REVIEW

The effect of smoking on arterial stiffness

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A systematic literature review was conducted using PubMed, Embase and the Cochrane Library to determine the effect of acute, chronic and passive smoking on arterial stiffness and to determine whether these effects are reversible after smoking cessation. A total of 39 relevant studies were identified and included. Acute smoking was found to cause an acute increase in arterial stiffness. Similarly, passive smoking increased arterial stiffness acutely and chronically. The majority of studies identified chronic smoking as a risk factor for increasing arterial stiffness. However, some studies found no statistical difference in arterial stiffness between nonsmokers and long-term smokers, although chronic smoking seems to sensitize the arterial response to acute smoking. In addition, whether arterial stiffness is reversed after smoking cessation and the timeline in which this may occur could not be determined from the identified literature. The effect of smoking discontinuation on arterial stiffness remains to be established by prospective smoking cessation trials.

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INTRODUCTION

Cigarette smoking has long been established as a cardiovascular risk factor and is the major preventable cause of death and disability in developed and developing countries.^{1,2} Smoking accounts for ~1 200 000 deaths each year in Europe, 440 000 in the United States and 50 000 in Canada.^{1–3} Smoking can cause cardiovascular damage by inducing endothelial dysfunction and harmful hemodynamic effects, such as increased arterial stiffness.^{4–6} Furthermore, a number of factors and conditions, such as alcohol consumption, dyslipidemia, hypertension, renal dysfunction, obesity and chronic obstructive pulmonary disease cause changes in arterial stiffness.^{7–14} These effects may interact with the effects of smoking to alter arterial stiffness and cardiovascular risk profiles.

The measurement of vessel hemodynamics is gaining popularity as a means to assess arterial stiffness and endothelial function. Accordingly, various noninvasive methods have been developed to measure arterial stiffness, including applanation tonometry, echotracking, Doppler and ultrasound.¹⁵ These techniques could be useful in clinical practice, particularly applanation tonometry, as numerous studies have shown that increased arterial stiffness as measured by aortic pulse wave velocity (PWV) and augmentation index (AIx) is directly and independently associated with increased risk of cardiovascular complications and events.^{16–22} Although aortic PWV (typically measured by carotid-femoral PWV (cfPWV)) has the most evidence to support its predictive value for cardiovascular events, it is important to understand the differences between PWV measured in various vascular beds; smoking may affect particular areas of the vascular

system in different ways. cfPWV reflects the stiffness of the central elastic arteries, crPWV (carotid-radial PWV) and brPWV (brachial-radial PWV) reflect the stiffness of peripheral muscular arteries, and brachial-ankle PWV (baPWV) is an intermediate measurement, providing information about the stiffness of both peripheral muscular and central elastic arteries.^{15,16}

The purpose of this systematic review was to assess the effect of acute, chronic and passive smoking on arterial stiffness, as well as the effect of smoking cessation on arterial stiffness.

METHODS

Data sources and study selection

Studies were identified through PubMed, Embase and the Cochrane Library using the keywords shown in Figure 1. Relevant articles were extracted using search terms, reference lists and the 'related article' links of articles selected for review. We included all relevant clinical studies that enrolled chronic smokers and nonsmokers in whom arterial stiffness was measured. The search for articles was limited to those published between 1985 and November 2009, and written in English. Two independent researchers (RJD and AH) conducted the search.

RESULTS

A total of 39 studies were identified, confirmed by all authors and included in this review. Figure 1 illustrates the search and study selection procedure. Tables 1–4 summarize the findings of the included studies, and Supplementary Tables 1–4 summarize the patient characteristics of the included studies.

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Figure 1 Search strategy.

Acute smoking

The acute effects of cigarette smoking on arterial stiffness have been explored previously (Table 1). A number of studies have shown that arterial stiffness increases acutely after cigarette or cigar smoking as measured by AIx, cfPWV, brPWV or crPWV.^{23–26} Another study between chronic and nonsmokers reported that at baseline, the baPWV was not significantly different but was significantly higher in chronic smokers 5 min after cigarette smoking and remained higher for 30 min ($P<0.05$); in both groups, baPWV was significantly higher at 5 min when compared with baseline (both $P<0.001$) and returned to baseline at 45 min.²⁷

Rhee *et al.*²⁸ reported a significant smoking-induced acute increase in heart-femoral PWV ($P<0.05$). However, after adjustment for total cholesterol, time-dependent heart rate and brachial mean arterial pressure, this association lost statistical significance.

The acute effects of smoking were also evaluated on aortic, carotid, radial and brachial distensibility and compliance; in all studies, distensibility and compliance decreased in all arterial beds stu-

died.^{29–34} Swampillai *et al.*³⁵ reported a significant smoking-induced increase in stiffness index (SI) 15 min after smoking ($P<0.05$), but did not observe changes in wave speed in the carotid artery.

