

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Lipoprotein Lipase Activity Is Associated With Severity of Angina Pectoris

John J. P. Kastelein, J. Wouter Jukema, Aeilko H. Zwinderman, Suzanne Clee, Ad J. van Boven, Hans Jansen, Ton J. Rabelink, Ron J. G. Peters, Kong I. Lie, George Liu, Albert V. G. Brusckhe and Michael R. Hayden

Circulation 2000;102;1629-1633

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

Copyright © 2000 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/102/14/1629>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Lipoprotein Lipase Activity Is Associated With Severity of Angina Pectoris

John J.P. Kastelein, MD, PhD; J. Wouter Jukema, MD, PhD; Aeilko H. Zwinderman, PhD; Suzanne Clee, MD; Ad J. van Boven, MD, PhD; Hans Jansen, PhD; Ton J. Rabelink, MD, PhD; Ron J.G. Peters, MD, PhD; Kong I. Lie, MD, PhD; George Liu, PhD; Albert V.G. Brusckhe, MD, PhD; Michael R. Hayden, MD, PhD; for the REGRESS Study Group

Background—Raised triglyceride-rich lipoproteins significantly increase the risk for cardiovascular disease. Variation in the activity of the enzyme lipoprotein lipase (LPL), which is crucial in the removal of these lipoproteins, may therefore modulate this risk.

Methods and Results—Postheparin levels of LPL activity and mass were measured in a large cohort of male coronary artery disease patients participating in the Regression Growth Evaluation Statin Study (REGRESS), a lipid-lowering regression trial. In addition, the relationships between LPL activity and mass and severity of angina pectoris according to the NYHA classification and silent ischemia on 24-hour ambulatory ECG monitoring were assessed. Patients in different LPL activity quartiles and mass had different severities of angina; a total of 47% of patients in the lowest LPL quartile reported class III or IV angina. In contrast, only 29% in the highest activity quartile ($P=0.002$) had severe angina. These parameters were supported by ambulatory ECG results, for which the total ischemic burden in the lowest LPL activity quartile was 36.5 ± 104.1 mm \times min compared with 14.8 ± 38.8 mm \times min in the highest quartile of LPL activity ($P=0.001$). LPL activity levels were strongly correlated with LPL mass ($r=0.70$, $P<0.0001$). A significant association between the LPL protein mass and NYHA class ($P=0.012$) was also demonstrated.

Conclusions—We have demonstrated a significant relationship between LPL mass and activity and severity of ischemia as defined by angina class and ambulatory ECG. These results suggest that LPL influences risk for coronary artery disease by both catalytic and noncatalytic mechanisms. (*Circulation*. 2000;102:1629-1633.)

Key Words: angina ■ ischemia ■ lipoproteins

Plasma triglyceride (TG) levels, as a marker for TG-rich lipoproteins, are now considered an established risk factor for coronary artery disease (CAD) independent of other lipoproteins.^{1,2} Moreover, recent evidence suggests that elevated levels of these lipoproteins in the fasting or postprandial state promote the development of those atherosclerotic plaques with lipid-rich cores that are particularly vulnerable to rupture.³

See p 1600

Because the new paradigm of CAD dictates that clinical prognosis is not determined by the extent of a single stenosis but rather by the biological composition of the plaque, TG-rich lipoproteins are increasingly considered important contributors to outcome.⁴ Thus, both LDL particles and TG-rich lipoproteins may contribute, in different ways, to the

cascade of events resulting in the development of atherosclerotic plaques and ultimately CAD.

The initial event in atherogenesis is alteration of endothelial function. It is noteworthy that dyslipidemia per se has direct deleterious effects on endothelial cells, at least in part by reducing the bioavailability of nitric oxide (NO).⁵ Even very modest elevations of LDL cholesterol (LDL-C) are associated with endothelial dysfunction, which in turn has now been demonstrated to lead to myocardial perfusion defects and ischemia.^{6,7}

Transient hypertriglyceridemia can also decrease endothelium-dependent vascular reactivity, suggesting a prominent role for TG-rich lipoproteins in this process.⁸ These earlier observations are now supported by 2 recent studies that document impaired endothelium-dependent vasomotor responses in the coronary vasculature, again elicited by TG-rich

Received March 23, 2000; revision received April 20, 2000; accepted May 8, 2000.

