REVIEW ARTICLE

Drugs 1998 Aug; 56 (2): 177-187
0012-6667/98/0008-0177/$11.00/0

Management of the Hypertensive Patient Who Smokes

Helios Pardell,[1,2,3] *Ricard Tresserras*,[2,3] *Esteve Saltó*,[2,3] *Pedro Armario*[1,3] and *Raquel Hernández*[1,3]

1 Department of Internal Medicine, Unit of Hypertension and Cardiovascular Risk, Consortium of the Red Cross Hospital, Hospitalet de Llobregat, Barcelona, Spain
2 Division of Public Health, Ministry of Health and Social Security, Government of Catalonia, Barcelona, Spain
3 Division of Health Sciences, School of Medicine, University of Barcelona, Barcelona, Spain

Contents

Abstract

Smoking and arterial hypertension are highly prevalent at the community level. While the coexistence of both risk factors is less frequent, the potentiation of cardiovascular risk when both are present makes the association highly relevant in terms of a preventive approach.

There are many interrelationships between smoking and high blood pressure at the clinical, epidemiological and pathophysiological levels. Those demonstrable links compel us to review the usual explanation of the influence of smoking on blood pressure.

Pharmacological treatment of the hypertensive patient who smokes must be adapted to the patient's risk profile, using the most efficacious antihypertensive agents. With the exception of nonselective β-blockers, all the available antihypertensive drugs can be prescribed.

Minimal intervention and nicotine replacement constitute the most well tested interventions in helping smokers to quit their habit. Nicotine replacement is currently a well tolerated intervention, even in patients with cardiovascular disease.

Hypertension is a leading cardiovascular risk factor; the disease causes an estimated 2 918 000 annual deaths worldwide, which equates to 5.8% of total deaths, and represents about 3% of global health expenditure in many countries.[1]

Cigarette smoking is the main cause of avoidable death, being responsible for 2 million annual deaths in developed countries, most of them from cardiovascular diseases.[3] Thus, cigarette consumption is also a principal cardiovascular risk factor, and is the most important and strongest independent risk factor for ischaemic heart disease in Western countries.[4]

When hypertension and smoking coexist in the same individual, the final cardiovascular risk rises dramatically. In addition, several relationships exist between some tobacco smoke compounds and blood pressure. All of this supports the assertion by Black[5] that 'although cigarette smoking may not be associated with the development of essential hypertension, it has a significant impact on prognosis for hypertensives, on the appropriate choice of therapy, and on the development of several unusual but important consequences and secondary forms of hypertension'.

1. Links Between Smoking and High Blood Pressure

The existing links between smoking and high blood pressure can be analysed from 3 different points of view: epidemiological, clinical and pathophysiological.

1.1 Epidemiological Data

Both smoking and high blood pressure are highly prevalent in developed countries and even in developing ones. Hypertension (defined as a blood pressure of 140/90mm Hg or more) accounts for more than 30% of the adult population,[1] and more than 35% of people aged 18 years and older smoke cigarettes regularly.[2] The prevalence of the association between smoking and hypertension by age group in Catalonia, Spain in 1994 is shown in figure 1.

In contrast to other cardiovascular risk factors

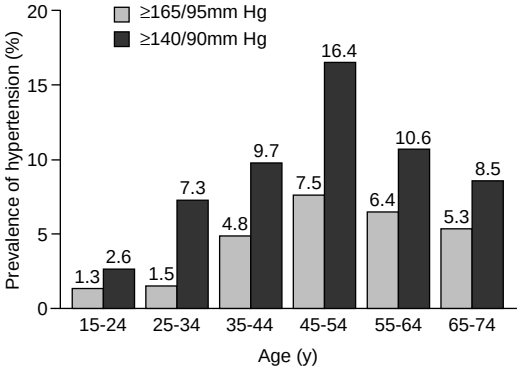

Fig. 1. The prevalence of the hypertension among smokers by age group in Catalonia, Spain, 1994.

which are much more prevalent in hypertensive individuals, the prevalence of smoking in the hypertensive population is similar to that in the general population, and lower than in normotensive individuals. In the Framingham Study 38% of hypertensive men and 34.4% of hypertensive women were smokers.[6] In the Multiple Risk Factor Intervention Trial (MRFIT) cohort the proportion of smokers was 35%;[7] in the hypertensive population in Spain this figure has been reported to be 22.4%.[8] This is probably due to the higher proportion in Spain of women among people older than 40 years with hypertension and to the great number of former smokers among hypertensive men.

Less attention has been given to the prevalence of the association of both smoking and hypertension at the population level. When analysing that association in a cross-sectional study carried out in Catalonia, we found that 14% of men and 3.5% of women were smokers and were also hypertensive.

Although some epidemiological studies have shown a positive association between smoking and blood pressure, particularly systolic blood pressure,[9,10] the most accepted view is that smokers have lower blood pressure than nonsmokers.[11,12] The reason is not clear but many authors suggest that the lower bodyweight of smokers may explain this inverse association between smoking and blood pressure.[13,14] Another explanation could be an adaptation or rebound effect[15] by which smokers might have blood pressure levels slightly lower

than nonsmokers in smoking-free intervals. If, in epidemiological studies, blood pressure was measured in these intervals, the small difference in blood pressure between smokers and nonsmokers could be accounted for.[16]

A recent study demonstrates that smoking, together with several factors such as systolic blood pressure at rest, systolic blood pressure rise after 600 kpm/m, physical resistance, age, body mass index and forced expiratory volume in 1 second (FEV_1), is a consistent prognostic factor for changes in blood pressure over a 7-year period in middle-aged men.[17] Although systolic blood pressure during physical exercise was not modified during that period in nonsmokers, it increased by a significant 6.5mm Hg in smokers.

