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Severity of coronary atherosclerosis related to lipoprotein concentration

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Summary and conclusions

The influence of individual lipoproteins on the severity of coronary atherosclerosis was studied in 41 patients undergoing coronary angiography. The extent of atherosclerosis was quantified by a coronary atherosclerosis score (CAS) based on the number and severity of lesions in eight proximal segments of the coronary circulation. The concentration of high-density lipoprotein (HDL) showed a strong inverse association with CAS, which was independent of the effects of age and other lipoproteins. On multivariate analysis concentrations of other lipids—namely, total plasma cholesterol, low-density lipoprotein (LDL) cholesterol, and the combined effect of LDL cholesterol plus very-low-density lipoprotein triglyceride—showed direct, significant correlations with CAS, but these were weaker than that of HDL.

This study shows that concentrations of several circulating lipoproteins are related to the severity of coronary atherosclerosis, HDL having an apparent retarding effect. These findings may partly explain the influence of lipoproteins on the development of clinical coronary heart disease.

Introduction

Recent epidemiological studies have elucidated the importance of individual lipoproteins in predicting future clinical coronary heart disease. High-density lipoproteins (HDLs) appear to exert the greatest influence independently of other lipoproteins,[1-3] with low-density lipoproteins (LDLs) having a weaker, though still significant, independent relation with coronary heart disease.[1 2] This correlates negatively with HDL and positively with LDL, so probably HDL retards while LDL accelerates the development of clinical events. While this does not necessarily indicate a similar influence on the progression of underlying atherosclerotic disease, the influx and efflux of cholesterol in tissues are closely linked to the metabolism of LDL and HDL respectively,[4-6] and therefore the severity of atherosclerosis could be related to these two variables. We attempted to verify this by relating the concentrations of circulating plasma lipids and lipoproteins to the extent and severity of coronary atherosclerosis as quantified by angiography.

Patients and methods

We studied 151 consecutive patients referred to the cardiovascular diagnostic unit at Alfred Hospital for coronary angiographic evaluation of chest pain suggestive of coronary heart disease. One of us (PJN) selected a subgroup of 41 patients (28 men, 13 women), without knowledge of the clinical history or coronary anatomy, on the basis of plasma lipid concentrations, ensuring that the ranges of ages and lipid profiles resembled those of the whole group. This subgroup therefore included patients with both normal and raised plasma cholesterol and triglyceride concentrations. There was no significant difference in mean whole-plasma cholesterol and triglyceride concentrations between the entire patient population and the selected subgroup. None of the patients had valvular disease. Table I shows their clinical characteristics.

TABLE I—*Clinical data on patients*

	Men (n = 28)	Women (n = 13)
Mean age in years (range)	48·8 (34–61)	55·6 (41–65)
No (%) with proved myocardial infarction	16 (57)	5 (38)
No (%) with risk factors for coronary disease:		
High blood pressure (>160/100) ..	5 (18)	3 (23)
Smoked more than 10 cigarettes daily within past 5 years	16 (57)	6 (46)
Fasting glucose (concentration above 6·7 mmol/l (120 mg/100 ml)) ..	2 (7)	1 (8)
Mean (±SD) body surface area (m^2) ..	1·88 ± 0·14	1·60 ± 0·30

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LIPID MEASUREMENTS

Total cholesterol and triglyceride concentrations in whole plasma, very-low-density lipoprotein (VLDL), LDL, and HDL were measured on the morning that coronary arteriography was performed, after a 12-hour overnight fast. While many of the patients were being treated with one or more of several drugs—namely, beta-adrenergic blockers, cardiac glycosides, diuretics, and organic nitrites—none had received a lipid-lowering drug during the six months before coronary angiography. At the time of coronary angiography no patient had glycosuria or clinical evidence of hypothyroidism. Three patients had impaired renal function (serum creatinine concentration 0·15-0·32 mmol/l (1·7-3·6 mg/100 ml)). Liver function tests gave normal results in all patients. None of the women was taking an oestrogen preparation.

Plasma lipoproteins were isolated by ultracentrifugation and precipitation. VLDLs (dl < 1·006) were separated from an aliquot of plasma by centrifuging for 16 hours at 100 000 *g*; VLDLs and LDLs were precipitated with manganous chloride and heparin from a second aliquot of plasma, leaving HDL in the supernatant solution.[7] Plasma concentrations of LDL lipids were calculated as the difference between whole-plasma lipids and VLDL+HDL lipids and included the intermediate-density lipoproteins (IDL; relative density 1·006-1·019).