Chronic smoking

Several studies reported the relationship between PWV and smoking (Table 2). In one study, brPWV was significantly increased in smokers;³⁶ another study reported higher PWV in smokers, but did not report the arterial segment that was measured.³⁷ Similarly, increases in aortic stiffness were also noted in smokers in other studies.^{38,39} In fact, cigarette smoking was found to be a significant predictor of increased aortic PWV in White and Black individuals ($R^2=0.13$ and $R^2=0.14$, respectively; $P<0.05$).³⁹ In contrast, Yufu *et al.*⁴⁰ found no significant differences between smokers and non-smokers when evaluating baPWV. In addition, three different groups found no significant correlation between smoking status and increased cfPWV.^{41–43} However, AIx was increased in smokers (17.25%) compared with nonsmokers (11.75%; $P=0.004$) in one of the same subject

Table 1 Acute smoking studies

Study	Inclusion criteria	Comparison	Outcome	P-value
Rhee <i>et al.</i> ²⁸	Apparently healthy male CS	Before vs. after smoking	hfPWV Increased by 7% at 5 min Return to baseline at 15 min After adjustment for total cholesterol, time-dependent heart rate and MAP, there was no change faPWV No change after smoking	<0.05 NS NS
Lemogoum <i>et al.</i> ²³	Healthy White and Black CS	Before vs. after smoking, and sham smoking	cfPWV (m s^{-1}) Acute smoking: increase from 5.9 ± 1.7 to 7.0 ± 1.5 at 10 min crPWV (m s^{-1}) Acute smoking: increase from 8.2 ± 1.3 to 9.7 ± 1.7 at 10 min Aix (%) Acute smoking: increase from 7.7 ± 9.0 to 14.8 ± 18.0 at 10 min PP (mm Hg) Acute smoking: increase from 47 ± 6 to 55 ± 6 at 10 min Sham smoking: no change throughout	=0.02 =0.01 =0.01 =0.04 NS
Swampillai <i>et al.</i> ³⁵	Healthy CS	Before vs. after smoking, and sham smoking	β -Stiffness index Acute smoking: increase from 7.4 to 9.2 at 15 min Sham smoking: no change Carotid wave speed (m s^{-1}) Acute smoking: no change Sham smoking: no change	<0.05 NS NS NS
Sassalos <i>et al.</i> ⁵¹	Healthy male CS	Before vs. after smoking, and sham smoking	PP (mm Hg) Acute smoking: increase of 5.8 ± 4.3 Sham smoking: no change Aortic distensibility ($\text{cm}^2 \times \text{dyne}^{-1} \times 10^{-6}$) Acute smoking: decrease of 0.53 ± 0.86 Sham smoking: no change	<0.001 NS NS NS
Zamir <i>et al.</i> ³¹	Healthy CS and Non-S	Before vs. after smoking, and sham smoking in Non-S	Arterial compliance CS: 2.55 ± 0.1 at baseline, 2.34 ± 0.1 5 min after smoking, 2.3 ± 0.1 15 min after smoking Non-S: no change after sham smoking	<0.01 NS
Kim <i>et al.</i> ²⁷	Healthy young male CS and Non-S	Before vs. after smoking	baPWV (m s^{-1}) CS: increase from 11.69 to 12.69 at 5 min, return to baseline at 45 min Non-S: increase from 11.57 to 12.23 at 5 min return to baseline at 45 min CS increase higher than Non-S from 5 to 30 min Both increases still significant after adjustment for MAP PP (mm Hg) CS: no change Non-S: no change	<0.001 NS NS NS NS NS
Vlachopoulos <i>et al.</i> ²⁶	Healthy male CS and cigar smokers	Before vs. after cigar smoking, and sham smoking	cfPWV (m s^{-1}) Cigar smoking: increase by 0.8 at 1 h, increase began immediately and lasted 2 h Sham smoking: no change After adjustment for MAP Aix (%) Cigar smoking: increase by 6.1 at 90 min, increase began immediately and lasted 2 h Sham smoking: no change After adjustment for MAP	<0.001 NS NS NS NS NS
Mahmud and Feely ²⁴	Healthy CS and Non-S	Before vs. after smoking	Aix (%) Acute groups CS: 6.45 ± 18 at baseline, increased 15 min after smoking Non-S: -11 ± 15 at baseline, increased 15 min after smoking cfPWV (m s^{-1}) Acute groups CS: increase after smoking, significant for 15 min Non-S: increase after smoking, significant for 15 min but less increased than CS	<0.05 NS NS NS NS NS