Even though smokers do not have a higher prevalence of hypertension than nonsmokers, individuals with hypertension have higher rates of cardiovascular complications. Indeed, it is broadly accepted that the coexistence of smoking and hypertension dramatically increases cardiovascular risk, either for coronary heart disease or for stroke or peripheral artery disease. The associated coronary risk of smoking in hypertensive people is dose-dependent (fig. 2), ranging from 1.0 for nonsmokers to 3.5 for smokers of 15 to 24 cigarettes per day in the Nurse's Health Study.[18]

In the large trials reporting on the benefits of treating hypertension, hypertensive patients who smoke have been less likely to benefit from antihypertensive therapy in terms of cardiovascular mortality and morbidity reduction, particularly when receiving β-blockers.[19-22] In addition, the reduction in blood pressure achieved in hypertensive individuals receiving β-blockers has been smaller when they smoke.[23] In our study mentioned above, patients whose hypertension was controlled (blood pressure values below 160/95 mm Hg) [16.6% of patients] were more likely to be nonsmokers or former smokers than hypertensive patients who were not under control (27.5% of patients; $p < 0.02$).

Following on from the increased difficulties in controlling hypertension in individuals who smoke, hypertensive individuals who smoke have shown a substantial reduction in life expectancy in comparison with treated hypertensive patients who do not smoke.[24]

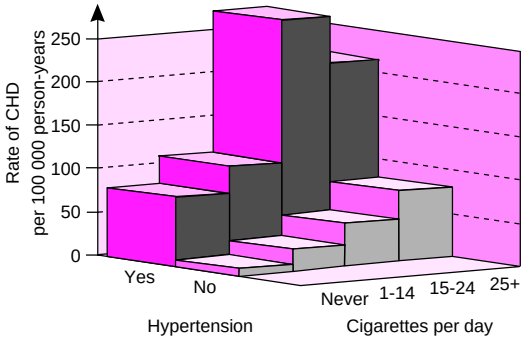

Fig. 2. Influence of cigarette consumption on coronary heart disease risk, by hypertension status (from Hansen et al.,[18] with permission). **CHD** = coronary heart disease.

1.2 Data from Clinical Studies

There are conflicting data on whether individual smokers have higher blood pressure than nonsmokers at the clinical level. Influenced by the epidemiological studies mentioned in section 1.1, the traditional assumption has been that smokers show lower blood pressure figures than nonsmokers. However, several studies have demonstrated the opposite.

Using noninvasive 24-hour blood pressure monitoring techniques, several studies have clearly shown that smokers consistently present higher blood pressure readings over time than nonsmokers: differences have ranged from 3 to 7mm Hg for systolic blood pressure and from 0 to 6.4mm Hg for diastolic blood pressure.[25-28] Daytime blood pressure variability is greater in smokers than in control patients.[29] Additionally, it has been found that smokers have a diminished 'white coat effect', probably as a consequence of their persistently augmented sympathetic tone.[30]

On the other hand, some cases of refractory hypertension can be reasonably attributed to the persistence of smoking in treated hypertensive patients, particularly among heavy smokers (more

than 25 to 30 cigarettes per day).[31,32] Similarly, McNagny et al.[33] have found that in African-Americans, current cigarette smoking is strongly associated with severe uncontrolled hypertension in patients who are compliant with antihypertensive medication.

Some years ago, Freestone and Ramsay[34] proved the effect on blood pressure of cigarettes alone or in combination with caffeine. In the first case, blood pressure elevation persisted for 15 minutes, while in the second that elevation was maintained for up to 2 hours. In the same way, more recently it has been reported that daytime systolic blood pressure in mildly hypertensive smokers who drink 4 or more cups of coffee per day is approximately 6mm Hg higher than in mildly hypertensive non-smokers who abstain from coffee.[35]

Moreover, some preliminary studies suggest that the main proportion of dyslipidaemias among drug-treated hypertensive patients could be attributed to the deleterious effects of tobacco compounds on the lipid profile, particularly when glucose tolerance is impaired.[36] Furthermore, it is very well known that the lipid profile of smokers is characterised by a 3% elevation of total cholesterol, a 1.7% increase in the low density lipoprotein (LDL) cholesterol fraction, a 10.4% decrease in the very low density lipoprotein (VLDL) cholesterol fraction, a 5.7% diminution in the high density lipoprotein (HDL) cholesterol fraction and a 4.2% decrease in the level of apolipoprotein A1.[37]

Still more relevant is the association found between smoking and 2 forms of hypertension. At least 4 case-control studies have described a significantly increased risk for smokers of developing malignant hypertension,[38-41] and another 4 studies have consistently demonstrated smokers' higher risk of presenting with renovascular hypertension secondary either to atherosclerosis or to fibromuscular dysplasia.[42-45]

The most exceptional smoking-related blood pressure elevation is the paroxysmal crisis of phaeochromocytoma induced by cigarette smoking or using tobacco snuff.[46,47]

1.2.1 The Role of Cadmium

A very interesting finding is the association between cadmium and blood pressure. This relationship is controversial but there is some evidence to suggest that it could be an underlying mechanism explaining the harmful effect of smoking on blood pressure. In effect, the cadmium concentration in the kidneys of smokers is double that of nonsmokers, and the urinary excretion of this trace element is 40 to 50 times higher in smokers than in non-smokers.[48] Certain studies have found a positive correlation between the prevalence of hypertension and urinary cadmium excretion.[49]