From the Departments of Vascular Medicine (J.J.P.K.) and Cardiology (R.J.G.P., K.I.L.), Academic Medical Center, Amsterdam; Departments of Cardiology (J.W.J., A.V.G.B.) and Biostatistics (A.H.Z.), Leiden University Medical Center, Leiden; Interuniversity Cardiology Institute of the Netherlands (J.W.J., A.H.Z., A.V.G.B.), Utrecht; Department of Cardiology, University Hospital Groningen, Groningen (A.J.v.B.); Department of Biochemistry, University Hospital Rotterdam, Rotterdam (H.J.); Department of Nephrology and Hypertension, University Hospital Utrecht, Utrecht (T.J.R.), the Netherlands; and Centre for Molecular Medicine and Therapeutics, University of British Columbia (S.C., M.R.H.), Vancouver, Canada.

Correspondence to John J.P. Kastelein, Academic Medical Center, Department of Vascular Medicine, G1-146, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands. E-mail e.vandongen@amc.uva.nl

© 2000 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

remnant lipoproteins.^{9,10} Even a single high-fat meal, as a source of postprandial TG-rich lipoproteins, can transiently impair endothelial function, induce red cell aggregation, and promote disturbances in coagulation and fibrinolysis.^{11,12}

Therefore, elevated TG-rich lipoprotein levels not only may promote a more rapid progression of atherosclerosis but also could lead directly to myocardial ischemia, particularly in subjects with the high-TG/low-HDL trait, which is frequently present in CAD patients and is an important marker for TG-rich lipoproteins.¹³

Lipoprotein lipase (LPL) is the crucial enzyme in the metabolism of these TG-rich lipoproteins. It is synthesized in parenchymal cells of adipose tissue and skeletal and cardiac muscle, where it is transferred to binding sites at the vascular side of endothelial cells on capillaries and epicardial vessels in the case of myocardium.¹⁴

We previously demonstrated that low levels of LPL activity, as encountered in patients with partial LPL deficiency, are associated with premature atherosclerosis and accelerated progression of atherogenesis.^{15,16} In contrast, patients with genetically elevated levels of LPL activity, such as carriers of the LPL S447X truncation variant, exhibit lower TG levels, higher HDL-C, and CAD risk, and their frequency is increased among centenarians.¹⁷⁻¹⁹

Because low levels of LPL activity are strongly associated with the high-TG–low-HDL-C trait, we examined whether low LPL enzyme activity was related to symptoms of CAD by assessment of LPL activity and subjective and objective measures of myocardial ischemia in a large cohort of men who participated in a lipid-lowering regression trial (the Regression Growth Evaluation Statin Study, REGRESS).²⁰ To further define this possible interaction and determine its independence from TG-rich lipoproteins, we also assessed the concentration of the LPL protein in a subset of these patients.

Methods

Patients

A total of 884 men taking part in REGRESS were eligible for this study. REGRESS, described in detail elsewhere, was designed as a double-blind, placebo-controlled, multicenter study to assess the effect of pravastatin treatment on the progression and regression of coronary atherosclerosis.²⁰ All patients were men of Caucasian descent, were <70 years of age, and had angiographically documented CAD (>50% stenosis of 1 major vessel). Patients who had unstable angina or who suffered a myocardial infarction within the preceding 6 months of the study were excluded; angina pectoris classification was based on the Rose questionnaire. All patients had total cholesterol levels between 4 and 8 mmol/L and TG levels <4 mmol/L.

Lipid and Lipoprotein Analysis

All lipid laboratory tests were carried out at the Lipid Reference Laboratory, as published previously.²⁰ The Lipid Reference Laboratory is an international member of the USA National Cholesterol Reference Method Laboratory Network, chaired by the Centers for Disease Control and Prevention (Atlanta, Ga). Serum cholesterol, HDL-C, and TG were measured on fasting blood samples by standard techniques at all visits. LDL-C was calculated according to the Friedewald formula.