Table 1 Continued

Study	Inclusion criteria	Comparison	Outcome	P-value
Stefanadis <i>et al.</i> ³⁴	Male CS undergoing cardiac catheterization for evaluation of chest pain	Before vs. after smoking, and sham smoking	Aortic distensibility Decreased by 27% after smoking 1 cigarette	<0.001
			No change after sham smoking	NS
Failla <i>et al.</i> ²⁹	Healthy CS	Before vs. after smoking, and sham smoking	Radial distensibility Acute smoking: no change during smoking, reduced by 41.3% after smoking Sham smoking: no change	<0.01 NS
			Carotid distensibility Acute smoking: decreased by 33.3% during smoking Decreased by 27.2% after smoking Sham smoking: no change	<0.01 <0.05 NS
Stefanadis <i>et al.</i> ³³	Healthy male CS	Before vs. after smoking, and sham smoking	PP (mm Hg) Acute smoking: increase from 55.4 ± 2.2 to 59.3 ± 2.7 after smoking Sham smoking: no change	=0.031 NS
			Aortic Distensibility (cm ² × dyne ⁻¹ × 10 ⁻⁶) Acute smoking: decrease from 2.08 ± 0.12 to 1.54 ± 0.07 at 5 min Sham smoking: no change	<0.001 NS
Giannattasio <i>et al.</i> ³⁰	Healthy CS	Before vs. after smoking, and sham smoking	Radial compliance index acute smoking: reduced by 22.5 ± 4.2% after smoking Sham smoking: no change	<0.01 NS
Kool <i>et al.</i> ³²	Healthy CS	Before vs. after smoking	Distensibility coefficient (10 ⁻³ per kPa) Carotid artery: no difference before and after smoking Brachial artery: decreased after smoking from 22.5 ± 2.3 to 18.4 ± 2.0 Compliance coefficient (mm ² per kPa) Carotid artery: no difference before or after smoking Brachial artery: decreased after smoking from 0.24 ± 0.03 to 0.20 ± 0.02	NS <0.01 NS <0.05
Berlin <i>et al.</i> ²⁵	Healthy male CS	Before vs. after smoking	brPWV Acute smoking: increase by 28% 15 min after smoking, return to baseline at 30 min	P<0.05

Abbreviations: AIx, augmentation index; baPWV, brachial-ankle pulse wave velocity; brPWV, brachial-radial pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; CS, current smoker; faPWV, femoral-ankle pulse wave velocity; hfPWV, heart-femoral pulse wave velocity; MAP, mean arterial pressure; Non-S, nonsmoker; NS, not significant; PP, pulse pressure.

populations.⁴² A number of other studies found AIx to be increased in chronic smokers compared with nonsmokers.^{24,41,44,45} Furthermore, Tomiyama *et al.*⁴⁶ showed that AIx was independently correlated with smoking status in men and women.

Some of the identified studies evaluated arterial stiffness using ultrasonographic methods: SI, distensibility and compliance. Two studies reported that smokers had significant increases in the SI when compared with nonsmokers.^{47,48} However, another study only reported significant increases in SI in female smokers ($P=0.041$).⁴⁹ Aortic compliance⁵⁰ and aortic distensibility⁵¹ were significantly decreased in smokers compared with nonsmokers. In a study of smoking adolescents, the normalized pressure strain in smokers was higher than in nonsmokers ($P=0.001$).⁵² McVeigh *et al.*⁵³ found that the damping of diastolic oscillation was significantly increased in smokers, and that the derived oscillatory compliance estimate was reduced compared with nonsmokers. Another study also found stiffer arteries in chronic smokers; however, this was limited to the popliteal artery.⁵⁴ Nevertheless, one study found no difference in carotid and brachial artery distensibility between nonsmokers and chronic smokers.³²

Passive smoking

Three different studies found that exposure to environmental tobacco smoke (ETS) for 5–60 min leads to increased arterial stiffness (Table 3).^{34,55,56} However, in one study, this change was noted only in male subjects.⁵⁶ No change was observed after exposure to non-tobacco smoke in any of the studies.^{34,55,56} Interestingly, administration of sublingual nicotine was associated with increased AIx ($P=0.001$).⁵⁵ Another study reported a significant correlation between carotid arterial SI and ETS exposure. In older individuals, or in those with increased intima-media thickness, the adjusted SI was increased with increasing number of ETS sources ($P=0.09$ and $P=0.05$, respectively). In individuals with a higher body mass index, or in those with increased intima-media thickness, the adjusted SI was increased within hours of exposure to ETS (both $P=0.04$).⁵⁷

Smoking cessation

The effect of smoking cessation in reversing increased arterial stiffness is not well established (Table 4). Oren *et al.*⁵⁸ and Polonia *et al.*⁵⁹ observed a decrease in AIx after 6 months of smoking cessation; continuing smokers showed no such change.^{58,59} Rehill *et al.*⁴²

