Predictive value of the ear-crease sign in coronary artery disease

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The value of the ear-crease sign in predicting the presence of coronary artery disease was studied in 340 consecutive patients who underwent coronary arteriography. In this selected population, 75.6% of whom had coronary artery disease, the sensitivity of the sign was 59.5%, the specificity 81.9% and the positive predictive value 91.1%. The sign was associated with increasing age but was also independently associated with obstructive coronary artery disease. No significant correlation was found between the sign and the presence of risk factors or other signs of such disease, except for corneal arcus.

In symptomatic patients the sign suggested the presence of more extensive coronary artery disease. In an asymptomatic population with a low prevalence of coronary artery disease it appears to be of limited value in predicting obstructive coronary artery disease. However, it may identify a subset of patients prone to early ageing and to the early development of coronary artery disease, whose prognosis might be improved by early preventive measures.

Les auteurs ont étudié la valeur prévisionnelle du signe du pli du lobule de l'oreille à l'égard de la maladie coronarienne chez 340 patients consécutifs qui ont subi une coronarographie. Chez cette population choisie, au sein de laquelle la prévalence de la maladie coronarienne était de 75.6%, la sensibilité du signe était de 59.5%, sa spécificité de 81.9% et sa valeur prévisionnelle positive de 91.1%. La prévalence du signe augmentait avec l'âge, mais on a noté également une association indépendante avec la présence de la maladie coronarienne. Aucune corrélation significative n'a été retrouvée entre le signe du pli du lobule de l'oreille et la présence de facteurs de risque ou d'autres signes de cette maladie, à part l'arc cornéen.

Chez les sujets symptomatiques ce signe suggère la présence d'une maladie coronarienne plus étendue. Chez les sujets asymptomatiques, chez qui la prévalence de la maladie coronarienne est faible, ce signe semble avoir une valeur limitée pour prédire la présence de la maladie coronarienne obstructive. Toutefois, il pourrait identifier un sous-groupe de patients susceptibles de vieillissement précoce et au développement précoce de la maladie coronarienne, dont le pronostic pourrait être amélioré par la mise en oeuvre précoce de mesures préventives.

Interest in the early diagnosis and prevention of ischemic heart disease has stimulated the search for simple noninvasive predictors of coronary artery disease. Over the past decade the presence of a diagonal crease in the earlobe has been shown to be associated with such disease.[1-12] However, it is unclear whether this sign is independently related to coronary atherosclerosis or only indirectly, through an association with age.[3] We assessed the predictive value of this sign and its relation to age and to other factors known to affect the risk of coronary artery disease.

Methods

One of us (M.S.) examined the earlobes of 340 patients consecutively admitted to the Montreal Heart Institute for coronary arteriography that had been requested because of chest pain in 178, recurrent symptoms after a myocardial infarction in 115 and suspected valvular or primary myocardial disease in 47. Without knowing the results of the coronary arteriography the examiner assessed the earlobe for the presence of a clear-cut diagonal crease of the lobular portion of either auricle as described by Lichstein and associates.[2] In addition, we included patients in whom the crease extended for a distance greater than half the diagonal length of the earlobe (Fig. 1). If a crease in the earlobe
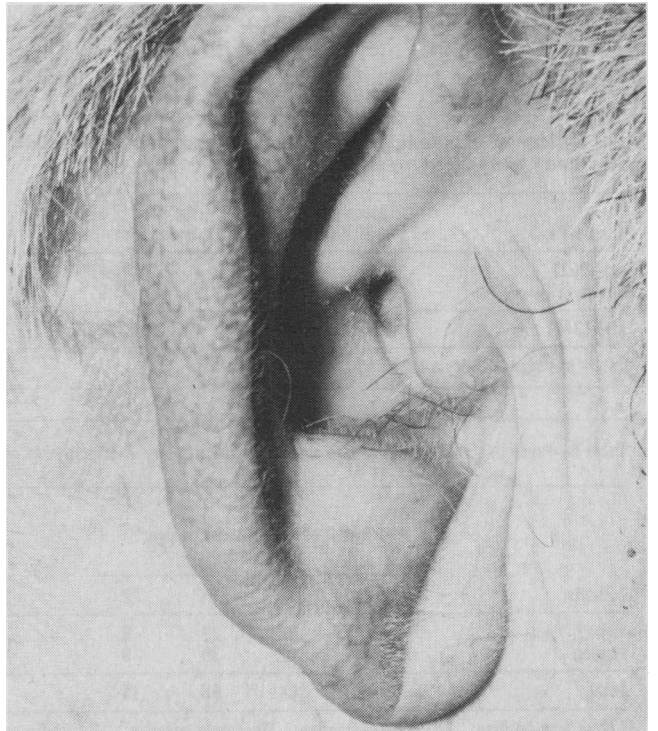

FIG. 1—Ear-crease sign.

was not typical, the ear-crease sign was considered to be absent.