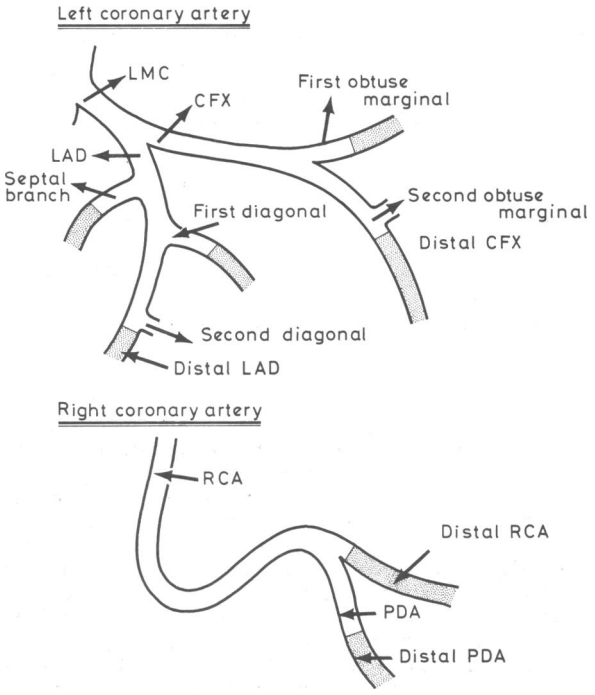
Cholesterol and triglyceride concentrations were measured with a Technicon AutoAnalyzer II modified for enzymatic techniques. Table II shows the concentrations of the plasma lipids and lipoproteins.

Whole-plasma cholesterol and triglyceride concentrations had been estimated previously in 16 patients (39%) between five years and two months before angiography. There was no significant difference between the lipid concentrations at and before angiography.

INTERPRETATION AND SCORING OF CORONARY ANGIOGRAMS

Coronary angiography was performed by the Judkins technique.[8] Angiograms were recorded at 50 frames/sec on 35 mm Ilford FB-4 film, a Philips 7-in (17·8-cm) caesium iodide image intensifier being used. Multiple transverse projections of the right and left coronary arteries were recorded until all lesions were satisfactorily delineated. Cineangiograms were simultaneously recorded on videotape, and the tapes were reviewed for adequacy before the catheters were withdrawn. All cineangiograms were interpreted by two of us (PJJ and RWH) without knowledge of the patient's clinical history or lipid profile.

For our study we divided the coronary circulation into eight proximal segments (fig); disease in the distal segments was not considered because of difficulty in quantifying the severity of lesions. The eight proximal segments were: the left main coronary artery; the left anterior descending artery (LAD) up to and including the origin of its second diagonal branch; the proximal third of the major septal branch of the LAD; the proximal third of the major diagonal branch of the LAD; the circumflex (CFX) artery up to and including the origin of its second obtuse marginal branch; the first third of the major obtuse marginal branch of the CFX; the right coronary artery up to and including the origin of the posterior descending artery (PDA); and the first third of the PDA.



Proximal segments of coronary artery used in assessing coronary atherosclerosis.
LMC=Left main coronary artery. CFX=Circumflex artery. LAD=Left anterior descending artery. RCA=Right coronary artery. PDA=Posterior descending artery.

The percentage by which each lesion in the proximal coronary circulation narrowed the artery was assessed according to the maximal narrowing of the diameter in all projections of the artery. The extent and severity of the proximal coronary disease was assessed by assigning points to each lesion as follows: less than 50% stenosis of the luminal diameter, 1; 50-74% stenosis, 2; 75-99%, 3; and total obstruction, 4. The points for each lesion in the proximal coronary circulation were summed and a coronary atherosclerosis score (CAS) obtained. Sixteen angiograms were reanalysed several months later without knowledge of the previous score. The coefficient of variation between the two readings was 4·9%.

Results

The mean CAS, as a measure of total atherosclerotic disease, was 9·0±SD 6·5 for men and 13·8±11·9 for women. The men, however,

TABLE II—*Mean (±SD) plasma lipid and lipoprotein concentrations (mmol/l)*

	Plasma cholesterol	Plasma triglyceride	HDL cholesterol	VLDL triglyceride	LDL cholesterol	LDL triglyceride	VLDL cholesterol
Men (n=28)	6·11±1·24	2·28±1·64	1·11±0·26	1·50±1·44	4·09±1·30	0·58±0·41	0·83±0·60
Women (n=13)	7·15±1·30	2·51±2·51	1·35±0·39	1·55±2·08	4·79±1·37	0·68±0·47	1·01±1·17
All patients (n=41)	6·45±1·32	2·35±1·93	1·19±0·31	1·53±1·64	4·30±1·35	0·61±0·43	0·91±0·80

Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 39 μg/100 ml. Triglyceride: 1 mmol/l ≈ 89 mg/100 ml.

