad MF, Shea S, et al. Hypertension and smoking are associated with reduced regional left ventricular function in asymptomatic: individuals the Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol 2006;47:1150–8.
27. Saijonmaa O, Nyman T, Fyhrquist F. Regulation of angiotensin-converting enzyme production by nicotine in human endothelial cells. Am J Physiol Heart Circ Physiol 2005;289:H2000–4.
28. Ljungberg LU, Persson K. Effect of nicotine and nicotine metabolites on angiotensin-converting enzyme in human endothelial cells. Endothelium 2008;15:239–45.
29. Rizas KD, Ippagunta N, Tilson 3rd MD. Immune cells and molecular mediators in the pathogenesis of the

abdominal aortic aneurysm. Cardiol Rev 2009;17:201–10.
30. Caralis DG, Deligonul U, Kern MJ, Cohen JD. Smoking is a risk factor for coronary spasm in young women. Circulation 1992;85:905–9.
31. D'Alessandro A, Boeckelmann I, Hammwhöner M, Goette A. Nicotine, cigarette smoking and cardiac arrhythmia: an overview. Eur J Cardiovasc Prev Rehabil 2011 May 25 [E-pub ahead of print].
32. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135–43.
33. Grassi D, Desideri G, Ferri L, et al. Oxidative stress and endothelial dysfunction: say NO to cigarette smoking! Curr Pharm Des 2010;16: 2539–50.
34. Jensen EJ, Pedersen B, Frederiksen R, Dahl R. Prospective study on the effect of smoking and nicotine substitution on leucocyte blood counts and relation between blood leucocytes and lung function. Thorax 1998;53:784–9.
35. Tracy RP, Psaty BM, Macy E, et al. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. Arterioscler Thromb Vasc Biol 1997;17:2167–76.
36. Tuut M, Hense HW. Smoking, other risk factors and fibrinogen levels: evidence of effect modification. Ann Epidemiol 2001;11:232–8.
37. Mendall MA, Patel P, Asante M, et al. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. Heart 1997;78:273–7.
38. Mazzone A, Cusa C, Mazzucchelli I, et al. Cigarette smoking and hypertension influence nitric oxide release and plasma levels of adhesion molecules. Clin Chem Lab Med 2001;39: 822–6.
39. Edirisinghe I, Arunachalam G, Wong C, et al. Cigarette-smoke-induced oxidative/nitrosative stress impairs VEGF- and fluid-shear-stress-mediated signaling in endothelial cells. Antioxid Redox Signal 2010;12: 1355–69.
40. Toda N, Toda H. Nitric oxide-mediated blood flow regulation as affected by smoking and nicotine. Eur J Pharmacol 2010;649:1–13.
41. Barua RS, Ambrose JA, Srivastava S, DeVoe MC, Eales-Reynolds LJ. Reactive oxygen species are involved in smoking-induced dysfunction of nitric oxide biosynthesis and upregulation of endothelial nitric oxide synthase: an in vitro demonstration in human coronary artery endothelial cells. Circulation 2003;107: 2342–7.
42. Ichiki T. Collaboration between smokers and tobacco in endothelial dysfunction. Cardiovasc Res 2011;90:395–6.
43. Zhang WZ, Venardos K, Chin-Dusting J, Kaye DM. Adverse effects of cigarette smoke on NO bioavailability: role of arginine metabolism and oxidative stress. Hypertension 2006;48:278–85.
44. Cooke JP, Ghebremariam YT. DDAH says NO to ADMA. Arterioscler Thromb Vasc Biol 2011;31:1462–4.
45. Barbieri SS, Zacchi E, Amadio P, et al. Cytokines present in smokers' serum interact with smoke components to enhance endothelial dysfunction. Cardiovasc Res 2011;90: 475–83.
46. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science 1997;275:964–7.
47. Di Stefano R, Barsotti MC, Felice F, et al. Smoking and endothelial progenitor cells: a revision of literature. Curr Pharm Des 2010;16: 2559–66.
48. Mayr M, Niederseer D, Niebauer J. From bench to bedside: what physicians need to know about endothelial progenitor cells. Am J Med 2011;124:489–97.
49. Hagensen MK, Raarup MK, Mortensen MB, et al. Circulating endothelial progenitor cells do not contribute to regeneration of endothelium after murine arterial injury. Cardiovasc Res 2012;93:223–31.
50. Hill JM, Zalos G, Halcox JP, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med 2003;348:593–600.
51. Rosenzweig A. Circulating endothelial progenitors – cells as biomarkers. N Engl J Med 2005;353:1055–7.
52. Schmidt-Lucke C, Rossig L, Fichtlscherer S, et al. Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events: proof of concept for the clinical importance of endogenous vascular repair. Circulation 2005;111: 2981–7.
53. Vasa M, Fichtlscherer S, Aicher A, et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. Circ Res 2001;89:E1–7.
54. Michaud SE, Dussault S, Haddad P, Groleau J, Rivard A. Circulating endothelial progenitor cells from healthy smokers exhibit impaired functional activities. Atherosclerosis 2006;187:423–32.
55. Criqui MH, Wallace RB, Heiss G, et al. Cigarette smoking and plasma high-density lipoprotein cholesterol. The Lipid Research Clinics Program Prevalence Study. Circulation 1980;62:IV70–6.
56. Muscat JE, Harris RE, Haley NJ, Wynder EL. Cigarette smoking and plasma cholesterol. Am Heart J 1991;121:141–7.
57. Craig WY, Palomaki GE, Haddow JE. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. BMJ 1989;298:784–8.
58. Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. Prev Med 2003;37:283–90.