Table 2 Chronic smoking studies

<i>Study</i>	<i>Inclusion criteria</i>	<i>Comparison</i>	<i>Outcome</i>	<i>P-value</i>
Tomiyama <i>et al.</i> ⁴⁶	Subjects who underwent screening at Health Care Center of Tokyo	CS vs. Non-S	Alx (%) Smoking independently correlated with Alx: Men < 50 years: $r=0.21$ Men > 50 years: $r=0.19$ Women < 50 years: $r=0.15$ Women > 50 years: $r=0.08$	All < 0.01
Binder <i>et al.</i> ³⁷	Young healthy CS and Non-S	CS vs. Non-S	PWV (m s^{-1}) CS: 7.89 ± 0.73 Non-S: 7.25 ± 0.53 RI (%) CS: 42.49 ± 6.71 Non-S: 35.46 ± 0.06	< 0.001 < 0.001
Nguyen <i>et al.</i> ³⁹	Healthy White and Black, CS and Non-S	CS vs. Non-S	afPWV Smoking correlated with afPWV Black CS: $\beta=0.14$ White CS: $\beta=0.13$	< 0.05 < 0.001
Yufu <i>et al.</i> ⁴⁰	Healthy CS and Non-S	CS vs. Non-S	baPWV (cm s^{-1}) CS: 1232 ± 160 Non-S: 1201 ± 161	NS
Rehill <i>et al.</i> ⁴²	Healthy CS and Non-S	CS vs. Non-S	Alx (%) CS: 17.25 Non-S: 11.75 Smoking status related to Alx, $\beta=0.223$ cfPWV (m s^{-1}) CS: 5.9 Non-S: 5.6	=0.004 < 0.001 NS
Sassalos <i>et al.</i> ⁵¹	Healthy male CS and Non-S	CS vs. Non-S	PP (mm Hg) CS: 37.5 ± 8.9 Non-S: 35.7 ± 9.0 Aortic Distensibility ($\text{cm}^2 \times \text{dyne}^{-1} \times 10^{-6}$) CS: 2.22 ± 0.93 Non-S: 2.75 ± 1.07	NS < 0.005
Filipovsky <i>et al.</i> ⁴¹	Healthy CS and Non-S	CS vs. Non-S	cfPWV No correlation with smoking status Peripheral Alx Increased in CS compared with Non-S	NS < 0.01
Van Trijp <i>et al.</i> ⁴⁴	Healthy male CS and Non-S	CS vs. Non-S	Alx (%) Relation of Alx to pack-years: $\beta=0.31\%$ per pack-year	< 0.05
Levent <i>et al.</i> ⁵²	Healthy adolescent CS and Non-S	CS vs. Non-S	Aortic strain Non-S: 0.262 ± 0.056 CS: 0.198 ± 0.042	< 0.0001
Fennessy <i>et al.</i> ⁴⁵	Healthy male CS and Non-S	CS vs. Non-S	Aortic Alx (%) CS: 136 ± 34 Non-S: 100 ± 20	NS
Mahmud and Feely ²⁴	Healthy CS and Non-S	CS vs. Non-S	Alx (%) CS: 0.7 ± 13 Non-S: -5.7 ± 14	< 0.05
Liang <i>et al.</i> ⁴⁷	Healthy CS and Non-S	CS vs. Non-S	SI CS: 5.22 ± 2.46 Non-S: 3.65 ± 1.82	< 0.001

Table 2 Continued

Study	Inclusion criteria	Comparison	Outcome	P-value
Nakanishi <i>et al.</i> ³⁸	Healthy Japanese CS, Non-S and FS	CS vs. Non-S and Non-S vs. FS	Stiffness incidence (% of study subjects with cfPWV ≥ 8 m s ⁻¹) CS: 23.7% Non-S: 16.5% FS: 23.2% Hazard ratio for incidence of stiffness CS: 1.54 Non-S: reference FS: 1.37	=0.017 =0.109 =0.005
McVeigh <i>et al.</i> ⁵³	Healthy CS and Non-S	CS vs. Non-S	Pulse contour analysis Damping of diastolic oscillation (s ⁻¹) CS: 18 $\pm$ 13 Non-S: 8 $\pm$ 6 Oscillatory compliance (ml per mm Hg) CS: 0.04 $\pm$ 0.02 Non-S: 0.07 $\pm$ 0.03 Large artery compliance (ml per mm Hg) CS: 1.70 $\pm$ 0.63 Non-S: 1.85 $\pm$ 0.60	<0.01 NS
Jonason <i>et al.</i> ⁴⁸	Healthy CS and Non-S	CS vs. Non-S	SI Correlated with pack-years of smoking: $r=0.19$	<0.01
Sonesson <i>et al.</i> ⁴⁹	Healthy CS and Non-S	CS vs. Non-S	Aortic stiffness (β -index) Men: no difference between CS and Non-S Women: increased β -index in CS vs. Non-S	=0.222 =0.041
Terenzi <i>et al.</i> ⁵⁰	Healthy CS and Non-S	CS vs. Non-S	Aortic compliance (%) CS: 4.9 $\pm$ 1.7% Non-S: 21.3 $\pm$ 3.7%	<0.001
Wollersheim <i>et al.</i> ⁵⁴	Healthy CS and Non-S	CS vs. Non-S	Elastic modulus (kPa) Popliteal artery CS: 127.90 $\pm$ 63.0 Non-S: 76.98 $\pm$ 18.97 No significant difference in CCA, BA, CFA	=0.006 NS
Taquet <i>et al.</i> ⁴³	Healthy CS and Non-S females	CS vs. Non-S	No association between cigarette smoking and increased cfPWV	NS
Kool <i>et al.</i> ³²	Healthy CS and Non-S	CS vs. Non-S	Distensibility coefficient (10 ⁻³ per kPa) Carotid artery: no difference between CS and Non-S Brachial artery: no difference between CS and Non-S Compliance coefficient (mm ² per kPa) Carotid artery: no difference between CS and Non-S Brachial artery: no difference between CS and Non-S	NS NS NS NS
Levenson <i>et al.</i> ³⁶	Healthy CS and Non-S	CS vs. Non-S	brPWV (m s ⁻¹) CS: 9.25 $\pm$ 0.5 NS: 7.3 $\pm$ 0.9	<0.05