TABLE III—*Correlations between age and plasma lipid and lipoprotein concentrations*

	Plasma cholesterol	Plasma triglyceride	HDL cholesterol	LDL cholesterol	VLDL cholesterol	LDL triglyceride	VLDL triglyceride
Men	0·142	0·443*	−0·293	0·024	0·455*	0·115	0·476**
Women	0·618*	0·304	−0·435	0·521	0·304	0·153	0·306
All patients	0·301	0·378*	−0·453**	0·176	0·363*	0·127	0·403**

*P<0·05; **P<0·01.

TABLE IV—*Correlations between coronary artherosclerosis scores and age and lipid and lipoprotein concentrations*

	Age	Plasma cholesterol	Plasma triglyceride	HDL cholesterol	LDL cholesterol	VLDL cholesterol	LDL triglyceride	VLDL triglyceride
Univariate analyses								
Men	0·359	0·423*	0·388*	−0·484**	0·272	0·393*	0·207	0·356
Women	0·258	0·411	0·361	−0·533*	0·245	0·327	0·548*	0·286
All patients	0·306	0·416**	0·372*	−0·508***	0·250	0·353*	0·364*	0·316*
Multivariate analyses†								
All patients		0·338*		−0·452**			0·320*	

*P<0·05; **P<0·01; ***P<0·001; †Performed with age held constant.

were on average younger than the women (49 and 55 years respectively) and there was a trend for the CAS to rise with advancing age, though this just failed to reach significance (r = 0·306).

The importance of age was also evident in the correlations between age and the plasma lipid and lipoprotein concentrations (table III). Age was significantly related to plasma triglyceride, VLDL triglyceride, and VLDL cholesterol concentrations (positively) and HDL cholesterol concentration (negatively). The relation between CAS and lipid concentrations was examined by univariate analysis and, to exclude the effect of age, multivariate analysis; the results are shown in table IV. In men and women combined the plasma cholesterol and triglyceride concentrations and each lipoprotein moiety, apart from LDL cholesterol, were significantly correlated with CAS; for HDL cholesterol there was a strong inverse correlation (P < 0·001). Multivariate analysis, with the effect of age held constant, showed that the only significant residual relations between CAS and lipid concentrations were those between CAS and total cholesterol (positive) and HDL cholesterol (negative).

There were significant interrelations among the lipoproteins. HDL cholesterol concentrations were inversely and significantly related to both LDL cholesterol (men only) and VLDL triglyceride concentrations (men and women combined; table V). There was a trend for LDL cholesterol to be inversely related to VLDL triglyceride, but this just failed to be significant. Multivariate analysis was therefore carried out to determine the contributions of individual lipoprotein concentrations to CAS that were independent of other lipoproteins; only the inverse correlation with HDL cholesterol remained highly significant (r = −0·452 for men and women combined, P < 0·01). This analysis, however, disclosed one further interesting correlation—namely, that LDL cholesterol, which on univariate analysis failed to show a significant correlation with CAS, became significantly correlated when VLDL triglyceride was held constant (r = +0·385 for men and women combined; P < 0·05). This might have been obscured by the negative relation between LDL cholesterol and VLDL triglyceride concentrations.

Clearly, therefore, of the three major lipoproteins, only the HDL concentration (measured as HDL cholesterol) was consistently and highly significantly related to CAS. Nevertheless, there was evidence, albeit weaker than that for HDL, that LDL (measured as LDL cholesterol) and VLDL (measured as VLDL triglyceride) concentrations were also related to CAS. We therefore analysed the combined influence of LDL cholesterol and VLDL triglyceride, with HDL cholesterol held constant: the relation with CAS was significant for men and for men and women combined (P < 0·05 in both cases). The augmented effect of both lipids might partly be due to the inclusion in the LDL fraction of the IDL moiety, the catabolic product of VLDL metabolism; support for this was derived from the independent relation between CAS and LDL triglyceride concentration (table IV), which is an indirect index of IDL accumulation.