One of the most important sources of cadmium accumulation in the human body is tobacco. Since the content of cadmium in tobacco smoke is about 0.1 to 0.2 μg per cigarette, it has been estimated that a person who smokes 30 cigarettes a day, after a 40-year period of smoking, can accumulate 13 to 52mg of cadmium.[50]

The mechanisms through which cadmium can cause hypertension are not clear but it has been suggested that they could lie in the elevation of plasma renin activity, impairment of catecholamine metabolism, direct vasoconstrictor effects or a renal antinatriuretic action (proximal tubule).[51] Nevertheless, the available data suggest that more studies are needed to elucidate the possible role of cadmium in the chronic elevation of blood pressure in humans.[52]

1.3 Pathophysiological Effects Due To Tobacco Smoke Components

More than 4000 compounds have been identified in tobacco smoke, many of them being responsible for its harmful effects on human health.[53] With regard to the cardiovascular consequences of smoking, nicotine and carbon monoxide are the two most relevant detrimental elements of smoke, although a third element, cadmium, shows an intriguing connection with blood pressure elevation as discussed in section 1.2.1.

1.3.1 Nicotine

For decades we have known the short and long term effects of nicotine administration on the

cardiovascular system. Those classical effects can be summarised as follows:[54] a transitory rise of blood pressure and heart rate occurs, accompanied by an increase in the cardiac ejection fraction and a strong vasoconstriction which results in a dramatic drop of cutaneous temperature of the fingers and toes and a significant reduction of blood flow in the legs. These effects are directly related to the release of noradrenaline (norepinephrine) and the significant increase in plasma noradrenaline and adrenaline (epinephrine) levels. Furthermore, cardiac output and myocardial contractility also rise and the ventricular fibrillation threshold decreases. Increased plasma levels of growth hormone, corticotrophin (adrenocorticotropic hormone; ACTH), cortisol and vasopressin, but not plasma renin activity, have been described. Nicotine reduces the production of prostaglandin I_2 (PGI_2) by blood vessels, increases the urinary elimination of thromboxane B_2 and also increases platelet aggregation and thrombus formation.

Coronary blood flow and coronary reserve fall under the effects of nicotine. It has been suggested that these effects could be mediated by α-adrenoceptor stimulation, responsible for coronary vasoconstriction.[55] A marked reduction in cerebral blood flow, which may be of particular interest in hypertension, has also been described.[56]

1.3.2 Carbon Monoxide

Carbon monoxide, through its strong affinity for haemoglobin, reduces the oxygen-carrying capacity of the blood and causes an impairment of tissue oxygenation which entails structural abnormalities of the myocardium, a negative inotropic effect, a decrease in the fibrillation threshold and an increase in platelet aggregation and adhesiveness.[54]

1.3.3 Cadmium

As described in section 1.2.1, cadmium is an important trace element that has neeb demonstrated to produce clinically relevant blood pressure elevations. In the laboratory, cadmium has also shown a capacity to produce blood pressure elevations in rats (average elevation of systolic blood pressure of 20mm Hg after an 18-month period of high cadmium intake).[57] The accumulation of the metal in the kidney and the liver can be reversed by means of chelation agents, after which rats have become normotensive again.[58]

1.3.4 Other Effects

Tobacco smoke as a whole causes a marked increase in plasma fibrinogen levels, an increase which is dose-dependent. It has been estimated that in Western populations the 2 major determinants of plasma fibrinogen levels are age and smoking, the levels in current smokers being about 0.3 g/L higher than in nonsmokers.[59] Estimates to date suggest that 25 to 50% of the relation of cigarette smoking to the occurrence of atherosclerotic cardiovascular disease is attributable to the effect of smoking on fibrinogen levels, which in turn enhances thrombotic tendencies, leading to occlusive clinical events.[60]

Tobacco smoke also produces lipid profile abnormalities (section 1.2), causes elevation of the leucocyte count and impairment of red blood cell distensibility and size as well as other haematorheological disturbances, and accelerates coagulation in a variety of ways. One of these ways is the augmentation of platelet aggregability due to the impairment of platelet-derived nitric oxide release,[61] mediated via α_2-adrenergic receptors.[62]

Another interesting feature is the influence of smoking on oxidative stress, which is closely related to atherogenesis, via LDL oxidative modification,[63] and, as some recent research findings suggest, to angiotensin II–induced experimental hypertension.[64] Indeed, smoking is one of the most important exogenous sources of free radicals, since the gas phase of tobacco smoke contains 10^{14} free radicals per puff and the tar phase 10^{17} per gram.[65] The levels of circulating products of lipid peroxidation (F_2-isoprostanes) are increased in smokers.[66] Also, endothelial smoke injury mediated by oxidative stress is now well documented.[67,68] On the other hand, smokers' dietary patterns are characterised by a significantly lower proportion of antioxidant intake,[69] which contributes to the potentiation of the harmful effects of smoke free radicals.

Under the effects of oxygen-derived free radicals, cigarette smoke extracts induce contraction of isolated porcine coronary arteries via the superoxide anion-mediated degradation of endothelium-derived relaxing factor (EDRF),[68] and smoking also stimulates the release of endothelin, a potent endogenous vasoconstrictor agent.[70] Recently, unfavourable effects of smoking on the elastic properties of the human aorta have been reported.[71]

In conclusion, from the analysis of the available information, it can be inferred that the existing epidemiological, clinical and pathophysiological links between both the hypertension and smoking risk factors strongly support the hypothesis that smoking could be a predisposing factor for hypertension, in addition to its role as a major cardiovascular risk factor (fig. 3). Nevertheless, more studies are needed to confirm that preliminary assertion.