59. Chapman MJ, Ginsberg HN, Amarenco P, et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J 2011;32:1345–61.
60. Gastaldelli A, Folli F, Maffei S. Impact of tobacco smoking on lipid metabolism, body weight and cardiometabolic risk. Curr Pharm Des 2010;16:2526–30.
61. Freeman DJ, Caslake MJ, Griffin BA, et al. The effect of smoking on postheparin lipoprotein and hepatic lipase, cholesteryl ester transfer protein and lecithin:cholesterol acyl transferase activities in human plasma. Eur J Clin Invest 1998;28:584–91.
62. Campbell SC, Moffatt RJ, Stamford BA. Smoking and smoking cessation—the relationship between cardiovascular disease and lipoprotein metabolism: a review. Atherosclerosis 2008;201:225–35.
63. Kong C, Nimmo L, Elatrozy T, et al. Smoking is associated with increased hepatic lipase activity, insulin resistance, dyslipidaemia and early atherosclerosis in type 2 diabetes. Atherosclerosis 2001;156:373–8.
64. Evans M, Khan N, Rees A. Diabetic dyslipidaemia and coronary heart disease: new perspectives. Curr Opin Lipidol 1999;10:387–91.
65. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 2004;43:1731–7.
66. Jessup W, Kritharides L. Metabolism of oxidized LDL by macrophages. Curr Opin Lipidol 2000;11: 473–81.
67. McCall MR, van den Berg JJ, Kuypers FA, et al. Modification of LCAT activity and HDL structure: new links between cigarette smoke and coronary heart disease risk. Arterioscler Thromb 1994;14:248–53.
68. Foy CG, Bell RA, Farmer DF, et al. Smoking and incidence of diabetes

among U.S. adults: findings from the Insulin Resistance Atherosclerosis Study. Diabetes Care 2005;28:2501–7.
69. Willi C, Bodenmann P, Ghali WA, et al. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2007;298: 2654–64.
70. Tonstad S. Cigarette smoking, smoking cessation, and diabetes. Diabetes Res Clin Pract 2009;85:4–13.
71. Manson JE, Ajani UA, Liu S, et al. A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. Am J Med 2000;109:538–42.
72. Wannamethee SG, Shaper AG, Perry IJ. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. Diabetes Care 2001;24:1590–5.
73. Facchini FS, Hollenbeck CB, Jeppesen J, et al. Insulin resistance and cigarette smoking. Lancet 1992;339:1128–30.
74. Eliasson B, Mero N, Taskinen MR, Smith U. The insulin resistance syndrome and postprandial lipid intolerance in smokers. Atherosclerosis 1997;129:79–88.
75. Targher G, Alberiche M, Zenere MB, et al. Cigarette smoking and insulin resistance in patients with non-insulin dependent diabetes mellitus. J Clin Endocrinol Metab 1997;82:3619–24.
76. Madsbad S, McNair P, Christensen MS, et al. Influence of smoking on insulin requirement and metabolic status in diabetes mellitus. Diabetes Care 1980;3:41–3.
77. Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 1998;316:823–8.
78. Adler AI, Stevens RJ, Neil A, et al. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. Diabetes Care 2002;25: 894–9.
79. Chuahirun T, Khanna A, Kimball K, Wesson DE. Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. Am J Kidney Dis 2003;41: 13–21.
80. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. Metabolism 2011;60:1456–64.
81. Fagard RH, Nilsson PM. Smoking and diabetes—the double health hazard! Prim Care Diabetes 2009;3:205–9.
82. Berlin I. Smoking-induced metabolic disorders: a review. Diabetes Metab 2008;34:307–14.
83. Fusegawa Y, Goto S, Handa S, et al. Platelet spontaneous aggregation in platelet-rich plasma is increased in habitual smokers. Thromb Res 1999;93:271–8.
84. Murray JJ, Nowak J, Oates JA, FitzGerald GA. Platelet-vessel wall interactions in individuals who smoke cigarettes. Adv Exp Med Biol 1990;273:189–98.
85. Rängemark C, Benthin G, Granström EF, et al. Tobacco use and urinary excretion of thromboxane A2 and prostacyclin metabolites in women stratified by age. Circulation 1992;86:1495–500.
86. Freedman JE, Ting B, Hankin B, et al. Impaired platelet production of nitric oxide predicts presence of acute coronary syndromes. Circulation 1998;98:1481–6.
87. Sawada M, Kishi Y, Numano F, Isobe M. Smokers lack morning increase in platelet sensitivity to nitric oxide. J Cardiovasc Pharmacol 2002;40: 571–6.
88. Blann AD, McCollum CN. Adverse influence of cigarette smoking on the endothelium. Thromb Haemost 1993;70:707–11.
89. Sambola A, Osende J, Hathcock J, et al. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. Circulation 2003;107:973–7.
90. Newby DE, McLeod AL, Uren NG, et al. Impaired coronary tissue plasminogen activator release is associated with coronary atherosclerosis and cigarette smoking: direct link between endothelial dysfunction and atherothrombosis. Circulation 2001;103:1936–41.
91. Shimasaki Y, Saito Y, Yoshimura M, et al. The effects of long-term smoking on endothelial nitric oxide synthase mRNA expression in human platelets as detected with real-time quantitative RT-PCR. Clin Appl Thromb Hemost 2007;13:43–51.
92. Haustein KO, Krause J, Haustein H, et al. Effects of cigarette smoking or nicotine replacement on cardiovascular risk factors and parameters of haemorheology. J Intern Med 2002;252: 130–9.