We further investigated the association of coronary atherosclerosis with the three lipoprotein lipids by comparing the CAS for patients in the bottom and top tertiles for each lipoprotein. Table VI shows that in the pooled data for men and women CAS was significantly higher among patients in the top tertiles for VLDL triglyceride and LDL cholesterol and in the bottom tertile for HDL cholesterol. The ages of the patients in these two tertiles did not differ significantly, though the age-related trends, shown by regression analyses, were again apparent.

TABLE V—*Intercorrelations between lipoprotein concentrations*

	Lipoproteins	VLDL triglyceride	LDL cholesterol
Men	HDL cholesterol	−0·151	−0·388*
	VLDL triglyceride		−0·252
Women	HDL cholesterol	−0·499	−0·116
	VLDL triglyceride		−0·393
All patients	HDL cholesterol	−0·322*	−0·177
	VLDL triglyceride		−0·306

*P<0·05.

TABLE VI—*Mean ± SE of mean coronary atherosclerosis scores for patients in bottom and top tertiles for lipoprotein lipid concentrations*

Lipoprotein lipid	Coronary atherosclerosis score		P
	Bottom tertile	Top tertile	
HDL cholesterol	11·4 ± 1·9	5·1 ± 1·9	<0·025
LDL cholesterol	6·7 ± 1·4	16·7 ± 2·8	<0·005
VLDL triglyceride	7·1 ± 2·3	14·8 ± 2·3	<0·025

Discussion

These results show that circulating lipoprotein concentrations are related to the severity of coronary atherosclerosis, a finding that may partly explain the influence of lipoproteins on the development of clinical manifestations of coronary artery disease seen in epidemiological surveys.[1–3] Furthermore, a similar order of importance may be attributed to the various lipoproteins in their relation to the extent of atherosclerosis as disclosed by angiography (tables IV and VI) and the incidence of coronary heart disease. The strong inverse correlation between CAS, our measure of atherosclerosis, and the concentration of HDL, which was independent of the effects of age and other lipoprotein concentrations, resembled observations made for clinical events in prospective studies of coronary heart disease.[1–3] As in those studies, the plasma cholesterol and LDL cholesterol concentrations also exerted independent effects on coronary atherosclerosis but to a weaker degree than did HDL cholesterol. The relations between plasma triglyceride and VLDL lipid concentrations and atherosclerosis are less certain; we found significant correlations between concentrations of these lipids and CAS only on univariate analysis, although the combination of LDL cholesterol plus VLDL triglyceride showed an independent effect on CAS. Epidemiological surveys in the United States have also accorded plasma triglyceride concentrations a less certain role as a risk factor for coronary heart disease,[1 2] although in certain groups of people such as middle-aged women hypertriglyceridaemia, together with obesity and glucose intolerance, appeared to predispose to clinical events.[9] By contrast, the Stockholm prospective study established plasma triglyceride concentration as a highly significant and independent risk factor for CHD.[10]

Previous reports of coronary angiography related the concentrations of plasma lipids to the presence or absence of coronary artery disease rather than to a quantified estimate of the atherosclerotic lesions.[11 12] In these studies the importance of the serum cholesterol concentration is confirmed but the indepen-

dent influence of the serum triglyceride concentration is disputed. In one study[12] patients with at least one coronary artery with 75% obstruction had significantly higher serum lipid concentrations than those with less disease; the incidence of the disease was related much more strikingly, however, with the serum cholesterol concentration than with serum triglyceride. In the Canadian survey of Davignon *et al*[13] the degree of coronary atherosclerosis (which they scored much the same as we did) tended to be more severe in patients with hypercholesterolaemia and hypertriglyceridaemia, but the correlations were not significant.

Although our results suggest that HDL is more important than the other lipoproteins in influencing atherosclerosis, this finding needs to be interpreted since there is a close metabolic interrelation between lipoprotein species. The catabolism of VLDL is closely linked to the functions of at least two key HDL proteins, which subserve the activation of lipoprotein lipase and the formation and transfer of cholesteryl esters to VLDL.[14] Important interactions also occur between HDL and LDL, which maintain cellular cholesterol homeostasis.[4-6] The stronger correlations for HDL with both coronary atherosclerosis and clinical coronary heart disease may reflect the fact that biological variability in any person is less for HDL cholesterol than for VLDL triglyceride concentrations; a single measurement of the HDL concentration may therefore be more representative of a person's usual lipid status than an isolated measurement of VLDL triglyceride.

