Risk factors for atherosclerosis — can they be used to identify the patient with multisystem atherosclerosis?

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Summary

Risk factors are often used in preventive care programmes to identify the patient at particular risk for developing atherosclerosis. Risk factors for atherosclerosis have also been shown to be linked to the presence of the disease at a given time, a fact that may be helpful when screening for additional atherosclerotic disease in the known arteriopath. Risk factors were recorded in 471 patients admitted to hospital with symptoms of atherosclerosis. In patients admitted primarily with peripheral vascular disease, risk factors linked to the presence of additional coronary artery disease were a family history of ischaemic heart disease (odds ratio = 2,6), the presence of carotid artery disease (odds ratio = 1,9) and high fasting serum triglyceride levels ($P < 0,04$). Grouping these factors together using logistic regression, ischaemic heart disease could be predicted with a sensitivity of 72% and a specificity of 43%. Patients admitted with carotid artery disease were more likely to have ischaemic heart disease in the presence of peripheral vascular disease (odds ratio = 1,9) and a raised serum cholesterol level ($P < 0,02$), while female gender (odds ratio = 2,9) and an increase in age ($P < 0,001$) were linked to an increased prevalence of concomitant atherosclerosis in patients admitted with acute myocardial infarction or for elective coronary artery bypass surgery. Using an age cut-off point, additional atherosclerosis could be predicted with a sensitivity of 32% and a specificity of 88% in these patients.

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Various risk factors are known precursors to atherosclerotic brain infarct, coronary artery disease and intermittent claudication.[1] The important factors identified are high blood pressure, raised serum cholesterol level, cigarette smoking, ECG evidence of left ventricular hypertrophy, and glucose intolerance. These factors have been shown to be useful in identifying the person at special risk for developing atherosclerotic disease, making preventive care possible.[2] Diamond and Forrester[3] demonstrated a linear correlation between age-related prevalence and the 6-year incidence of coronary artery disease as reported in the Framingham study. They suggested that these risk factors could be used to predict the likelihood of disease being present in an asymptomatic patient. This holds possibilities in the preoperative evaluation of cardiac status in patients presenting for peripheral vascular surgery, where a risk-factor profile can be used in conjunction with non-invasive methods to predict the presence of coronary artery disease. This screening process can be of assistance in deciding which patients need further evaluation by invasive methods such as coronary angiography.

A study was undertaken to record the presence of risk factors in the arteriopath admitted to our institution with symptoms of atherosclerotic disease, and to examine the possibility of using these factors to predict the presence of additional asymptomatic lesions.

Patients and methods

All patients admitted to Universitas Hospital, Bloemfontein, between February and December 1988 with acute myocardial infarction or for elective coronary artery bypass surgery were evaluated for additional atherosclerosis using non-invasive methods. Screening for peripheral vascular disease (PVD) was performed by measuring segmental pressures using a Kranzbühler-762 Doppler apparatus and carotid arteries were examined by an ATL-Mk 600 Duplex Doppler. Patients presenting with carotid artery stenosis (CAS) or PVD over a period of 20 months (February 1988 - September 1989) were subjected to arm ergometer exercise ECG testing on a Würburg ergometer. The protocol suggested by Williams *et al.*[4] was used.

Defining the risk factors

The presence of cigarette smoking, hypertension, diabetes mellitus, and a family history of myocardial infarction, and measurements of serum cholesterol level, triglycerides, haematocrit, platelet count and uric acid levels were recorded in all patients.

Smoking. This factor was considered to be present if the patient was an active smoker at the time of admission to hospital or if the habit had ceased < 5 years before admission. Smoking was quantified by multiplying the average number of cigarettes smoked per day by the number of years the patient had been smoking to arrive at the 'smoking double product'.

Hypertension. Patients with a history of hypertension and who were on antihypertensive therapy at the time of admission were judged to be hypertensive. The wide spectrum of patients involved, many of whom were admitted to the intensive care unit for vasodilator therapy for myocardial infarction, made quantified evaluation of blood pressure impractical.

Family history of myocardial ischaemia. This factor was taken to be positive if any direct family member had suffered a myocardial infarction or undergone coronary artery bypass surgery before the age of 55 years. Direct family members included sisters, brothers, mother or father.

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Diabetes mellitus. Patients requiring either insulin or oral hypoglycaemic therapy for control of blood glucose levels before admission to hospital were recorded. Fasting serum glucose levels were measured in those patients admitted with PVD or CAS, a level > 11 mmol/l being considered indicative of diabetes mellitus. Blood glucose levels between 7 mmol/l and 11 mmol/l were interpreted as glucose intolerance and the diagnosis was confirmed by a subsequent glucose tolerance test. In patients admitted with acute myocardial infarction the diagnosis of diabetes was made exclusively on the history given by the patient.