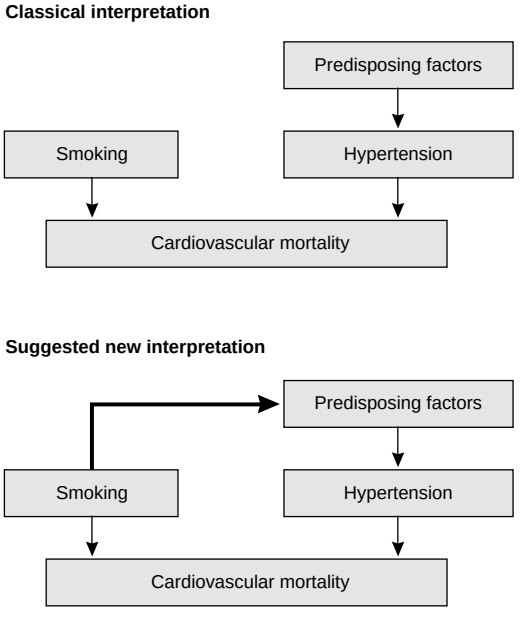

Fig. 3. Suggested reinterpretation of the relationship between smoking and blood pressure.

2. Choice of Antihypertensive Therapy

According to the latest guidelines,[32,72] the first-line antihypertensive drugs that can be used in addition to nonpharmacological measures include the following 5 available pharmacological groups: diuretics, β-blockers, α-blockers, calcium antagonists and angiotensin converting enzyme (ACE) inhibitors. The new class of angiotensin II receptor antagonists could also probably be added.

Several pharmacokinetic and pharmacodynamic properties distinguish those groups, but, in practice, all are able to decrease blood pressure to a similar extent. In the context of individualised strategy,[73] the selection of the most effective agent for each case is based on the pathophysiological and clinical traits of the patient and, in particular, on his or her cardiovascular risk profile.

In the case of hypertensive patients who smoke, the key element is that smoking not only aggravates their cardiovascular risk profile but, moreover, interferes with the pharmacological treatment of hypertension, as the main trials have clearly shown (see section 1.1).

In this context, nonpharmacological measures [mainly salt intake restriction, moderation of alcohol (ethanol) consumption, loss of extra weight and physical exercise] must be implemented, and in hypertensive individuals as a whole, it is particularly important to emphasise the need to give up smoking.

Smoking is a major component of cardiovascular risk stratification in patients with hypertension in therapeutic decision making.[32] Unfortunately, no trials exist comparing the effectiveness of different antihypertensive agents in smokers who are hypertensive; for that reason, we can only speculate about the expected advantages of certain antihypertensive drugs.

β-Blockers are the pharmacological group which has been most studied; nonselective agents such as propranolol, which also block vascular β_2-adrenoceptors, enhance unopposed cardiovascular responses mediated by α-adrenergic receptors and potentiate the negative effects of smoking. In healthy volunteers given propranolol, smoking causes a more pronounced rise in blood pressure and in forearm resistance, compared with atenolol, which could be due to the blockade of β_2-receptors.[74] In

fact, the higher the β_1-selectivity, the more the antihypertensive effect of β-blockade, either experimentally[75] or clinically.[76]

Smoking stimulates hepatic drug-metabolising enzymes and directly reduces plasma propranolol concentrations,[77] which could explain the lack of beneficial effects of that nonselective β-blocker on hypertension and on coronary risk. Therefore, while highly selective β-blockers (e.g. bisoprolol) can largely be used in the treatment of hypertensives who smoke, nonselective β-blockers such as propranolol should be avoided.

Diuretics do not seem to adversely influence the pharmacological treatment of hypertension in patients who smoke. Calcium antagonists and ACE inhibitors show clear efficacy in treating hypertensive smokers;[78] the former prevent smoking-induced constriction of the coronary arteries,[79] and ACE inhibitors may be superior to β-blockers in the treatment of hypertensive patients who smoke.[80]

α_1-Receptor blockers such as doxazosin have beneficial effects not only on raised blood pressure but also on smoking-induced changes in blood lipids and fibrinogen in hypertensive smokers.[81]

Finally, clonidine, an α_2-adrenergic receptor agonist, is a well tested antihypertensive agent which has also shown beneficial effects in trials of smoking cessation, particularly in women.[82]

3. Smoking Cessation Strategies

It is no longer appropriate to consider reduction of blood pressure as the only goal of antihypertensive therapy. On the contrary, the main objective in reducing blood pressure in hypertension is to reduce the absolute risk of premature mortality and morbidity secondary to accelerated vascular disease.[83]

Smoking cessation is the most potent and beneficial risk modification as many interventions have undoubtedly demonstrated.[84] Taking the findings of the most relevant studies and using a Markov cohort simulation model, it has been found that life expectancy gains from smoking cessation were substantially greater than the benefits of treating hypertension. Indeed, 75 to 80% of the greatest benefit expected from simultaneously treating hypertension and stopping smoking can reasonably be attributed to smoking cessation.[85] Furthermore, smoking cessation alone lowers fibrinogen levels by almost 0.40 g/L.[86]

Several barriers exist which make the active involvement of physicians in antismoking activities difficult.[87] Nonetheless, all of them can be overcome and today most practitioners are able to see the patient who smokes as a high risk individual who must be adequately diagnosed and managed much the same as a diabetic or hyperlipidaemic patient.[88]

