International Journal of Epidemiology

Vol. 10, No. 4
Printed in Great Britain

Varicose Veins: a Risk Factor for Atherosclerotic Disease in Middle-aged Men?

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Ducimetiere P [INSERM Unité 169 16 Bis Avenue, P.V. Couturier, 94800 Villejuif, France], Richard JL, Pequignot G and Warnet JM. Varicose veins: a risk factor for atherosclerotic disease in middle-aged men? *International Journal of Epidemiology* 1981, 10: 329–335.

Factors associated with the presence of varicose veins were studied among 7432 male employees aged 42–53 (Paris Prospective Study).

The prevalence of varicose veins was higher among lower social class subjects and was positively associated with a body-mass index, cigarette consumption and diastolic blood pressure. A detailed dietary survey in a subsample of the population showed a significantly higher total calory intake in men with varicose veins but no difference in the distribution of the various nutrients.

During follow up for subsequent atherosclerotic disease (average 6.6 yrs), men with varicose veins were at a significantly higher risk for intermittent claudication and, at least in the lower social class, for hard coronary heart disease. No association was found with angina pectoris incidence.

Varicose veins are very common in western populations and an association of this condition with diverticular disease has been reported.[1] The possibility that men with varicose veins are at higher risk of complications of atherosclerotic diseases is investigated in the present work.

MATERIAL AND METHODS

The Paris Prospective Study is a longitudinal study of risk factors for atherosclerosis in Paris policemen aged 42–53 at entry. Its protocol, fully described elsewhere[2,3] is outlined below.

Following an initial examination between 1967 to 1972, 7432 men, born in France, were considered to be free of clinical complications of atherosclerosis, including coronary heart disease, lower limb arterial insufficiency and cerebrovascular disease. They were followed up by annual examinations or in the case of retirement by mailed questionnaires, and new cases of atherosclerotic diseases and deaths were identified. By January 1, 1978, with mean follow-up time of 6.6 years, 250 cases of coronary heart disease, 58 cases of intermittent claudication and 30 cerebrovascular accidents had been diagnosed. This last set of diseases will not be treated here because of the relativity small number of cases.

All events were confirmed by a medical committee from documents available as follows:

– Angina pectoris and intermittent claudication. Standard Rose questionnaire conclusions with written comments of the examining physician.

– Myocardial infarction. Appearance of new Q waves on the electrocardiogram (Minnesota Code I-1 or I-2) or clinical symptoms with electrical changes. Enzymatic data were evaluated when available.

Some degree of comparability with other studies exists for coronary heart disease[3] but is doubtful for angina pectoris and intermittent claudication as the subjective opinions of the physicians might have intervened.

Angina pectoris was the first coronary event in 93 cases (mean annual incidence: 1.95/1000). A documented myocardial infarction occurred in 109

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Work of the 'Groupe d'Etude sur l'Epidémiologie de l'Athérosclérose' (G.R.E.A.) which associates INSERM and the 'Direction de l'Action Sanitaire et Sociale de la Préfecture de Paris' with a grant of the 'Ministère de la Santé et de la Sécurité Sociale'.

cases (including 6 with prior angina pectoris) (2.28/1000). Finally 54 deaths, besides those occurring with myocardial infarction, were presumed due to coronary heart disease: either sudden deaths or heart failure of unknown cause (1.13/1000). We will refer to myocardial infarction and coronary disease deaths combined as hard coronary heart disease. The mean annual incidence of intermittent claudication (irrespective of coronary heart disease) was 1.19/1000. At the initial examination, a number of clinical and biological parameters were determined for each subject, in particular: systolic and diastolic blood pressure by standard cuff technique in supine position: weight and height in underwear and socks (a body mass index (BMI) was computed as 1000 Log W/H^2 with W=weight (grams) and H=height (centimeters)): smoking habits by a questionnaire (the mean cigarette consumption during the last five years is used in the study): and serum cholesterol[4] and triglycerides[5] from a venous blood sample taken in the fasting state.

On the medical history, men stating that they had been treated (by diet or drugs) for diabetes were classed as diabetic. During the examination, the clinician visually inspected and palpated the legs of each subject and noted any venous enlargement or tortuosity. The severity of the varicosities when present were coded as mild or moderate. Some elements of information were missing for some subjects for technical reasons and the exact numbers will be given in the section on results.