Abbreviations: afPWV, aorta-femoral pulse wave velocity; AIx, augmentation index; BA, brachial artery; baPWV, brachial-ankle pulse wave velocity; CCA, common carotid artery; CFA, common femoral artery; cfPWV, carotid-femoral pulse wave velocity; CS, current smoker; FS, former smoker; Non-S, nonsmoker; NS, not significant; PP, pulse pressure; PWV, pulse wave velocity; RI, reflection index; SI, stiffness index.

reported similar results after only 4 weeks of smoking cessation. In contrast, another study reported no significant change in arterial stiffness between persistent smokers and in individuals who stopped smoking for 2 years as assessed by the distensibility of the carotid and femoral arteries.⁶⁰ Furthermore, Polonia *et al.*⁵⁹ found that no change occurred in cfPWV after 6 months of smoking cessation.

DISCUSSION

In this systematic review, we presented results obtained from 39 studies evaluating the effect of smoking on arterial stiffness. These studies show that acute, chronic and passive smoking has a detrimental effect on arterial stiffness, and that smoking cessation may improve arterial stiffness. However, further work is required to

Table 3 Passive smoking studies

Study	Inclusion criteria	Comparison	Outcome	P-value
Argacha <i>et al.</i> ⁵⁵	Healthy male Non-S, not regularly exposed to ETS	Before vs. after ETS, NTS, or nicotine tablet	Alx ETS: increased during exposure Increased after exposure NTS: no change during or after exposure Sublingual nicotine: associated with an increase in Alx Largest increase in serum nicotine was associated with greatest increase in Alx, $r=0.84$ T_r ETS: decreased during exposure Decreased after exposure NTS: No change during or after exposure	=0.01 NS =0.001 NS =0.02 NS NS
Mahmud and Feely ⁵⁶	Healthy Non-S, not regularly exposed to ETS	Before vs. after ETS and NTS	Alx (%) Passive smoking males: increase from -1.7 ± 5.2 to 14 ± 4.8 at 60 min Passive smoking females: no significant change T_r (ms^{-1}) No change in either men or women	<0.001 NS NS
Mack <i>et al.</i> ⁵⁷	Non-S exposed or not exposed to ETS	ETS vs. no ETS exposure	β -Stiffness index Adjusted β -index increased with number of ETS sources in subjects: $\text{IMT} \geq 0.707$ mm $\text{BMI} \geq 27.1 \text{ kg m}^{-2}$ Adjusted β -index increased with hours of exposure in subjects with: $\text{BMI} \geq 27.1 \text{ kg m}^{-2}$ or $\text{IMT} \geq 0.707$ mm	=0.05 =0.48 =0.04 =0.04
Stefanadis <i>et al.</i> ³⁴	Male Non-S undergoing cardiac catheterization for evaluation of chest pain	Before vs. after ETS	Aortic distensibility Decreased by 21% after passive smoking	<0.001

Abbreviations: Alx, augmentation index; BMI, body mass index; ETS, environmental tobacco smoke; IMT, intima-media thickness; Non-S, nonsmoker; NS, not significant; NTS, non-tobacco smoke; T_r , transit time.

definitively determine whether arterial stiffness is improved over time after smoking cessation and the timeline in which this occurs.

The effect of acute smoking is clear cut, causing an acute increase in arterial stiffness in both chronic smokers and nonsmokers. All studies, except one, found that acute smoking causes a significant increase in arterial stiffness in chronic smokers. The study that found no effect was small (30 patients) which actually showed, before adjustment, an increase in heart-femoral PWV after acute smoking.²⁸ Interestingly, chronic smokers had a greater increase in arterial stiffness after acute smoking than did nonsmokers.^{24,27} These results are in line with those of previous studies measuring acute smoke-induced endothelial dysfunction measured by flow-mediated dilatation (FMD); endothelial dysfunction was more prolonged in smokers than in nonsmokers.⁶¹

The effect of chronic smoking on endothelial dysfunction is also detrimental; studies comparing the FMD of habitual smokers and nonsmokers found smoking to be associated with greater endothelial dysfunction.^{6,62} However, the effect of chronic smoking on arterial stiffness is slightly more controversial. Most studies found that chronic smoking increases arterial stiffness as measured by PWV, Alx, SI, compliance and distensibility.^{24,36–39,47–53,63} However, a few other studies did not consistently find this effect.^{32,40–42} For example, Filipovsky *et al.*⁴¹ and Rehill *et al.*⁴² found that Alx was significantly higher in smokers than in nonsmokers, while differences in PWV did not reach significance. Kool *et al.*³² also did not find significant differences between

smokers and nonsmokers when measuring compliance and distensibility; however, they only included 14 nonsmokers. Yufu *et al.* also failed to show a significant difference in baPWV between smokers and nonsmokers; however, they included young, healthy smokers with small cumulative tobacco consumption. Furthermore, in this study, the FMD was strongly correlated with the baPWV ($P < 0.005$).⁴⁰ It is also noteworthy that PWV was not measured in the same sites in the vascular bed between studies.