After the earlobe had been assessed, we looked for the following risk factors and other indicators of coronary artery disease in all patients: a personal history of documented myocardial infarction, a family history of myocardial infarction or sudden death before the age of 55 years, cigarette smoking, corneal arcus, age, systolic and diastolic blood pressures, and levels of cholesterol, triglycerides and glucose in blood collected while the patient fasted. Corneal arcus was considered present when it fitted the description given by Rosenman and colleagues[13] — a translucent segment in the lower and upper peripheral cornea, or a semitranslucent or opaque ring, usually separated from the limbus by a clear zone.

Coronary arteriography was performed by the percutaneous femoral artery approach.[14] A cardiac radiologist analysed the cineangiograms and classified them as abnormal if they showed that the lumen of any artery had been narrowed by 30% or more. The severity of the narrowing was graded as follows: grade 1, a 30% to 50% reduction in the diameter of one or more of the main vessels; grade 2, narrowing greater than 50% in one or two main vessels; grade 3, narrowing greater than 50% in three main vessels.

The sensitivity, specificity and predictive value of the ear-crease sign were computed. Statistical analysis was carried out with the aid of a computer by means of chi-square and t-tests.

Results

Table I shows the mean age of the patients and the proportion with coronary artery disease, by sex and in the total group. Table II shows the sensitivity, specificity and predictive value of the ear-crease sign in the patients examined, by sex and in the total group. Coronary artery disease was demonstrated in 91.1% of the patients with the ear-crease sign (the positive predictive value of the sign) and in 60.5% of those without this sign (the difference was significant at P <

0.001); thus, the predictive value of the absence of the sign (the negative predictive value) was 39.5%. The positive predictive value of the sign was even higher for the men when considered separately — 95.7%. For the women the positive predictive value of the sign was much lower — 66.7%.

Table III shows that the ear-crease sign was significantly more common (P < 0.001) among patients with grade 3 coronary artery disease.

The risk factors and other indicators of coronary artery disease in the patients who had the ear-crease sign were compared with those in the patients who did not have a crease (Table IV). The two groups differed only in the presence of corneal arcus (P < 0.01) and in age (P < 0.01): patients with the ear-crease sign were more likely to have corneal arcus and were older. Although corneal arcus may reflect in part the influence of more advanced age,[13] the presence of both the ear-crease sign and corneal arcus further increased the probability of coronary artery disease: 93% of the patients with both signs had abnormal coronary arteries.

We compared the prevalence of coronary artery disease in the patients with and without the ear-crease sign by age group (Fig. 2). Coronary artery disease was significantly more common in the patients with the ear-crease sign in all age groups except above 60 years of age. A linear correlation between age and the ear-crease sign was observed both in the patients with coronary artery disease (correlation coefficient [r] = 0.987) and in those without such disease (r = 0.990) (Fig. 3). Among the patients below 34.5 years of age the ear-crease sign was not observed in those with normal coronary arteries but was noted in 27.7% of those with coronary artery disease. Among the patients 34.5 years of age and older the increase in the prevalence of the

Table I—Mean age of patients undergoing coronary arteriography and proportion with coronary artery disease, by sex and in total group

Patients (no.)	Mean age ± SD* (yr)	No. (and %) with coronary artery disease
Men (252)	49.7 ± 8.3	217 (86.1)
Women (88)	49.2 ± 8.8	40 (45.5)
Total (340)	49.5 ± 8.4	257 (75.6)

*SD = one standard deviation.

Table III—Correlation of severity of coronary artery disease with presence of ear-crease sign

Ear-crease sign	Grade of coronary artery disease;* no. of patients			Total
	1	2	3	
Present	28	46	79†	153
Absent	23	45	35†	103
Total	51	91	114	256

*1 = 30% to 50% reduction in diameter of one or more main vessels; 2 = narrowing greater than 50% in one or two main vessels; 3 = narrowing greater than 50% in three main vessels.
†Difference significant at P < 0.001.