Advice/minimal intervention and pharmacological treatment are the 2 best known interventions for smokers. For the former, a number of studies have clearly demonstrated the usefulness of regular advice and delivery of educational materials by general practitioners[89-91] as well as its cost effectiveness.[92] Some years ago Glynn and Manley[93] suggested the '4A' approach which has been disseminated worldwide (table I). The Agency for Healthcare Policy and Research has recently published a more comprehensive smoking cessation clinical practice guideline.[94]

Pharmacological treatment is mainly based on nicotine replacement strategies but the use of clonidine is very attractive because of its combined effect on hypertension and on smoking cessation. In fact, it has been used as a smoking cessation agent in many controlled trials with reasonable success, in either oral or transdermal form.[95]

The two main available nicotine replacement techniques are nicotine gum and nicotine patches. In some countries, 2 other nicotine replacement techniques have been introduced more recently: nasal spray and nicotine inhaler. All of these supply nicotine to the smoker with the aim of avoiding or alleviating the withdrawal syndrome in order to make the quitting process easier and to prevent relapse. A nicotine patch delivers transdermal nicotine over 16 or 24 hours, while the other techniques offer the smoker the possibility of self-regulating nicotine administration. This enables the physician

Table I. Protocol from the US National Cancer Institute Guidelines[93]

Ask the patient about smoking habits at each patient visit
Advise smokers to stop at every opportunity
Assist smokers by helping them set a quit date, providing self-help material and prescribing pharmacological adjuncts as appropriate
Arrange follow-up contact with the patient to prevent relapse

to adapt the strategy more accurately to each smoker, it being possible to combine the two different techniques (i.e. nicotine gum and nicotine patch).

Many randomised clinical trials have been carried out using those nicotine replacement techniques, alone or in combination (mainly nicotine gum and nicotine patch). On average, the cessation rate at 1-year follow-up ranges from 20 to 40%, depending on the strategy and the optional combination with psychological support.[96-99] The risk-benefit assessment of nicotine replacement strategies undoubtedly proves that benefits far outweigh risks.[100]

Taking into account the harmful effects of nicotine on the cardiovascular system, a crucial question in the case of the hypertensive patient who smokes are the potential risks *vs* benefits of nicotine replacement. Two published trials demonstrate that transdermal nicotine replacement is well tolerated by patients with coronary or cardiac disease. In one,[101] the nicotine patch did not affect angina frequency, overall cardiac symptoms status, nocturnal events, arrhythmias or episodes of ischaemic ST segment depression. In the other,[102] neither primary end-points (death, myocardial infarction, cardiac arrest and admission to hospital due to increased severity of angina, arrhythmias or congestive heart failure) nor secondary end-points (admission to hospital for other reasons and outpatient visits necessitated by increased severity of heart disease) were affected by the nicotine patch. In addition, in both studies the placebo group suffered more complications and blood pressure was not significantly modified in the treatment group.

Furthermore, the article by Allen et al.[103] demonstrated that smoking cessation using a transdermal nicotine patch entailed a positive effect on cardiovascular risk due to significant HDL-cholesterol increases and LDL-cholesterol decreases in abstinent patients. In this group, the systolic blood pressure and heart rate also decreased significantly, while diastolic blood pressure significantly increased only in the 21 mg/day transdermal nicotine group.

In summary, the use of nicotine replacement in hypertensive patients who smoke seems to be well tolerated enough to be recommended as an important aid to their giving up smoking.[104] Nevertheless, more studies in this field are needed to confirm this preliminary assertion.

4. Conclusion

Considering the existing links between smoking and high blood pressure, a reinterpretation of the association between both cardiovascular risk factors is postulated.

The choice of pharmacological treatment of the hypertensive patient who smokes must take into account the interference of the smoking habit with some antihypertensive agents, namely nonselective β-blockers. Bearing in mind the potentiation of final risk, a more active clinical intervention must be recommended, starting with earlier treatment than in hypertensive patients who do not smoke.

Minimal support and, optionally, nicotine replacement are two available strategies that have clearly shown their usefulness and cost effectiveness in helping smokers to give up their habit.

Finally, beyond the individual approach to the hypertensive patient who smokes, the existing problem at the community level stresses the need to implement joint antihypertension-antismoking programmes, which have widely demonstrated their efficiency and effectiveness.[105,106]

References

1. Pardell H, Armario P, Hernandez R, et al. Hypertension: epidemiology and cost of illness. Dis Manage Health Outcomes 1997; 1: 135-40
2. Nicolaides-Bouman A, Wald N, Forey B, et al. International smoking statistics. Oxford: Oxford University Press, 1993
3. Peto R, Lopez AD, Boreham J. In: Thun M, Heath Jr C, editors. Mortality from smoking in developed countries, 1950-2000. Oxford: Oxford University Press, 1994