Passive smoking clearly causes increased arterial stiffness. Three studies showed that acute exposure to ETS leads to increased stiffness,^{34,55,56} whereas one study found an association between the increased number of ETS sources and the increased time of exposure with a higher SI.⁵⁷ Furthermore, sublingual nicotine administration was shown to increase Alx, indicating that the effect of smoking on arterial stiffness may act through nicotine.⁵⁵ Second-hand smoke also causes endothelial dysfunction;^{5,64} a study comparing the endothelial function of nonsmokers who were currently or previously exposed to second-hand smoke found that being exposed for ≤ 1 h per day for ≤ 2 years can cause endothelial dysfunction lasting as long as 2 years after cessation of exposure.⁶⁴

It has been suggested that smoking-induced damage to the endothelium may be somewhat reversible; former active and passive smokers have better endothelial function than do current active or passive smokers.^{65,66} The beneficial effects of smoking cessation on the

Table 4 Smoking cessation studies

Study	Inclusion criteria	Study design	Comparison	Outcome	P-value
Polonia <i>et al.</i> ⁵⁹	CS	Longitudinal	FS vs. relapsed smokers	cfPWV (m s^{-1}) Successful quitters: 10.5 ± 0.3 at baseline vs. 10.2 ± 0.2 after 6 months Relapsed smokers: 10.4 ± 0.3 at baseline vs. 10.5 ± 0.3 after 6 months Alx (%) Successful quitters: 28.7 ± 1.9 at baseline vs. 19.5 ± 2.3 after 6 months Relapsed smokers: 27.8 ± 2.0 at baseline vs. 29.5 ± 1.9 after 6 months	NS NS <0.03 NS
Oren <i>et al.</i> ⁵⁸	Healthy CS who wanted to quit smoking	Longitudinal	CS vs. FS	Alx (%) CS: 60.2 ± 20 at baseline 61.3 ± 19 at 6 months FS: 63.1 ± 22 before cessation 50.6 ± 17 at 6 months cessation	NS <0.05
Rehill <i>et al.</i> ⁴²	Healthy CS	Longitudinal	FS vs. relapsed smokers	Alx (%) Successful quitters: median change -9.5 at 4 weeks Relapsed smokers: median change 5.0 at 4 weeks cfPWV (m s^{-1}) 4 weeks of smoking cessation did not change cfPWV	=0.013 NS
van den Berkmortel <i>et al.</i> ⁶⁰	Healthy CS, Non-S and FS	Longitudinal	CS, Non-S and FS	Cross-sectional compliance/distensibility coefficients CS, Non-S, FS: no significant differences at baseline or changes after 24 months smoking cessation in the RCCA/LCCA/RCFA between all groups	NS
Nakanishi <i>et al.</i> ³⁸	Healthy Japanese CS, Non-S and FS	Cross-sectional	CS, Non-S and FS	Stiffness incidence (% of study subjects with $\text{cfPWV} \geq 8 \text{ m s}^{-1}$) CS: 23.7% Non-S: 16.5% FS: 23.2% Hazard ratio for incidence of stiffness CS: 1.54 Non-S: Reference FS: 1.37	=0.017 =0.109 =0.005

Abbreviations: Alx, augmentation index; cfPWV, carotid-femoral pulse wave velocity; CS, current smoker; FS, former smoker; LCCA, left common carotid artery; Non-S, nonsmoker; NS, not significant; RCCA, right common carotid artery; RCFA, right common femoral artery.

Figure 2 Mechanisms of smoking-induced increases in arterial stiffness. TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GFR, glomerular filtration rate; ROS, reactive oxygen species; NO, nitric oxide; BP, blood pressure.

risk for cardiovascular disease^{67–69} and for endothelial dysfunction^{65,66} have been established. However, it remains controversial whether arterial stiffness improves after smoking cessation; some studies show rapid improvement in Alx after smoking cessation,^{42,58,59}

whereas cfPWV did not improve after 6 months,⁵⁹ and another study showed no improvement in distensibility after 2 years.^{59,60} A cross-sectional study of middle-aged hypertensive patients found that Alx, cfPWV and T_r (transit time) returned to baseline levels only after 10

years of smoking cessation.⁷⁰ These inconclusive results emphasize the need for long-term longitudinal studies to clarify the controversy on the effect of smoking cessation on arterial stiffness.

Mechanisms

Lipids. Active and passive smoking alters lipid metabolism acutely and chronically (Figure 2).^{71,72} Cigarette smoke alters catecholamine release and lipoprotein lipase activity; consequently, free fatty acid release is altered and triglycerides cannot be cleared from the blood.⁷² This causes an increase in triglycerides and low-density lipoprotein, and a decrease in high-density lipoprotein in the plasma of smokers.^{71,72} Changes in lipid metabolism contribute to structural changes of the arterial wall including intima-media thickening and atherogenesis^{73,74} and may lead to an increase in arterial stiffness. Furthermore, treatment of the underlying hypercholesterolemia using statins has been shown to decrease arterial stiffness.^{75,76}

Kidney function. Chronic smoking damages the kidney by causing a loss of filtration rate and contributes to kidney failure.^{77,78} In fact, smoking is also correlated with albuminuria in healthy individuals.⁷⁸ As even mild renal insufficiency leads to collagen accumulation in elastic arteries as well as calcification,⁷⁹ these smoking-induced alterations in kidney function increase arterial stiffness by altering the structure of the arteries.