A dietetician made a detailed dietary survey in 497 men recruited consecutively in 1969–1970. Average daily calory intakes of various nutrients were calculated from a week's average diet history for each man.[6]

Conventional Chi-square and Student t tests and analysis of variance were used. Multivariate analysis of the relationship between annual incidence rates and different variables was performed by an exponential model with covariates which allowed for unequal follow-up durations[7] (see Appendix).

RESULTS

The clinical classification of varicose veins was recorded on 7425 men and 731 (9.9%) were deemed to have moderate and 1217 (16.4%) mild varicosities. The partially subjective nature of this classification was evidenced by significant differences in the observations of individual clinicians. Among the 12 physicians who examined at least 200 men (totalling 82%), the observed prevalence varied from 14% (of which 5% were moderate) to 40% (15% moderate).

When classified by rank, Table 1 shows a lower prevalence of varicose veins was found in officers than among subofficers and policemen, and policemen seemed to have slightly more severe varicosities than the subofficers.

After adjustment for rank, mean values of some parameters measured at entry into the study according to the presence of varicose veins are shown in Table 2. Higher values of diastolic blood pressure, body mass index and number of cigarettes were found among men with varicose veins, with a trend toward higher values with more severe varicosities. By contrast, the prevalence of diabetes and lipids level showed no relationship.

Among the 497 men who participated in the diet survey, 125 (25%) had varicose veins which were graded moderate in 57 cases (12%). Table 3 shows that men with varicose veins had a significantly greater average calory intake. This difference was consistent for each rank and for each class of nutrients except alcohol. However, only for total carbohydrates is the difference significant. Although

TABLE 1 *Prevalence of varicose veins according to rank*

	varicose veins		
	none	mild	moderate
Officers	998 (79%)	173 (14%)	99 (8%)
Subofficers	1385 (73%)	326 (17%)	184 (10%)
Policemen	3094 (73%)	718 (17%)	448 (11%)
Total	5477 (74%)	1217 (16%)	731 (10%)
$\chi^2_{d.f.} = 19.5$	$p < 0.001$		

TABLE 2 *Mean values of parameters according to varicosities after adjustment on rank*

	varicose veins				
	none	mild	moderate	standard error*	p**
age (years)	47.2	47.1	47.4	1.9	NS
systolic pressure (mm Hg)	139.5	138.9	140.5	21.2	NS
diastolic pressure (mm Hg)	79.7	80.4	81.0	13.5	0.02
body mass index	406	411	419	54	0.001
cigarette consump. (/day)	10.0	11.2	12.1	10.3	0.001
cholesterol (mmol/l)	5.7	5.7	5.7	1.1	NS
triglycerides (mmol/l)	1.5	1.5	1.5	1.3	NS
diabetes (%)	1.5	0.9	2.2	–	NS

*From residual variance in the two-way (varicosity and rank) analysis
**From F-test in the above analysis. NS: not significant

TABLE 3 *Daily calory intake according to rank and presence of varicose veins*

		Daily total calory intake	Daily calory intake from alcohol	proteins	lipids	carbohydrates
Officers	no varicose veins	2503	321	318	844	1020
	any	2703	392	330	887	1094
Subofficers	no varicose veins	2704	307	345	881	1170
	any	2748	268	350	942	1188
Policemen	no varicose veins	2797	344	349	927	1177
	any	2967	367	365	939	1296
	Standard error	687	219	79	234	400
Statistical tests:	–between variance groups F^1_{491}	4.75 $p< 0.05$	1.18 NS	2.48 NS	1.47 NS	4.53 $p< 0.05$
	–between rank F^2_{491}	8.10 $p< 0.001$	1.91 NS	7.51 $p< 0.001$	4.75 $p< 0.01$	8.47 $p< 0.001$
	–interaction F^2_{491}	0.29 NS	1.30 NS	0.14 NS	0.35 NS	0.43 NS

this parameter seems to discriminate best between men with and without varicose veins, the proportion of total calories obtained from carbohydrates does not differ. In the detailed list of carbohydrate sources (omitted here), no specific food was in excess for men with varicosities.

The number of new cases of atherosclerotic diseases during follow-up and the corresponding mean annual incidences by rank and presence or absence of varicose veins of any severity are given in Table 4.