LPL Activity and Mass

According to a standardized protocol, patients received an intravenous bolus of 60 IU heparin per 1 kg body weight. After the patient rested in a supine position for 15 minutes, 20 mL of EDTA blood was withdrawn from the contralateral arm and placed on ice. Tubes were then spun down in a cooled centrifuge for 15 minutes at 3000g. Cells and plasma were separated, and plasma was divided into Biofreeze tubes, snap-frozen in liquid nitrogen, and stored at -80°C until activity and mass measurements were performed.

Postheparin LPL Activity

LPL activity was measured with a radiolabeled triolein emulsion according to the method of Nilsson-Ehle and Schotz.²¹ One unit of enzyme activity corresponds to the amount required to release 1 mmol FFA/min at 37°C .

Postheparin LPL Mass

LPL immunoreactive protein was assayed by ELISA based on 2 antibodies (Ab), the monoclonal antibody (mAb) 5D2 raised against purified bovine milk LPL (a generous gift from Dr John Brunzell, University of Washington, Seattle) and a chicken antibody raised against the C-terminal end of the human LPL peptide. The 5D2 mAb conjugated with horseradish-peroxidase served as the detection Ab in a sandwich ELISA to assess LPL immunoreactive mass, with the chicken Ab serving as the capture Ab. This sandwich ELISA was verified in this laboratory and found to recognize both human and cat LPL immunoreactive mass.

Quantitative Coronary Angiography

Quantitative coronary angiography procedures are described in detail elsewhere.²⁰ Briefly, baseline coronary cinearteriography was performed 5 to 10 minutes after administration of 5 to 10 mg isorbide dinitrate sublingually and analyzed by quantitative coronary angiography with the Cardiovascular Measurement System (CMS-MEDIS, Medical Imaging System). The coronary tree was divided into 13 segments according to the American Heart Association classification, excluding the posterolateral branches. Minimum obstruction diameter, mean segment diameter, and percent diameter stenosis were calculated for each qualifying segment. To calculate an average per patient, the minimum obstruction diameter, mean segment diameter, and percent diameter stenosis of all qualifying segments were added and divided by the number of contributing segments.

Ambulatory ECG Monitoring

In the participating centers, the leads of the ECG recorders were attached in a standardized manner. Tapes were analyzed in the ambulatory ECG core laboratory (University Hospital Groningen) by experienced technicians. At each ischemic episode, heart rate at onset of ischemia was noted.

Patients, physicians, and ambulatory ECG technicians were blinded to the results of randomization throughout the study (details described elsewhere).²² The attending physicians were unaware of the results of the ambulatory ECG. Ambulatory ECG monitoring was performed at baseline. Not included in the ambulatory ECG study were patients with initial ST-segment abnormalities, for example, because of intraventricular conduction delay or right bundle-branch block. For the recording and analysis of transient myocardial ischemia, a 3-channel Marquette system was used. During the time of the ambulatory ECG, anti-ischemic medication was continued. Transient myocardial ischemia was defined as the presence of episodes showing ≥ 0.1 -mV horizontal or downsloping ST-segment depression, 80 ms after the J point, lasting for ≥ 60 seconds and separated by ≥ 60 seconds from the next ischemic episode. Ischemic burden was defined as the product of ischemic duration in minutes multiplied by ST-segment depression in millimeters. Ambulatory ECG recordings of poor technical quality were rejected, and recording periods in which the ST segment was changed because of a change in body position (during sleep) were not included in the study.

TABLE 1. Lipid and Lipoprotein Levels According to LPL Activity

	LPL<77 mU/mL	77<LPL<103 mU/mL	103<LPL<132 mU/mL	LPL>132 mU/mL	P
TC, mmol/L	5.96 (0.85)	5.97 (0.84)	6.12 (0.87)	6.15 (0.84)	0.06
HDL, mmol/L	0.88 (0.26)	0.89 (0.21)	0.96 (0.23)	1.02 (0.23)	<0.0001
LDL, mmol/L	4.21 (0.80)	4.23 (0.74)	4.37 (0.76)	4.43 (0.77)	0.013
TG, mmol/L	1.94 (0.71)	1.88 (0.82)	1.75 (0.71)	1.55 (0.62)	<0.0001

Values are mean (SD). TC indicates total cholesterol.