Insulin resistance. Smoking increases insulin release and causes insulin resistance,^{72,80} both of which have been shown to increase arterial stiffness.^{81–83} Gordin *et al.*⁸¹ showed that mean daily glucose correlated with aortic PWV in diabetic subjects. Similar results have been found in various patient groups.^{82,83} In fact, aortic PWV has been shown to increase even in early insulin-resistance states.⁸³ Smoking is also frequently associated with decreased physical activity and poor diet, further increasing adiposity and insulin-resistant states.⁸⁰

Oxidative stress. Acute and chronic smoking has been shown to induce oxidative stress, altering vascular tone and increasing arterial stiffness.^{4,84} Smoking increases the production of reactive oxygen species, which decreases the activity of nitric oxide synthase (NOS), inhibiting nitric oxide (NO) production by the endothelium.^{85,86} Platelet-derived NO production also decreases contributing to a hypercoagulable state.⁸⁷ Moreover, active and passive smoking decrease total body antioxidant levels,⁷¹ which increases endothelial dysfunction and arterial stiffness.^{85,88,89} In fact, total antioxidant capacity is inversely associated with AIx ($r = -0.24$, $P < 0.02$).⁸² Treatment of smokers with antioxidants or L-arginine, a NOS substrate, improves FMD and arterial stiffness.^{85,90}

Inflammation. Smoking has also been shown to cause an inflammatory state by simultaneously increasing proinflammatory and decreasing anti-inflammatory cytokines.⁹¹ Various studies have shown strong associations between inflammatory markers and arterial stiffness.^{92–94} For example, Vlachopoulos *et al.* used a Salmonella typhi vaccine to induce inflammation in healthy subjects.⁹⁵ They found a vaccine-induced increase in cPWV and a decrease in AIx, which were associated with increases in C-reactive protein and interleukin-6 (biochemical markers of inflammation). Inflammation also causes vascular calcification and release of matrix metalloproteinases, which contribute to vascular remodeling.⁹⁶

Hypertension. Smoking increases blood pressure and the risk for hypertension.^{97–100} Studies have shown that in subjects with hypertension, arterial stiffness is increased compared with normotensive subjects of the same age.^{101–103} This increased stiffness leads to

elevated systolic pressure and a widened pulse pressure which, in turn, leads to further tension on the arterial wall generating a positive feedback effect.^{104,105} The wall tension induces mechanical vessel wall damage, vascular hypertrophy, increased collagen and calcium deposition, smooth muscle cell restructuring and extracellular matrix deposition, which leads to increases in arterial stiffness and end-organ damage, such as left ventricular hypertrophy.^{105–110} Treatment of hypertension may help to decrease arterial stiffness; a number of studies have found that antihypertensive therapy can lead to decreased arterial stiffness in addition to blood pressure lowering.^{111–115} However, smoking has been found to blunt the arterial stiffness-lowering effect of antihypertensive therapy. Matsui *et al.*¹¹³ treated hypertensive smokers and nonsmokers with amlodipine for 6 months and noted that reduction in baPWV in smokers only reached the level of nonsmokers after 6 months of treatment. Therefore, it seems that smoking and hypertension exert synergistic effects on arterial stiffness, potentially through oxidative stress and the production of reactive oxygen species leading to degradation of NO, and by changes in production of endothelin-1 and prostacyclins.^{14,106,116–121}

Endothelial dysfunction. As discussed above, numerous previous studies have shown that smoking causes significant endothelial dysfunction as assessed by FMD.^{5,6,61,62,64} However, it is important to note that FMD has been previously shown to be significantly associated with arterial stiffness under a number of conditions and disease states.^{122–126} Wright *et al.*¹²⁷ noted that this association was weak and suggested that measurements of arterial stiffness should not replace FMD. However, they used neither AIx nor cPWV (the 'gold standard') as arterial stiffness measurements in their study. Furthermore, Yufu *et al.*⁴⁰ found FMD to be strongly correlated with baPWV in healthy smokers ($P < 0.005$). In addition, Siasos *et al.*^{90,128} showed that smokers under L-arginine treatment have an increase in FMD concurrently with decreases in both AIx and cPWV.

Blood markers. A number of blood markers carry potential to monitor the progression of arterial stiffness in smokers. Smokers have significantly higher plasma levels of homocysteine, fibrinogen, C-reactive protein, interleukin-6, triglycerides, low-density lipoprotein, as well as decreased high-density lipoprotein and apolipoprotein A1 levels.^{129–131} Many of these blood markers and others (such as lycopene, uric acid, adiponectin) have been related to increased arterial stiffness and may also have value in monitoring arterial stiffness in smokers and former smokers.^{39,94,95,132–137} However, it has been suggested that the use of multiple blood markers is of little prognostic value,^{96,138} and that even the use of single markers such as C-reactive protein or homocysteine did not improve prediction of outcome using the Framingham risk score.¹³⁸ Perhaps simply measuring cPWV and AIx may prove the simplest and most effective method to assess and monitor vascular health in smokers.