Table II—Predictive value of ear-crease sign for coronary artery disease, by sex and in total group of patients

Patients	Result of examination for sign;* no. of patients				Sensitivity $\frac{TP}{TP + FN} \times 100$	Specificity $\frac{TN}{TN + FP} \times 100$	Positive predictive value $\frac{TP}{TP + FP} \times 100$
	TP	FN	TN	FP			
Men	135	82	29	6	62.2	82.9	95.7
Women	18	22	39	9	60.0	81.2	66.7
Total	153	104	68	15	59.5	81.9	91.1

*TP = true-positive; FN = false-negative; TN = true-negative; FP = false-positive.

ear-crease sign with age was similar in the two groups.

Discussion

Epidemiologic studies in the past decade have provided a profile of the potential candidate for coronary disease.[13,15-20] Frank[1] was the first to report, in 1973, that patients with the ear-crease sign tended to have the characteristics known as risk factors for cardiovascular disease and to actually have such disease prematurely. Other authors confirmed the association between the ear-crease sign and coronary artery disease. More recently, however, Haft and colleagues[9] raised doubts about the predictive usefulness of this sign in asymptomatic individuals, and it remains unclear, from a survey of the literature,[2-12] whether age alone is responsible for the sign.

We have shown that the ear-crease sign has a high predictive value for coronary artery disease, but that its absence does not rule out such disease. In the patients we studied, the overall proportion with coronary artery disease was 75.6%; however, the proportion with coronary artery disease of the subset of patients with the ear-crease sign was 91.1%. This compares well with the predictive value for coronary artery disease of elec-

trocardiographic changes observed during exercise testing in patients with a similar prevalence of coronary artery disease.[21] We found a significantly higher prevalence of coronary artery disease in all the groups of patients with the ear-crease sign who were under 60 years of age; it was particularly high for men (95.7%). As well, the coronary arteries were generally more severely affected in the patients with the ear-crease sign, consistent with the postmortem findings of Lichstein and associates[4] and the findings of Kaukola.[8] However, contrary to the data of Mehta and Hamby[3] our data show that, in addition to a positive association with ageing, the ear-crease sign also has an independent correlation with the presence and severity of coronary artery disease. Thus, the use of the ear-crease sign could improve the clinician's ability to estimate the probability of coronary artery disease in patients before they undergo diagnostic testing.[22]

Caution must be exercised in generalizing from our results. The high proportion of patients with coronary artery disease in our study group accounts, to a large extent, for the high predictive accuracy of the sign. Its lower predictive value in the women we studied may
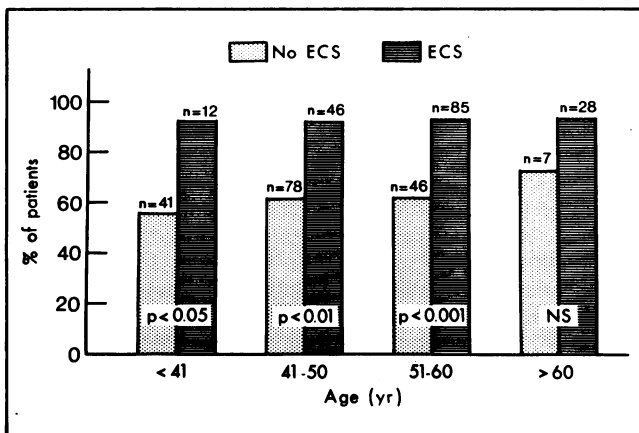
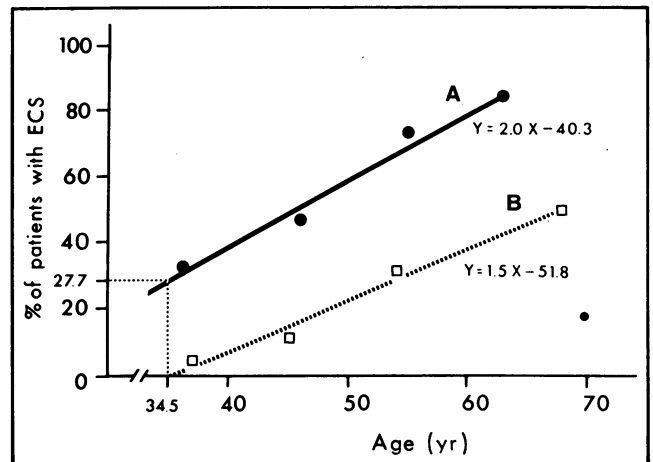FIG. 2—Prevalence of coronary artery disease in patients with and without ear-crease sign (ECS) by age group.