The first thing to note is the absence of any trend by rank for the incidence of angina, hard coronary heart disease or intermittent claudication. The results of statistical tests for differences in incidence by rank are not given in the table, but

TABLE 4 *Incidence of atherosclerotic disease with presence of varicose veins after adjustment on rank*

		rank			total number of cases	
ANGINA		officers	subofficers	policemen	observed	expected**
varicose	none	2.3*(14)	1.7(15)	2.0(41)	70	69.0
veins	any	1.2(2)	2.2(7)	1.9(14)	23	24.0
	total	2.1(16)	1.8(22)	2.0(55)	93	93.0
					$\chi^2_{d.f.} = 0.06$	NS
HARD CORONARY HEART DISEASE						
varicose	none	3.3(21)	3.1(28)	2.9(54)	103	119.2
veins	any	3.1(5)	3.4(11)	5.9(44)	60	43.8
	total	3.3(26)	3.2(39)	3.7(98)	163	163.0
					$\chi^2_{d.f.} = 8.19$	$p < 0.005$
INTERMITTENT CLAUDICATION						
varicose	none	0.8(5)	0.9(8)	1.1(22)	35	42.8
veins	any	1.8(3)	1.5(5)	2.0(15)	23	15.2
	total	1.0(8)	1.0(13)	1.3(37)	58	58.0
					$\chi^2_{d.f.} = 5.42$	$p < 0.02$

*mean annual incidence/1000 (number of cases)
**sum of expected number of cases in each rank

they are far from significant.

When adjusted for rank, the incidence of angina is the same in subjects with and without varicosities: the last 2 columns show that the number of cases expected, assuming no difference in incidence by varicosity status is practically the same as the number observed. By contrast, significantly higher incidences of hard coronary heart disease and intermittent claudication were experienced by men with varicosities. This pattern appeared to be consistent for each rank in the case of intermittent claudication but was restricted to policemen in the case of hard coronary heart disease, with a doubling of risk in this group ($\chi^2_{1d.f.} = 12.07$, $p < 0.001$).

Finally, in the whole population, risk increase for hard coronary heart disease and intermittent claudication is comprehensively graded according to severity of varicose veins; annual rates were respectively 2.9/1000 and 1.0/1000 among men without varicose veins, 4.4 and 1.9 among men with mild veins and 5.7 and 1.7 among men with moderate veins.

A multivariate analysis of the incidence of atherosclerotic events was performed in order to see whether the relationships with presence of varicosities was independent of other risk factors.

The set of factors for coronary heart disease (all forms) derived from the Paris Prospective Study data analysis[4] includes systolic blood pressure, serum cholesterol, cigarette consumption and presence of diabetes. In the present analysis, age and body mass index were also introduced. The coefficient of each variable and its t-value in the exponential model for hard coronary heart disease and intermittent claudication are shown in Table 5. The presence of varicose veins carries a significant independent risk of hard coronary heart disease, and the coefficient in the case of claudication is of borderline significance. In this latter disease the significantly negative coefficient of the body mass index is noteworthy.

DISCUSSION

Varicose veins are common among adults of both sexes in western countries and the social and economic costs of this ailment are important. By contrast, their prevalence in underdeveloped countries has generally been found low and poses no significant public health problem. The latter statement is now well-documented,[8] though mostly on the level of scattered observations rather than true epidemiological work. However, some well-designed studies have yielded similar results.[9,10,11] All geographical comparisons including population gradients within countries such as India[12] or New Zealand[13] appear to implicate environmental rather than racial

TABLE 5 *Coefficient, t-value and significance of each variable in the prediction of risk of hard coronary heart disease and intermittent claudication*

	Hard coronary heart disease (n=164)		Intermittent claudication (n=59)	
Constant	$7.585\ 10^{-6}$		$5.551\ 10^{-5}$	
Cigarette cons. (/day)	0.039	6.35 p< 0.001	0.062	6.66 p< 0.001
Systolic blood pressure (mm Hg)	0.018	5.91 p< 0.001	0.015	2.61 p< 0.01
Cholesterol (mmol/l)	0.312	5.05 p< 0.001	0.124	0.82 NS
Varicose veins (0=none, 1=mild, 2=moderate)	0.289	2.79 p< 0.01	0.324	1.87 p< 0.07
Diabetes (0=no, 1=yes)	0.662	1.45 NS	0.290	0.29 NS
Age (years)	0.019	0.42 NS	0.044	0.61 NS
Body mass index	−0.000	−0.04 NS	−0.007	−2.88 p< 0.01

factors. Searching in western populations for the epidemiological features of varicose veins including their associations with more serious ailments such as coronary heart disease, may help to identify these factors and give a deeper insight into Burkitt's thesis.