Statistical Analysis

A baseline LPL measurement was available in 731 REGRESS patients; mass measurements were performed in a randomly selected subset of 405 patients. The association between LPL activity and baseline patient characteristics was assessed with ANOVA and univariate and multiple regression analyses. In the assessment of these relations, lipids baseline levels were always adjusted to account for regression to the mean. Throughout, a value of $P<0.05$ was considered to indicate significance.

Results

LPL Activity Measurements

LPL activity was available at baseline in 731 patients with mean levels of 107.0 ± 46 mU/mL. CAD patients were divided into LPL activity groups: the first quartile (LPL activity, 13 to 77 mU/mL) contained 191 patients, the second and third quartile (LPL activity, 77 to 132 mU/mL) contained 361 patients, and the fourth quartile (LPL activity, 132 to 293 mU/mL) contained 179 patients. The quartiles were originally defined as 77, 103, and 132 mU/mL; however, 12 patients had an exact LPL activity measurement of 77, and 7 patients had an exact value of 132. We decided to include those in the first and fourth quartiles, respectively, which resulted in the observed uneven distribution. However, when patients at an LPL activity value of 77 mU/mL were included in the second quartile and patients at 132 mU/mL were added to the third

quartile, results did not change appreciably, and statistical significance ($P=0.02$ for the difference) remained intact.

Distribution of CAD risk factors and medication did not differ among LPL quartiles. No differences were found for age, body mass index, systolic and diastolic blood pressures, left ventricular ejection fraction, smoking, insulin, glucose, or fibrinogen; moreover, the frequency of treatment with pravastatin, long-acting nitrates, β -blocking agents, calcium channel blockers, and ACE inhibitors was also similar (data not shown). β -Blockers, calcium antagonists, and long-acting nitrates were used in 72%, 59%, and 56% of the population, respectively. CAD patients in the lowest LPL activity quartile displayed increased TG (0.58 ± 0.43 versus 0.35 ± 0.42 mmol/L; log-transformed $P<0.0001$) and decreased HDL-C (0.86 ± 0.26 versus 1.02 ± 0.23 mmol/L; $P<0.001$). Levels of total cholesterol, HDL-C, LDL-C, and TG differed significantly between LPL activity quartiles, as can be deduced from Table 1.

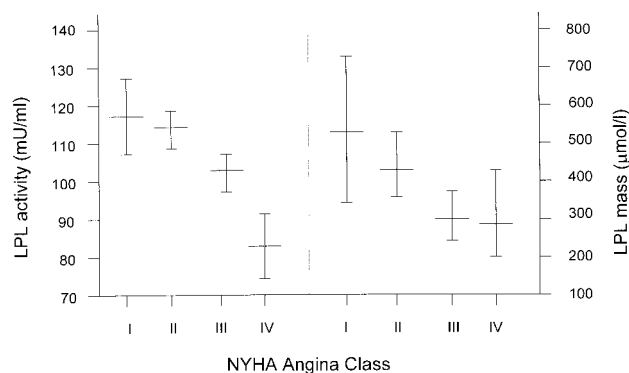
Neither extent of CAD nor baseline angiographic measurements differed between LPL activity quartiles (Table 2). However, NYHA classification for angina pectoris was significantly different between LPL quartiles. NYHA angina class could be scored in 726 of 731 patients in whom LPL activity measurements were available: 79 in class I, 363 in class II, 237 in class III, and 47 in class IV.

TABLE 2. CAD Parameters According to LPL Activity

	LPL<77 mU/mL (n=191)	77<LPL<132 mU/mL (n=361)	LPL>132 mU/mL (n=179)	P
Extent of CAD, n (%)				
1 vessel	69 (43)	125 (39)	76 (47)	0.21
2 vessel	49 (30)	119 (37)	49 (30)	0.21
3 vessel	44 (27)	73 (24)	36 (22)	0.60
Angina class, n (%)				
I	22 (12)	32 (9)	25 (14)	0.20
II	79 (42)	180 (50)	104 (68)	0.009
III	66 (35)	123 (34)	48 (27)	0.15
IV	22 (12)	23 (6)	2 (2)	0.0006
Angiography,* mm				
MSD	2.75 (0.39)	2.75 (0.37)	2.72 (0.39)	0.69
MOD	1.76 (0.33)	1.77 (0.37)	1.75 (0.36)	0.89
Ischemia*				
Duration, min	16.2 (43.4)	7.2 (21.5)	8.3 (22.2)	0.013
Episodes, n	2.6 (6.5)	1.3 (3.6)	1.3 (2.8)	0.012
Burden, min \times n	36.5 (104.1)	12.3 (37.6)	14.8 (38.8)	0.001

MSD indicates mean segment diameter; MOD, mean obstruction diameter.