Blood lipids. Serum triglyceride and total serum cholesterol levels were recorded wherever possible. Blood samples for this investigation were taken after a 10-hour fasting period.

Other factors. The following additional factors were recorded in all patients: (*i*) haematocrit value; (*ii*) platelet count; and (*iii*) uric acid level.

The prevalence of these risk factors in the presence of single-organ atherosclerotic involvement was compared with their prevalence in patients with multi-organ atherosclerosis. An approximate estimate of the relative risk for having multi-organ disease as opposed to single-organ disease was obtained by calculating the odds ratio in the case of binary data. An odds ratio of approximately $\geqslant 2$ was taken as meaningful. Significant differences in the averages of continuous data, such as the serum cholesterol value, were calculated by using Student's *t*-test. Important risk factors identified in this way were then subjected to logistic regressional analysis using the BMDP statistical software package.

Results

In total 471 patients were seen, 55% being admitted to hospital with acute myocardial infarction or for elective coronary artery bypass surgery (Table I). Patients admitted with PVD or aneurysms comprised 38% of the total and patients presenting with CAS 8%. The majority of patients seen were men (79%).

The average ages for patients in the three groups are given in Table II. Patients admitted primarily with ischaemic heart disease or for elective coronary artery bypass (group A) were, on average, younger than those in the other two groups ($P < 0{,}0001$), while those admitted with CAS (group B) were the oldest. In all three groups the women were on average noticeably older than the men, significantly so in group A ($P < 0{,}001$) and group C ($P < 0{,}05$).

The presence of risk factors for atherosclerosis in patients admitted with symptoms of PVD (group C) is summarised in Table III. Those patients with ischaemic heart disease are compared to those without ischaemic heart disease. Factors that occur more often in the presence of ischaemic heart disease in this group of patients are family history (odds ratio = 2,6), the presence of carotid artery disease (odds ratio = 1,9) and higher average fasting serum triglyceride values ($P = 0{,}04$). Although smoking does not appear to predispose to ischaemic heart disease in this group, patients with ischaemic heart disease were heavier smokers than those without, judging by the higher average 'double product'. The average 'double product' for the upper quartile of these patients was 1 200 compared with 1 000 in those who did not have ischaemic heart disease. In the group of patients with CAS, the presence of PVD (odds ratio = 1,9) and a raised serum cholesterol level ($P = 0{,}02$) appeared to be associated with the prevalence of ischaemic heart disease in this group (Table IV).

The prevalence of risk factors in group A is shown in Table V. Women in this group showed a clear predisposition to having atherosclerotic disease in a system other than the heart (odds ratio = 2,9), while an increase in age appeared to have the same effect ($P < 0{,}001$).

Grouping the factors together using logistic regression

Predicting the presence of CAS in patients admitted with ischaemic heart disease. Using the variables age and gender, patients in this group who have an increased chance of having carotid artery disease or PVD can be identified with a sensitivity of 32% and a specificity of 88%. The negative predictive value of this test is 61% and the positive predictive value 66% (predictive accuracy = 62%). The formula derived from these measurements is a simple age cut-off point for both sexes:

men at risk for concomitant atherosclerosis > 60 yrs
women at risk for concomitant atherosclerosis > 45 yrs.

Predicting the presence of ischaemic heart disease in patients presenting with PVD. Risk factors used for logistic regression in this case were the presence of CAS, raised triglyceride values and a family history of ischaemic heart disease. The presence of ischaemic heart disease in these patients can be predicted with a sensitivity of 72% and a specificity of 43%. The positive predictive value of this test is 68% and the negative predictive value 48% (predictive accuracy = 61%). The following formula to predict ischaemic heart

TABLE I. ANALYSIS OF ALL PATIENTS

	Group A		Group B		Group C		Total	
	No.	%	No.	%	No.	%	No.	%
All patients	**258**	**55**	**37**	**8**	**177**	**38**	**471**	**100**
Men	**213**	**45**	**29**	**6**	**132**	**28**	**373**	**79**
Women	**45**	**10**	**8**	**2**	**45**	**10**	**98**	**21**