In a companion study of 38 patients undergoing coronary artery surgery we found that the cholesterol content of atrial muscle was influenced by lipoproteins in a similar direction to that noted for coronary atherosclerosis.[15] The highest atrial cholesterol concentrations were found in patients with one or more of three lipoprotein abnormalities—namely, high LDL, high VLDL, and low HDL concentrations. Studies of experimental atherosclerosis also suggest that several lipoprotein species can participate in atherogenesis. Apart from LDL, the atherogenic potential of which is most clearly seen in patients with homozygous hypercholesterolaemia, several triglyceride- and cholesterol-enriched lipoproteins—which probably represent remnants of chylomicron and VLDL metabolism—appear to contribute to atherosclerosis in cholesterol-fed animals.[16] The counteracting effect of HDL is equally clearly shown by the lack of atherosclerosis in species of animals that transport the bulk of their circulating cholesterol in HDL.

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ONE HUNDRED YEARS AGO I think I may now say something about the treatment of patients after ovariotomy; and, first, I will allude to warmth and diet, and to the amount of alcohol that should be given. Twenty years ago, when I first began to perform ovariotomy, the operation was done in a room which was heated to 70 or 75 deg Fahr, and it was made moist by steam from a kettle. The kettle was placed on the fire, a long spout brought from the kettle, and the room filled with the steam of boiling-water. The room in which the patient was kept after the operation was also heated in the same way with moistened air, and the patient was kept in a continual bath of perspiration by an abundance of bedclothes. A great deal of opium was given, as a rule, whether the patient was in pain or not, with the intention of keeping the bowels quiet several days; and also, as a rule, stimulants were given very freely. The first innovation I made in this routine practice was to operate in a room of comfortable temperature, the air being as pure as I could obtain it, without any admixture of steam, making no attempt to maintain excessive perspiration; only giving enough opium to moderate pain, and only giving stimulants when the failing power of the patient appeared to call for their use.

Of late years, I have noticed a less frequent necessity for stimulants, as a rule, and they have certainly been used in smaller quantities; but I cannot agree with those who say that they never administer alcoholic stimulants after surgical operations. One of my colleagues at the Samaritan Hospital has lately published a valuable little practical essay, in which he says he has never seen stimulants do any good, that he never administers them, and that he believes "all cases of operation are better without them." I, on the contrary, believe that I have more than once seen a dying woman called back to life by the free administration of brandy; that I have seen her powers maintained by a combination of food and stimulants when food alone would not be digested; and I trust that members of this College, or of any other profession, however warmly they may feel on this subject, however anxious they may be to check the terrible evils of intemperance, however great may be their desire to see the experiment tried of the comparative efficiency of a hospital where stimulants are never used and other hospitals where they are used in moderation or even in excess, will not suppose that, because any of us feel it to be our duty occasionally to administer alcohol very freely, we are less anxious than the most enthusiastic total abstainer can be to lessen the evils of intemperance in this country.

As a means of lowering temperature, supposing it rises after ovariotomy, as it often does, sometimes we have tried aconite in small doses, quinine in large doses, salicylic acid in the form of salicylate of soda—in fact, almost every medicine that has been suggested as a means of lowering temperature; but all these trials have ended in disappointment. We have, however, succeeded distinctly in lowering temperature, and in keeping it low, by the application of ice or iced-water to the head. The first trials were made after a suggestion of Dr Richardson, by putting an ice-bag round the neck. Dr Richardson believed that, by icing blood that went through the carotids to the brain and blood that came back through the jugulars, we should directly lower the temperature of the brain itself; and probably it may have been done experimentally, but in practice it was not found easy to do. It was difficult to keep any sort of cravat or collar that we tried filled with ice round the neck of the patient; it slipped off, and so we were reduced to the old India-rubber bag, or the ice-helmet which is so well known in lunatic asylums. But that was inefficient; it did some good, but it was not enough; and, after a time, Mr Thornton contrived this form of cap, which answers the purpose extremely well. A pail of water, with a large lump of ice in it, is placed by the bedside of the patient, and the stream of iced-water runs through the cap, which is formed of a series of tubes of India-rubber, lined with linen. That is placed upon the patient's head. It is made of different sizes to fit different shaped and sized heads; and this other tube is put into a second pail on the other side of the bed, and by this means the head is iced. The effect in lowering temperature is very marked.—T SPENCER WELLS at the Royal College of Surgeons of England. (*British Medical Journal*, 1878.)