*Values are mean (SD).



Relation between NYHA angina class and postheparin LPL activity (left) and mass (right) levels in 726 and 405 CAD patients, respectively, of REGRESS cohort.

There was a highly significant difference in mean LPL activity level in patients in NYHA classes I through IV; mean \pm SD LPL activity levels were 117 ± 47 , 114 ± 47 , 102 ± 43 , and 83 ± 29 mU/mL in each angina class, respectively ($P < 0.0001$; the Figure). After adjustment for angiographic and lipid parameters, risk factors, and history of CAD, mean \pm SE levels were 117 ± 6.4 , 114 ± 2.8 , 104 ± 3.4 , and 87 ± 7.9 mU/mL, respectively ($P = 0.002$). Patients in the highest NYHA class were more often treated with antianginal medication and were subjected more often to revascularization (CABG or PTCA). Even after adjustment for these factors, the differences in LPL activity between NYHA angina classes remained significant ($P = 0.013$). LPL activity levels, however, were not predictive of progression of disease in terms of change in mean segment diameter or minimum obstruction diameter or cardiovascular events in either placebo- or pravastatin-treated groups (data not shown).

Of patients in the lowest LPL activity quartile, 47% reported angina in class III or IV; in contrast, only 29% in the highest LPL activity quartile had similar NYHA classification ($P < 0.001$). Angina class could be predicted by LPL activity in 67% of patients. Subsequent analysis of 48-hour ambulatory ECG monitoring confirmed subjective categorization and revealed a significant increase in both the number (2.6 ± 6.5 versus 1.3 ± 2.8 , $P = 0.013$) and duration (16.2 ± 43.4 versus 8.3 ± 22.2 minutes, $P = 0.012$) of ischemic episodes, as well as an increased total ischemic burden (36.5 [104.1] versus 14.8 [38.8] ST-segment depression [mm] times ischemic [minutes]) in patients with low versus high LPL activity. These differences in frequency of both silent and symptomatic ischemia between patients in the lowest versus the highest LPL activity quartile were highly significant ($P = 0.001$; Table 2).

Both LPL mass and activity data were available in 405 patients; in 326 patients, only LPL activity could be measured because of a shortage of plasma. Mass and activity were strongly correlated ($r = 0.70$, $P < 0.0001$), and mass data in different NYHA classes confirmed activity data and exhibited a similar relationship between LPL concentration and angina. NYHA angina class could be scored in 401 of 405 patients in whom LPL mass data were available; 38 in class I, 195 in class II, 133 in class III, and 35 in class IV. LPL concentrations represented as geometric means were 498, 416, 308, and 300 μ mol/L in NYHA classes I through IV, respectively

($P = 0.02$; the Figure). Within LPL quartile groups, the TG-to-HDL ratio was not related to angina class. In the lowest quartile, the correlation was zero; in the highest class, it was 0.12. For all, $P > 0.10$.

Discussion

Heparin releases LPL from its endothelial binding sites into the circulation and postheparin LPL activity reflects total LPL mass at the vascular endothelium of different tissues, including adipose tissue and skeletal and cardiac muscle.^{23,24} Postheparin LPL activity in this group of CAD patients was not related to CAD risk factors or physical characteristics but exhibited significant correlations with plasma TG levels and myocardial ischemia.

It should be noted, however, that diabetic patients were excluded from REGRESS, which might explain the lack of association between body mass index, glucose, insulin, and LPL activity. Therefore, our results should be interpreted with caution and cannot be generalized to a diabetic population with definite CAD. Nevertheless, this is the first report examining the relation between LPL activity and mass, angina, and the severity of ischemia on ambulatory ECG monitoring. All ambulatory ECG recordings were performed during conventional anti-ischemic treatment, and mean heart rates at onset of ischemia were low. This type of ischemia is considered to represent abnormal coronary vasomotion caused by endothelial dysfunction.