TABLE II. MEAN AGES (YRS) OF PATIENTS

	Group A		Group B		Group C		Total	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Men	**55**	**30 - 78**	**64**	**43 - 79**	**62**	**42 - 83**	**59**	**30 - 83**
Women	**60**	**40 - 86**	**67**	**58 - 83**	**66**	**42 - 84**	**64**	**40 - 86**
Group	**56**	**30 - 86**	**65**	**43 - 83**	**64**	**42 - 84**	**60**	**30 - 86**

TABLE III. PREVALENCE OF RISK FACTORS IN PATIENTS ADMITTED TO HOSPITAL WITH PVD

	Ischaemic heart disease		No ischaemic heart disease		
	No.	%	No.	%	Odds ratio
Total No. of patients	117		59		
Men	85	73*	46	78	
Women	32	27	13	22	1,3
Hypertension	55	47	23	39	1,4
Family history	35	42	14	24	2,6
Diabetes	11	9	6	10	0,9
Smoking	86	74	49	83	0,6
Femoropopliteal disease	82	70	40	68	1,1
Carotid artery disease	32	27	10	17	1,9
Average					*P* value
Mean age (yrs)	64		62		0,3
Men (yrs)	63		61		
Women (yrs)	66		67		
Double product†	899		800		0,3
Haematocrit	44		46		0,15
Platelet count	252		265		0,4
Cholesterol	6,05		5,97		0,8
Triglyceride	2,42		1,87		0,04
Uric acid	0,38		0,38		0,99

*Percentage of total No. in the group.
† Double product = No. of cigarettes × years.

TABLE IV. PREVALENCE OF RISK FACTORS IN PATIENTS ADMITTED TO HOSPITAL WITH CAS

	Ischaemic heart disease		No ischaemic heart disease		
	No.	%	No.	%	Odds ratio
Total No. of patients	32		5		
Men	24	75†	5	100	
Women	8	25	0		
Hypertension	17	53	3	60	0,8
Family history	12	38	2	40	0,9
Diabetes	4	13	0	0	
Smoking	18	56	5	100	
Peripheral disease	18	56	2	40	1,9
Average					*P* value
Mean age (yrs)	66		61		0,2
Men (yrs)	65		61		
Women (yrs)	68				
Double product*	704		825		0,6
Haematocrit	44		44		0,8
Platelet count	266		278		0,8
Cholesterol	7,16		5,34		0,02
Triglyceride	2,02		1,63		0,5
Uric acid	0,36		0,39		0,5

* Double product = No. of cigarettes × years.
† Percentage of total No. in the group.

disease was derived following application of logistic regression on these variables:

0,9 (family history) + 0,5 (CAS) + 0,08 (triglyceride level) > 0,14

Discussion

The 'risk factors for developing atherosclerosis' are all those individual characteristics that predict the probability of one or more of the sequelae of the disease. These factors influence the process by means of genetic-environmental interaction, each factor forming a part of a complex process with many intervening variables.[5]

As early as 1976 Kannel *et al.*,[6] after analysing the data from the Framingham study, suggested that a risk profile could be used to identify the person at high risk for developing atherosclerotic disease. Salel *et al.*[7] and Reed *et al.*[8] confirmed the accuracy of this numerical coronary profile, while Okumiya *et al.*[9] found that the degree of CAS at autopsy correlated

TABLE V. PREVALENCE OF RISK FACTORS IN PATIENTS ADMITTED TO HOSPITAL WITH MYOCARDIAL INFARCTION OR FOR CORONARY ARTERY BYPASS SURGERY

	Peripheral/ carotid disease		No peripheral/ carotid disease		
	No.	%	No.	%	Odds ratio
Total No. of patients	**56**		**202**		
Men	**38**	**68†**	**174**	**86**	
Women	**18**	**32**	**28**	**14**	**2,9**
Hypertension	**21**	**38**	**76**	**38**	**1**
Family history	**28**	**50**	**109**	**54**	**1,2**
Diabetes	**4**	**7**	**30**	**15**	**0,4**
Smoking	**36**	**64**	**125**	**62**	**1,1**
Average					*P* value
Mean age (yrs)	**60**		**55**		**0,001**
Men (yrs)	**59**		**54**		
Women (yrs)	**63**		**59**		
Double product*	**747**		**704**		**0,6**
Haematocrit	**46**		**45**		**0,6**
Platelet count	**237**		**247**		**0,5**
Cholesterol	**6,65**		**6,64**		**0,9**
Uric acid	**0,40**		**0,40**		**0,2**

* Double product = No. of cigarettes × years.
† Percentage of total No. in group.

positively with antecedent elevated blood pressure and with higher serum cholesterol levels.