FIG. 3 — Influence of age on prevalence of ECS in subjects with (A) and without (B) coronary artery disease.

Table IV—Comparison of risk factors and other indicators of coronary artery disease in patients with angiographically documented stenosis with and without the ear-crease sign

Risk factor	Ear-crease sign		P value*
	Absent (n = 105)	Present (n = 153)	
	% of patients		
Family history of heart disease	49.0	42.5	NS
Cigarette smoking	82.7	72.7	NS
Corneal arcus	40.4	66.0	< 0.01
	Mean of measure ± SD		
Age (yr)	46.6 ± 8.1	52.9 ± 7.3	< 0.01
Systolic blood pressure (mm Hg)	127.6 ± 23.9	127.5 ± 21.8	NS
Diastolic blood pressure (mm Hg)	77.2 ± 13.07	77.4 ± 12.5	NS
Blood levels			
Cholesterol (mmol/l)	6.26 ± 1.39	5.95 ± 1.14	NS
Triglycerides (g/l)	2.24 ± 1.38	2.13 ± 1.02	NS
Glucose (mmol/l)	5.37 ± 1.27	5.74 ± 3.51	NS

*NS = not significant.

reflect their lower rate of coronary artery disease. Thus, in a population in which the prevalence of coronary artery disease is lower, the likelihood that an examination for an ear crease will give false-positive results is greater and the predictive accuracy of the results is significantly reduced, as is the case for other clinical tests.[21-23]

Therefore, it may be argued that using the ear-crease sign to identify asymptomatic individuals with coronary artery disease in the general population is questionable. Haines' analysis[24] of Lichstein and associates' data[4] led to the same conclusion, and Haft and coworkers[9] emphasized that only one of every six asymptomatic men who have an ear crease will have obstructive coronary artery disease.

Because of this, the value of the ear-crease sign may have to be reconsidered apart from its immediate predictive value for coronary obstructive disease. We suggest that this sign may identify a subset of persons subject to premature ageing who are thus at higher risk of coronary disease than the general population.

The ear crease probably reflects general ageing of the skin, as it is absent at birth and usually appears only later in life. Although Sprague[25] has found the sign in very young patients (3, 4 and 17 years), the youngest patient in Kaukola's extensive series[8] was 26 years old, and he had had a myocardial infarction. Among patients beyond the age of 35 years, as we observed, the proportion in whom the sign is present increases with each decade. In a relatively young individual the presence of the ear-crease sign could reflect premature ageing of the skin, which has been shown to parallel the ageing of the coronary arteries.[26,27] In older individuals the ear-crease sign is less predictive since all tissues, including the coronary arteries, are likely to show signs of ageing. Thus, the ear-crease sign could be an indicator of biologic age as opposed to chronologic age and could identify individuals who are ageing more quickly than the general population. This could explain the close correlation of the sign with coronary artery disease, since ageing is similarly positively correlated with disease of these arteries. So far, the location of the ear crease is unexplained, but the unusual density of elastic fibres in the anterior as compared with the posterior region of the earlobe and with other areas of the skin could account for the vulnerability to creasing in this area (H. Bouissou: personal communication, 1978). Doering and collaborators[7] suggested that since the prevalence of both the ear-crease sign and coronary artery disease increases with age, both conditions could reflect changes in the vascular system. The earlobe, a highly vascular structure, may show these changes by starting to crease and fold. Shoenfeld and associates[28] reported significant tears in the elastic fibres in biopsy sections from earlobes at the site of the crease and thickening of the prearteriolar wall in patients with the ear-crease sign.