Because LPL represents the rate-limiting step for the removal of TG-rich lipoproteins from the circulation, the strong association in our cohort between low LPL activity and the high-TG-low-HDL trait is in line with our earlier studies in LPL-deficient heterozygotes.^{14,25,26} Fasting TG levels are an independent risk factor for CAD, and a reduction in these lipids may result in direct benefit with regards to coronary disease incidence.^{1-3,27} In addition, TG-rich lipoproteins preferentially promote the growth of unstable plaques and decrease endothelium-dependent vasodilatation.^{8-12,28,29} Very recently, hypertriglyceridemia has also been shown to lead to altered vasodilatation in the myocardial circulation, even in anatomically normal coronary arteries.³⁰

Low LPL activity is an important determinant of both fasting and postprandial hypertriglyceridemia. This may directly lead to impaired endothelium-dependent vasodilatation and result in functional changes in myocardial perfusion and ultimately ischemia.^{31,32}

Alternatively, LPL activity may have a direct effect on the vessel wall. Both the fact that LPL protein mass exhibits a similar relationship with ischemia as LPL activity and the absence of a relationship between angina and the TG-to-HDL ratio support a direct role for LPL in the vasculature. The LPL protein may influence vascular tone by affecting the synthesis or degradation of endothelium-derived relaxing factors such as NO. Endothelium-dependent vascular relaxation is abnormal in the setting of atherosclerosis, with a smaller proportion of endothelial cells producing NO synthase, the key enzyme in basal endothelial cell NO production.³³

LPL increases NO synthase production in macrophages, which leads to increased NO synthesis in vitro. LPL may well have a similar function in vivo in both macrophages and

endothelial cells and may therefore have an important influence on vascular tone.^{34,35}

In conclusion, our data show that low levels of LPL activity and mass in plasma are strongly associated with silent ischemia and angina pectoris in CAD patients, and it is conceivable that the clinical presentation in these patients may be partly influenced by LPL activity and protein mass at the endothelium of the coronary vasculature. These data extend the importance of the LPL protein for the coronary circulation in terms of both energy supply for the myocardium and modulation of vascular tone.

Compounds that increase LPL activity are currently in development and may have pleiotropic effects beyond their effects on lipoprotein metabolism, for which they were originally developed.^{36–38}

Acknowledgments

REGRESS was sponsored by Bristol-Myers Squibb Co, Princeton, NJ; the Medical Research Council of Canada; and the Heart and Stroke Foundation of British Columbia and Yukon. Dr Hayden is an established investigator at the BC Children's Hospital.