Diamond and Forrester[3] indicated that a linear correlation existed between the age-related prevalence and the 6-year incidence of coronary artery disease, as demonstrated by the Framingham study. Alluding to the practical problems concerning the sensitivity and specificity of non-invasive evaluation methods for coronary artery disease, they suggested the use of risk factors to predict the pre-test likelihood of a patient having coronary artery disease. This principle, based on Bayes' theorem of conditional probability, can facilitate decision-making when using sub-optimal evaluation methods to diagnose ischaemic heart disease. It is important to remember, however, that probability analysis is an aid to diagnosis and decision-making rather than a diagnosis in itself. Detrano *et al.*[10] pointed out that the advantages of this approach are that clinical hunches are quantified and clinical and non-invasive data are integrated to produce disease probabilities that may be more accurate than intuition.

Little information is available on the use of a risk profile to identify the known arteriopath who is at risk of having additional asymptomatic lesions. The aim of this study was to investigate this possibility. There are two areas where a profile could be of benefit to the physician confronted with the problem of possible multi-organ atherosclerosis. Firstly, identifying the patient presenting with PVD or CAS who has an increased risk of having coronary artery disease, and secondly deciding which patients presenting with ischaemic heart disease need to be evaluated further for carotid artery disease or PVD.

In patients with PVD important individual factors for predicting ischaemic heart disease were shown to be the presence of concomitant carotid artery disease (odds ratio = 1,9), a family history of ischaemic heart disease (odds ratio = 2,6) and raised serum triglyceride values ($P < 0,04$). These factors are very easily measured during routine pre-operative evaluation. Although lacking in specificity, this simple score may be used in parallel with other non-invasive methods of cardiac evaluation to facilitate decision-making concerning cardiac catheterisation in these patients.

Of note is the emergence of raised serum triglyceride levels in this group of patients as an important individual predictor of the presence of ischaemic heart disease. The association of raised serum triglyceride levels with coronary heart disease is not a clear-cut issue in the medical publications, with numerous studies refuting and numerous supporting its causative role.[11,12]

Patients seen with ischaemic heart disease primarily are under the care of physicians, and routine measurement of segmental pressures of the limbs and Duplex Doppler scanning of the carotid arteries are usually not performed because of the relatively low prevalence of concomitant CAS (4,5% at our institution — unpublished data). This low prevalence necessitates using a sifting method high in specificity to decide which of these patients should be subjected to non-invasive evaluation. In this group of patients important individual factors associated with PVD or carotid artery disease were female gender and an increase in age. A significant difference was found between the average age of patients in this group with additional atherosclerosis and those with ischaemic heart disease only ($P < 0,001$), and a significantly greater proportion of women than men were found to have additional atherosclerotic lesions (odds ratio = 2,9; $P < 0,01$). Using an age of 60 years in men and 45 years in women as a cut-off point, a simple measurement with a high specificity and negative predictive value was obtained. Patients admitted to hospital with myocardial infarction or for elective coronary artery bypass surgery who are above these ages should therefore be subjected to non-invasive evaluation of their carotid arteries and lower limbs.

In patients presenting with CAS, important factors associated with ischaemic heart disease were the presence of PVD (odds ratio = 1,9) and raised serum cholesterol levels ($P < 0,02$). Because this group was relatively small, comprising only 8% of the total, logistic regression was not applied to these variables. The prevalence of concomitant coronary artery disease in this group was, however, sufficiently high (81%) to justify routine examination of all patients by coronary angiography.

Conclusion

Measurement of segmental pressures of the limbs and Duplex scanning of the carotid arteries provide effective non-invasive evaluation for atherosclerotic disease in these areas. Routine

use of these examinations on asymptomatic patients, however, is neither warranted nor cost-effective. In patients admitted to hospital with myocardial ischaemia, we suggest that a simple age limit be used (> 60 years for men, > 45 years for women) to decide who should be examined for concomitant atherosclerotic lesions.

Cardiac evaluation of the asymptomatic patient is complicated by sub-optimal non-invasive investigations, and until such time as a method with adequate sensitivity and specificity is developed, the clinician will be forced to utilise all possible aids to identify the patient at high risk for having coronary artery disease and in whom subsequent coronary angiography is indicated. These aids include general risk factors for atherosclerosis. Although we have shown that these factors on their own have a relatively low specificity in the known arteriopath and do not have the same predictive value as in the general population, they can be of use when applied in parallel with other non-invasive methods. Grouping these factors together into a composite score may help to quantify the hunch a clinician might have concerning the presence of atherosclerotic disease, facilitating the decision as to whether the patient should be subjected to further investigations.

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