Finally, it is possible to speculate that there is a common genetic factor responsible for both the ear crease and coronary artery disease.[8] The variations in the prevalence of the ear crease and of coronary artery disease among ethnic groups[8,28-30] provide some support for this hypothesis. The association of the ear-crease sign with obesity in Japanese men suggested by Rhoads and colleagues[29] has not been confirmed in Caucasian subjects.[8] Thus, the correlation between the ear-crease sign and coronary artery disease suggested by our data may result from a common factor, possibly genetic,[28,31] responsible for both the premature destruction of elastic fibres in the skin and some early, unidentified alteration of the coronary arteries. The positive correlation between the ear-crease sign and diabetic retinopathy[32] supports this contention, suggesting a relation between generalized angiopathy and premature ageing of the skin.

Conclusion

Our study has indicated that the ear-crease sign could identify patients who are ageing more rapidly than is usual and are thus prematurely at risk of coronary artery disease. The integration of this sign into the coronary risk profile developed by the Framingham group[17,33] may increase the predictive accuracy of the profile for the presence and severity of coronary artery disease and thus allow the early introduction of preventive measures, such as the control of hypertension and smoking, before the disease advances.

Furthermore, close follow-up of patients who have the ear-crease sign and yet show no evidence of obstructive coronary artery disease may help detect the disease in its very early stages and may shed some light on the early development of coronary atherosclerosis.

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Bone marrow transplantation for leukemia and aplastic anemia: management of ABO incompatibility

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Between February 1971 and October 1980, 34 patients with leukemia or aplastic anemia received bone marrow transplants from HLA-identical siblings whose lymphocytes did not react in a mixed leukocyte culture. The donors of 10 patients were ABO-incompatible, and for five pairs the ABO incompatibility was major. Plasma exchanges followed by a red blood cell exchange transfusion reduced the anti-A titres to 1:4 or less in these patients. The ABO incompatibility had no adverse effect on the results of marrow transplantation. Twenty-two patients, including 16 of the 20 who received their transplant after Jan. 1, 1980, are still living. Seven of the 15 patients with acute leukemia have survived 89 to 466 days, and 4 of the 6 with chronic myelogenous leukemia (CML) have survived 117 to 545 days. Of the 13 patients with aplastic anemia, 11 are alive up to 8 years after transplantation.

Marrow transplantation, when possible, is the treatment of choice for young patients with acute leukemia in remission and for patients with aplastic anemia. Marrow transplantation may also prove to be effective in patients with CML.

Entre février 1971 et octobre 1980, 34 patients souffrant de leucémie ou d'anémie aplastique ont reçu une greffe de moëlle provenant d'un frère ou d'une soeur ayant un typage HLA identique et dont les lymphocytes ne réagissaient pas en culture mixte de leucocytes. Pour 10 patients les donneurs présen-taient une incompatibilité ABO, et pour cinq paires

cette incompatibilité était importante. Chez ces patients un échange plasmatique suivi d'une exsangui-no-transfusion de globules rouges a permis de réduire les titres d'anticorps anti-A à 1:4 ou moins. L'incompatibilité ABO n'a pas eu d'effet fâcheux sur les résultats de la greffe de moëlle. Vingt-deux patients, y compris 16 des 20 qui ont reçu leur greffe après le 1er janvier 1980, sont encore vivants. Sept des 15 patients atteints de leucémie aiguë ont survécu de 89 à 466 jours, et 4 des 6 patients souffrant de leucémie myéloïde chronique (LMC) ont survécu de 117 à 545 jours. Onze des 13 patients qui souffraient d'anémie aplastique sont vivants jusqu'à 8 ans après la greffe.

La greffe de moëlle, lorsqu'elle est possible, constitue le traitement de premier choix pour les jeunes patients ayant une leucémie aiguë en rémission et pour les patients atteints d'anémie aplastique. La greffe de moëlle peut également s'avérer efficace chez les patients souffrant de LMC.

Bone marrow transplantation may be curative treatment for patients with leukemia and aplastic anemia. After receiving marrow from a sibling who was identical at the HLA (human leukocyte antigen)-A and HLA-B loci and whose lymphocytes did not react with those of the patient in a mixed leukocyte culture, 65% of young patients with acute leukemia have had a long, disease-free survival.[1-3] Similarly, when histocompatible siblings have been used as donors, 75% of patients with aplastic anemia have had hematologic restoration and returned to normal life following marrow transplantation.[4]

Successful marrow transplantation between ABO-incompatible but HLA-compatible siblings has broadened the selection of donors.[5-12] A fatal hemolytic transfusion reaction due to the infusion of ABO-incom-