The accurate and reliable diagnosis of leg varicosities is a major difficulty in epidemiological surveys and the 2 clinical grades of severity used in the present study are far from satisfactory as witnessed by the recording variability among examiners. The overall prevalence rates, however, are remarkably similar to those given for men 40–49 in the Tecumseh population: 24% for any varicosities and 13% for grade 2+.[14] Uncertainty of diagnostic accuracy may obviously lead to a loss of power in establishing associations, but should not introduce any bias.

The slightly reduced prevalence of varicose veins in officers compared to lower ranks agrees with the results of Stewart et al[15] who found a lower prevalence in social classes I and II, and among commercial and clerical occupation groups. Consequently, the interpretation of our results may require the evocation of both socio-cultural and occupational factors. Among the latter the large amount of time spent by the average policeman standing relatively motionless at work may contribute to the development of leg varicosities.[16] Nutritional differences, in our population, may represent a socio-cultural phenomenon, since energy expenditures, although not ascertained on an individual basis, do not appear to differ much by rank. The calory intake gradient from officers to policemen with higher values for each of the broad nutrient categories is consistent with the pattern observed among men with varicose veins, implying that dietary habits may be a link between socio-cultural factors and varicosities. The inability to find any clearly different intake of a specific nutrient class is disappointing, however. For example, the higher calory intake of carbohydrates was found equally for simple or complex sugars (as in bread, rice, potatoes, noodles etc). No difference was found in the consumption of green vegetables and fruits and even though estimates of amount of dietary fibre were not made, the evidence is not in favour of differences in men with and without varicosities within each rank. Thus the low fibre hypothesis advocated by Cleave[17] and others is not supported by our data, but the dietary analysis was performed on a relatively small sample whereas individual variations were large.

The tendency to overweight in men and women with varicose veins has been observed among various populations[13,14,15] but not universally.[11,12] In the present study, average body mass index adjusted for rank showed an increasing trend with the degree of varicosity. The same pattern was observed for mean diastolic blood pressure but not for blood lipids.

The significantly higher cigarette consumption by men with varicosities does not appear to have been previously reported. This finding may be of value because both cigarette smoking[18] and the

presence of varicose veins[12] have been shown to be associated with decreased blood fibrinolytic activity. Reduced venous wall fibrinolytic activity has also been observed in the presence of varicose vein complications with skin changes.[19]

Men with varicose veins seem at higher risk of clinical atherosclerotic disease considered as a whole, even though the association with hard coronary heart disease was detected only among policemen, not higher ranks. The Kaiser Permanente retrospective study did not find such a relationship, but depended on a self-administered questionnaire to determine the presence of varicose veins.[20] However, not all manifestations of coronary heart disease exhibited this association: notably angina pectoris in which level of blood lipids but not cigarette smoking is a significant risk factor[21] contrary to our findings for varicose veins. By contrast, hard coronary heart disease and especially intermittent claudication are strongly related to cigarette smoking and are independently predicted by the presence of varicose veins.

The similarity of the pattern of risk associated with varicose veins and cigarette smoking suggests that a common aetiopathogenic link may connect them to the development of clinical atherosclerotic disease. Such an hypothesis was implicit in the epidemiological work of Malhotra[12,22] comparing both coronary heart disease incidence and varicose veins prevalence in 2 regions of India. However he put emphasis on the possible role of diet as did Burkitt. At this stage of our knowledge, fibrinolytic activity as a part of the haemostatic system seems to be a more likely factor. The present work, though demonstrating an association between the two conditions in individuals, unfortunately does not cast light on this.

APPENDIX

During follow up, the hazard rate for illness is assumed to be constant (r) for each subject. This assumption is equivalent to stating that the probability that the subject will get the illness before the instant t is $1 - \exp(-rt)$, the classical exponential survival model. The individual hazard rate, r, is chosen as an exponential function of the covariates $x_1 \ldots x_k$: $r = r_o \exp(b_1 x_1 \ldots + b_k x_k)$.

Writing the likelihood of observations for cases and non cases and maximising this quantity by an iterative technique gives an estimate of r_o and the b_j's as well as their asymptotic standard error, allowing a test of significance of the b_j's by a t test.

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(Revised version received 27 March 1981)

Referees and Reviewers

We wish to thank for their assistance,

E Alberman
M R Alderson
H R Anderson
J Avery
B Barber
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