4. Kannel WB, Higgins M. Smoking and hypertension as predictors of cardiovascular risk in population studies. J Hypertens 1990; 8 Suppl 5: S3-S5
5. Black HR. Smoking and cardiovascular disease. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis and management. 2nd ed. New York: Raven Press, 1995: 2621-47
6. Kannel WB. Blood pressure as a cardiovascular risk factor. JAMA 1996; 275: 1571-6
7. MRFIT Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. JAMA 1982; 248: 1465-7
8. Plans P, Pardell H, Salleras L. Epidemiology of cardiovascular disease risk factors in Catalonia, Spain. Eur J Epidemiol 1993; 9: 381-9
9. Dyer AR, Stamler J, Shekelle RB, et al. Pulse pressure: I. Level and associated factors in four Chicago epidemiologic studies. J Chron Dis 1982; 35: 259-73
10. Kahn HA, Medalie JH, Neufeld HN, et al. The incidence of hypertension and associated factors: the Israel Ischaemic Heart Disease Study. Am Heart J 1972; 84: 171-82
11. Seltzer CC. Effect of smoking on blood pressure. Am Heart J 1974; 87: 558-64
12. Green MS, Jucha E, Lue Y. Blood pressure in smokers and nonsmokers: epidemiologic findings. Am Heart J 1986; 111: 932-40
13. Goldbourt U, Medalie JH. Characteristics of smokers, nonsmokers and ex-smokers among 10,000 adult males in Israel: II. Physiologic, biochemical and genetic characteristics. Am J Epidemiol 1977; 105: 75-86
14. Jacobs DR, Gothenborg S. Smoking and weight: the Minnesota Lipid Research Clinic. Am J Pub Health 1981; 71: 391-6
15. Hansen KW, Pedersen MM, Christensen JS, et al. Night blood pressure and cigarette smoking: disparate association in healthy subjects and diabetic patients. Blood Press 1994; 3: 381-8
16. Omvik P. How smoking affects blood pressure. Blood Press 1996; 5: 71-7
17. Mundal R, Kjeldsen SE, Sandvik L, et al. Predictors of 7-year changes in exercise blood pressure: effects of smoking, physical fitness and pulmonary function. J Hypertens 1997; 15: 245-9
18. Willett WC, Green S, Stampfer MJ, et al. Relative and absolute risks of coronary heart disease among women who smoke cigarettes. N Engl J Med 1987; 317: 1303-9
19. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. BMJ 1985; 291: 97-104
20. Bühler FR, Vasenen K, Wathers JT, et al. Impact of smoking on heart attacks, strokes, blood pressure control, drug use, and quality of life aspects in the IPPPSH. Am Heart J 1988; 115: 282-8
21. Wilhelmsem L, Berglund G, Elmfeldt D, et al. Beta blockers versus diuretics in hypertensive men: main results from the HAPPY trial. J Hypertens 1987; 5: 561-72
22. Wikstrand J, Warnold I, Olsson G, et al. Primary prevention with metoprolol in patients with hypertension: mortality results from the MAPHY study. JAMA 1988; 259: 1976-82
23. Greenberg G, Thompson SG, Brennan PJ. The relationship between smoking and the response to antihypertensive treatment of mild hypertensives in the MRC trial of treatment. Int J Epidemiol 1987; 16: 25-30
24. Bulpitt CJ, Beilin LJ, Clifton P, et al. Risk factors for death in treated hypertensive patients. Lancet 1979; II: 134-7
25. Mann SL, James GD, Wang RS, et al. Elevation of ambulatory systolic blood pressure in hypertensive smokers: a case-control study. JAMA 1991; 265: 2226-8
26. Asmar RG, Girerd XJ, Brahimi M, et al. Ambulatory blood pressure measurement, smoking and abnormalities of glucose and lipid metabolism in essential hypertension. J Hypertens 1992; 10: 181-7
27. Gropelli A, Giorgi DM, Omboni S, et al. Persistent blood pressure increase induced by heavy smoking. J Hypertens 1992; 10: 495-9
28. Verdecchia P, Schillaci G, Borgioni C, et al. Cigarette smoking, ambulatory blood pressure and cardiac hypertrophy in essential hypertension. J Hypertens 1995; 13: 1209-15
29. Stewart MJ, Jyothinagaram S, McGinley IM, et al. Cardiovascular effects of cigarette smoking: ambulatory blood pressure and BP variability. J Hum Hypertens 1994; 8: 19-22
30. Mikkelsen KL, Wünberg N, Hoegholm A, et al. Smoking related to 24-h ambulatory blood pressure and heart rate. Am J Hypertens 1997; 10: 483-91
31. Setaro JF, Black HR. Refractory hypertension. N Engl J Med 1992; 327: 543-7
32. Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [editorial]. Arch Intern Med 1997; 157: 2413-46
33. McNagny SE, Ahluwalia JS, Clark S, et al. Cigarette smoking and severe uncontrolled hypertension in inner-city African Americans. Am J Med 1997; 103: 121-7
34. Freestone S, Ramsay LE. Effects of coffee and cigarette smoking on the blood pressure of untreated and diuretic-treated hypertensive patients. Am J Med 1982; 73: 348-53
35. Narkiewicz K, Maraglino G, Biaison T, et al. Interactive effect of cigarettes and coffee on daytime systolic blood pressure in patients with mild hypertension. J Hypertens 1995; 13: 965-70
36. Halkin H, Or J, Fuchs Z, et al. Smoking accounts for adverse effects of antihypertensive medications on plasma lipids: a population-based study. Hypertension 1989; 14: 210-7
37. Craig WY, Palomaki GE, Haddow JE. Cigarette smoking and serum lipid and lipoprotein concentration: an analysis of published data. BMJ 1989; 298: 784-8
38. Isles C, Brown JJ, Cumming AMM, et al. Excess smoking in malignant hypertension. BMJ 1979; 1: 579-81
39. Bloxham CA, Beevers DG, Walker JM. Malignant hypertension and cigarette smoking. BMJ 1979; 1: 581-3
40. Elliot JM, Simpson FO. Cigarettes and accelerated hypertension. N Z Med J 1980; 91: 447-9
41. Tuomilehto J, Elo J, Nissinen A. Smoking among patients with malignant hypertension [letter]. BMJ 1982; 284: 1086
42. Mackay A, Brown JJ, Cummings AMM, et al. Smoking and renal artery stenosis [letter]. BMJ 1979; 1: 770
43. Nicholson JP, Alderman MH, Pickering TG, et al. Cigarette smoking and renovascular hypertension. Lancet 1983; II: 765-6
44. Black HR, Cooper KA. Cigarette smoking and atherosclerotic renal artery stenosis. J Clin Hypertens 1986; 4: 322-30
45. Sang CN, Whelton PK, Hamper UH, et al. Etiologic factors in renovascular fibromuscular dysplasia: a case-control study. Hypertension 1989; 14: 472-9
46. Dungan WM. Pheocromocytoma and smoking. Arch Intern Med 1967; 120: 365-70
47. McPhaul M, Punzi HA, Sandy A, et al. Snuff-induced hypertension in pheochromocytoma. JAMA 1984; 252: 2860-2