Limitations

This review is limited by the comparability of the studies included. Protocols and methods were not standardized; the time of day the study took place, whether the subjects fasted or refrained from alcohol and caffeine before the study were different between protocols, and some did not report this information. Furthermore, the age groups of subjects, duration and intensity of smoking, body mass index, renal function, menopausal status, lipid profile, medication use, including statin use, were not uniform between studies or subject groups. These factors were also often not reported or corrected for; clearly, future studies investigating the effect of smoking on arterial stiffness should

recruit homogeneous populations. The majority of the identified studies are cross-sectional; however, population-based longitudinal studies would be better suited to study the effect of smoking on arterial stiffness and to better track the progression of improvement in arterial stiffness after smoking cessation. Perhaps the most pertinent limitation of the included studies is the different methods used to obtain information about arterial stiffness. cPWV is the 'gold standard' for measurement of arterial stiffness, and cPWV and AIx have the greatest amount of evidence to support their predictive value for cardiovascular events.^{16–22} Therefore, other parameters of arterial stiffness, such as local distensibility or compliance, may not be as valuable to assess the vascular effects of smoking and are not useful clinical parameters. These should be used sparingly compared with cPWV and AIx. Owing to these limitations of the included studies, a meta-analysis aiming to quantify the overall magnitude of the effect of smoking on arterial stiffness could not be conducted. However, the results of the included studies are comparable and point to smoking having a detrimental effect on arterial stiffness.

Clinical implications

Increased arterial stiffness is associated with increased risk of cardiovascular complications,^{16–22} and a strong correlation between arterial stiffness and the development of atherosclerosis at various sites in arteries has been noted.^{139,140} Therefore, measuring arterial stiffness can be a useful clinical tool for disease progression and monitoring of treatment efficacy, as recommended by the European Network for Non-invasive Investigation of Large Arteries¹⁵ and the 2007 European guidelines for the management of arterial hypertension.¹⁶ The use of arterial stiffness measurements may be particularly useful in assessing endothelial damage induced by certain cardiovascular risk factors, such as cigarette smoking. cPWV, the 'gold standard' for the assessment of aortic stiffness,^{15,16} has been used in numerous longitudinal studies, and has the greatest amount of epidemiological evidence to support its predictive value for cardiovascular events in the general and diseased populations.^{15–20,141–145} Therefore, cPWV should be the first choice in the assessment of arterial stiffness.

At present, 28% of European adults smoke,¹⁴⁶ 19% of the Canadian population aged 15 years and older are smokers,² and 21% of adults in the United States smoke;¹⁴⁷ this represents significant proportions of these populations. Moreover, although the general population smoking rates have been declining recently, young people seem to be picking up the habit; 20% of the youth smoked in Europe between the years 1999 and 2001, that number increased to 24% between 2002 and 2005.¹⁴⁶ A similar trend exists in Canada; the percentage of smokers in individuals aged 20–24 years is now 28%, up from 24% in 2007.² It is clear that smoking still represents a significant public health problem in North America and Europe, and the use of arterial stiffness assessments to monitor cardiovascular damage may be valuable from a clinical point of view. In addition, arterial stiffness measurements can also be used to assess the effectiveness of smoking cessation therapies, as well as the direct effect of the smoking cessation medications on arterial stiffness.

At present, there are several pharmacological options for smoking cessation available, such as nicotine replacement therapy (NRT),^{148,149} which can help people increase their chances of successfully stopping smoking by 50–70%.^{148,150} The market for over-the-counter nicotine gum, which is the most popular form of NRT, had annual sales of more than \$300 million at the end of September 2008 in the United States (<http://us.infores.com>). Although the use of nicotine gum is approved by the Food and Drug Administration and widely advertised, there is no evidence in the literature regarding its direct effect on

arterial stiffness. However, it has been shown that administration of nicotine can increase arterial stiffness acutely.^{55,151} Therefore, it is possible (although not yet studied) that NRT increases arterial stiffness for the duration of therapy. It is also possible that non-NRT smoking cessation options may not have these effects and thus may be more beneficial. However, these effects of NRT and non-NRT smoking options have yet to be investigated; future research needs to focus on the extent to which smoking cessation therapies (NRT and non-NRT) can lead to stabilization or even reversal of arterial stiffness.

Conclusions

To our knowledge, this is the first systematic review on the effect of smoking on arterial stiffness. We presented results obtained from 39 studies evaluating the effect of acute, chronic and passive smoking on arterial stiffness, and the reversibility of arterial stiffness after smoking cessation. Acute, chronic and passive smoking all have a detrimental effect on arterial stiffness, although the role of chronic smoking in increasing arterial stiffness is slightly more controversial. Chronic smoking was also shown to have a role in sensitizing arterial response to acute smoking. However, whether arterial stiffness is reversed after smoking cessation, and the timeline in which this occurs could not be determined from the available literature. Long-term longitudinal studies using the best recognized parameters of arterial stiffness (cPWV and AIx) are required to clarify this issue. Furthermore, with the large number of pharmacological options for smoking cessation available, it will become important to identify the direct effect of these medications on arterial stiffness.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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