48. Perry Jr HM, Erlanger M, Perry EF. Elevated systolic pressure following chronic low-level cadmium feeding. Am J Physiol 1977; 232: H114-21
49. Perry Jr HM, Schroeder HA. Concentrations of trace metals in urine of treated and untreated hypertensive patients compared with normal subjects [letter]. J Lab Clin Med 1955; 46: 396
50. Lewis GP, Jusko WJ, Coughlin LL. Cadmium accumulation in man: influencing of smoking, occupation, alcoholic habit and disease. J Chron Dis 1972; 25: 717-26
51. Saltmann P. Trace elements and blood pressure. Ann Intern Med 1983; 98: 823-7
52. Beevers DG. Trace elements and human hypertension. In: Birkenhäger WH, Reid JL, editors. Handbook of hypertension. Vol. 6. Epidemiology of hypertension (Bulpitt CJ, editor). Amsterdam: Elsevier, 1985: 206-15
53. Health consequences of smoking: cardiovascular disease. A report of the Surgeon General. Rockville (MD): US Department of Health and Human Services, Office of Smoking and Health, 1983
54. Pardell H. Smoking and arterial hypertension. Med Clin Barc 1987; 89 Suppl. 1: S23-9
55. Winniford MD, Wheelan KR, Kremers MS, et al. Smoking-induced coronary vasoconstriction in patients with atherosclerotic coronary artery disease: evidence for adrenergically mediated alterations in coronary artery tone. Circulation 1986; 73: 662-7
56. Cruickshank JM, Neil-Dwyer G, Dorrance DE, et al. Acute effects of smoking on blood pressure and cerebral blood flow. J Hum Hypertens 1989; 3: 443-9
57. Schroeder HA. Cadmium hypertension in rats. Am J Physiol 1964; 207: 62-6
58. Schroeder HA, Buckmen J. Cadmium hypertension: its reversal in rats by a zinc chelate. Arch Environ Health 1967; 14: 693-9
59. Lowe GDO. The impact of fibrinogen on arterial disease. Amsterdam: Excerpta Medica, 1993
60. Kutti J. Smoking, platelet reactivity and fibrinogen. In: Diana JN, editor. Tobacco smoking and atherosclerosis: pathogenesis and cellular mechanisms. New York: Plenum Press, 1990; 129-34
61. Ichiki K, Ikeda H, Haramaki N, et al. Long-term smoking impairs platelet-derived nitric oxide release. Circulation 1996; 94: 3109-14
62. Levine PH. An acute effect of cigarette smoking on platelet function: a possible link between smoking and arterial thrombosis. Circulation 1973; 58: 619-23
63. Steinberg D. Antioxidants and atherosclerosis: a current assessment. Circulation 1991; 84: 1420-5
64. Laursen JB, Rajagopalan S, Galis Z, et al. Role of superoxide in angiotensin II-induced but not catecholamine-induced hypertension. Circulation 1997; 95: 588-93
65. Church DF, Pryor WA. Free-radicals chemistry of cigarette smoke and its toxicological implications. Environ Health Perspec 1985; 64: 111-26
66. Morrow JD, Frei B, Longmire AW, et al. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers: smoking as a cause of oxidative damage. N Engl J Med 1995; 332: 1198-203
67. Noronha-Dutra AA, Epperlein MM, Woolf N. Effect of cigarette smoking on cultured human endothelial cells. Cardiovasc Res 1993; 27: 774-8
68. Murohara T, Kugiyama K, Ohgushi M, et al. Cigarette smoke extract contracts isolated porcine coronary arteries by superoxide anion-mediated degradation of EDRF. Am J Physiol 1994; 266: 874-80
69. Zondervan KT, Ocke MC, Smit HA, et al. Do dietary and supplementary intakes of antioxidants differ with smoking status? Int J Epidemiol 1996; 25: 70-9
70. Haak T, Jungmann E, Roab C, et al. Elevated endothelin-1 levels after cigarette smoking. Metabolism 1994; 43: 267-9
71. Stefanadis C, Tsiamis E, Vlachopoulos C, et al. Unfavorable effect of smoking on the elastic properties of the human aorta. Circulation 1996; 95: 31-8
72. Report of a WHO Expert Committee: hypertension control. WHO Technical Report Series 862. Geneva: World Health Organization, 1996
73. Pardell H, Armario P, Hernandez R. Progress in the 1980s and new directions in the 1990s with hypertension management. Drugs 1992; 43: 1-5
74. Trap-Jensen J, Carlsen JE, Lysbo T, et al. Cardiovascular and adrenergic effects of cigarette smoking during immediate non-selective and selective beta adrenoreceptor blockade in humans. Eur J Clin Invest 1979; 9: 181-3
75. Carruthers M. Modification of the noradrenaline related effects of smoking by beta blockade. Psychol Med 1976; 6: 251-6
76. Bühler FR, Berglund G, Anderson OK, et al. Double-blind comparison of the cardioselective beta blockers bisoprolol and atenolol in hypertension: the Bisoprolol International Multicenter Study (BIMS). J Cardiovasc Pharmacol 1986; 8 Suppl. 11: S122-7
77. Walle T, Conradi EC, Walle UK, et al. The predictable relationship between plasma levels and dose and chronic propranolol therapy. Clin Pharmacol Ther 1978; 24: 668-77
78. Fogari R, Zoppi A, Malamani GD, et al. Effects of calcium channel blockers on cardiovascular responses to smoking and hypertensive smokers. Int J Clin Pharmacol Res 1992; 12: 81-8
79. Kochar MS, Bindra RS. The additive effects of smoking and hypertension. Postgrad Med 1996; 100: 147-60
80. Kotamäki M, Manninen V, Laustiola KE. Enalapril versus atenolol in the treatment of hypertensive smokers. Eur J Clin Pharmacol 1993; 44: 13-7
81. Westheim A, Daac LNW, Kierulf P, et al. Selective alpha 1 inhibition with doxazosin in hypertensive smokers and non-smokers: haemodynamic and metabolic effects. J Hypertens 1990; 8 Suppl. 5: S41-6
82. Glassman AH, Stetner F, Walsh BT, et al. Heavy smokers, smoking cessation and clonidine: results of a double-blind, randomized trial. JAMA 1988; 259: 2863-6
83. McVeigh GE, Flack J, Grimm R. Goals of antihypertensive therapy. Drugs 1995; 49: 161-75
84. Kawachi I, Purdie G. Should treatment of mild to moderate hypertension be targeted? Results from a Markov cohort model incorporating multiple risk factors. J Hum Hypertens 1990; 4: 651-8
85. Kannel WB. Influence of fibrinogen on cardiovascular disease. Drugs 1997; 54 Suppl. 3: S32-40
86. US Department of Health and Human Services. The health benefits of smoking cessation: a report of the Surgeon General. Rockville (MD): US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Office on Smoking and Health, 1990
87. Pardell H, Saltó E, Salleras L. How to improve the physician's involvement in antismoking activities. Int J Smoking Cessation 1995; 4: 6-9
88. Pardell H, Saltó E, Salleras L. Handbook of diagnosis and treatment of smoking. Madrid: Ediciones Médica Panamericana, 1996

89. Russell MAH, Wilson C, Taylor C, et al. Effect of general practitioners' advice against smoking. BMJ 1979; 2: 231-5
90. Li VC, Coates TJ, Ewart CK, et al. The effectiveness of smoking cessation advice during routine medical care: physicians can make a difference. Am J Prev Med 1987; 3: 81-6
91. Rose G, Colwell L. Randomised controlled trial of antismoking advice: final (20 years) results. J Epidemiol Community Health 1992; 46: 75-7
92. Cummings SR, Rubin S, Oster G. The cost-effectiveness of counseling smokers to quit. JAMA 1989; 261: 75-9
93. Glynn TJ, Manley MW. How to help your patients to stop smoking. National Cancer Institute Manual for Physicians. Bethesda (MD): National Institutes of Health, 1989
94. US Department of Health and Human Services. Smoking Cessation: clinical practice guideline. No. 18. Rockville (MD): US Department of Health and Human Services, Public Health Service, Agency for Heath Care Policy and Research, 1996
95. Tonnesen P. Nicotine replacement and other drugs in smoking cessation. In: Bollinger CT, Fagerström KO, editors. The tobacco epidemic. Basel: Karger, 1997: 178-89
96. Law M, Sze PC, Sacks HS, et al. Meta-analysis of randomized controlled trials of nicotine chewing-gum. Lancet 1987; I: 27-30
97. Kottke TE, Battista RN, DiFriese GH, et al. Attributes of successful smoking interventions in medical practice: a meta-analysis of 39 controlled trials. JAMA 1988; 259: 2882-9
98. Tang JL, Law M, Wald N. How effective is nicotine replacement therapy in helping people to stop smoking? BMJ 1994; 308: 21-4
99. Silagy C, Mant D, Fowler G, et al. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. Lancet 1994; 343: 139-42
100. Hughes JR. Risk-benefit assessment of nicotine preparations in smoking cessation. Drug Saf 1993; 8: 49-56
101. Working Group for the Study of Transdermal Nicotine in Patients With Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. Arch Intern Med 1994; 154: 989-95
102. Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N Engl J Med 1996; 335: 1792-8
103. Allen SS, Hatsukami D, Gorsline J, et al. Cholesterol changes in smoking cessation using the transdermal nicotine system. Prev Med 1994; 23: 190-6
104. Fagerström KO, Säwe U. The pathophysiology of nicotine dependence: treatment options and the cardiovascular safety of nicotine. Cardiovasc Risk Factors 1996; 6: 135-43
105. Pardell H, Tresserras R, Saltó E, et al. Economic considerations for joint antihypertension-antismoking programs. Can J Cardiol 1993; 9 Suppl. D: 175D-7D
106. Hunink MGM, Goldman L, Tosteson ANA, et al. The recent decline in mortality from coronary heart disease, 1980-1990: the effect of secular trends in risk factors and treatment. JAMA 1997; 277: 535-42

Correspondence and reprints: Dr *H. Pardell*, Department of Internal Medicine, Unit of Hypertension and Cardiovascular Risk, Red Cross Hospital, Avenida José Molins, 29-41, 08906 Hospitalet de Llobregat, Barcelona, Spain.
E-mail: rtress@dsss.scs.es