References

- Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213–219.
- Gaziano JM, Hennekens CH, O'Donnell CJ, et al. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. *Circulation*. 1997;96:2520–2525.
- Gronholdt MLM, Nordestgaard BG, Wiebe BM, et al. Echo-lucency of computerized ultrasound images of carotid atherosclerotic plaques is associated with increased levels of triglyceride-rich lipoproteins as well as increased lipid content. *Circulation*. 1998;97:34–40.
- Davies MJ. Stability and instability: two faces of coronary atherosclerosis: the Paul Dudley White Lecture. *Circulation*. 1996;94:2013–2020.
- Quyyumi AA, Dakak N, Andrews NP, et al. Nitric oxide activity in the human coronary circulation. *J Clin Invest*. 1995;95:1747–1755.
- Steinberg HO, Bayazeed B, Hook G, et al. Endothelial dysfunction is associated with cholesterol levels in the high normal range in humans. *Circulation*. 1997;96:3287–3293.
- Hasdai D, Gibbons RJ, Holmes DR Jr, et al. Coronary endothelial dysfunction in humans is associated with myocardial perfusion defects. *Circulation*. 1997;96:3390–3395.
- Lundman P, Eriksson M, Schenck-Gustafsson K et al. Transient triglyceridemia decreases vascular reactivity in young, healthy men without risk factors for coronary heart disease. *Circulation*. 1997;96:3266–3268.
- Kugiyama K, Doi H, Ohgushi M, et al. Remnant lipoproteins impair endothelium-dependent vasomotor functions in human coronary arteries. *Circulation*. 1997;96(suppl I):I-2207. Abstract.
- Inoue T, Riichiro M, Kazuhiro H, et al. Serum levels of remnant like particles: cholesterol affects the endothelium dependent coronary vascular response in humans. *Circulation*. 1997;96(suppl I):I-2208.
- Vogel RA, Corretti MC, Plotnick GD. Effect of a single high fat meal on endothelial function in healthy subjects. *Am J Cardiol*. 1997;79:350–354.
- Baliga R, Rampling MW, Kooner JS. High fat meal induces changes in blood rheology in patients with coronary artery disease. *Circulation*. 1997;96(suppl I):I-2206.
- Hodis HN, Mack WJ. Triglyceride-rich lipoproteins and progression of coronary artery disease. *Curr Opin Lipidol*. 1995;6:209–214.
- Brunzell JD. Familial lipoprotein lipase deficiency and other causes of the chylomicronemia syndrome. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The Metabolic and Molecular Bases of Inherited Disease*. New York, NY: McGraw-Hill, Inc; 1995:1913–1932.
- Benlian P, de Gennes JL, Foubert L, et al. Premature atherosclerosis in patients with familial chylomicronemia caused by mutations in the lipoprotein lipase gene. *N Engl J Med*. 1996;335:848–854.
- Jukema JW, van Boven AJ, Groenemeijer BE, et al. The Asp₉Asn mutation in the lipoprotein lipase gene is associated with increased progression of coronary atherosclerosis. *Circulation*. 1996;94:1913–1918.
- Groenemeijer BE, Hallman MD, Reymer PWA, et al. Genetic variant showing a positive interaction with β -blocking agents with a beneficial influence on lipoprotein lipase activity, HDL cholesterol, and triglyceride levels in coronary artery disease patients. *Circulation*. 1997;95:2628–2635.
- Faure Delanef F, Zuoli H, Cohen D, et al. Prevalence of common lipoprotein lipase (LPL) gene mutation Ser447stop is increased while prevalence of Asn2911Ser mutation is decreased in centenarians. *Atherosclerosis*. 1997;134:26.
- Gagne SE, Larson MG, Pimstone SN, et al. A common truncation variant of lipoprotein lipase (S447X) confers protection against coronary heart disease: the Framingham Offspring Study. *Clin Genet*. 1999;55:450–454.
- Jukema JW, Bruschke AVG, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: the Regression Growth Evaluation Statin Study (REGRESS). *Circulation*. 1995;91:2528–2540.
- Nilsson-Ehle P, Schotz MC. A stable, radioactive substrate emulsion for assay of lipoprotein lipase. *J Lipid Res*. 1976;16:536–541.
- Van Boven, AJ, Jukema JW, Zwinderman AH, et al. Reduction of transient myocardial ischemia with pravastatin additional to the convenient treatment in patients with angina pectoris. *Circulation*. 1996;94:1503–1505.
- Olivecrona G, Hultin M, Savonen R, et al. Transport of lipoprotein lipase in plasma and lipoprotein metabolism. In: Woodford XPP, Davignon J, Sniderman A, eds. *Atherosclerosis*. In press.
- Vaziri ND, Liang K, Barton CH. Effect of increased afterload on cardiac lipoprotein lipase and VLDL receptor expression. *Biochim Biophys Acta*. 1999;1436:577–584.
- Reymer PWA, Gagné E, Groenemeijer BE, et al. A lipoprotein lipase mutation (Asn291Ser) is associated with reduced HDL cholesterol levels in premature atherosclerosis. *Nat Genet*. 1995;10:28–34.
- Kastelein JJP, Groenemeijer BE, Henderson H, et al. The Asn9 variant of lipoprotein lipase is associated with the -93G promoter mutation and an increased risk of coronary artery disease. *Clin Genet*. 1998;53:27–33.
- Criqui MH. Triglycerides and cardiovascular disease. *Eur Heart J*. 1998;19:A36–A39.
- Hodis HN, Mack WJ. Triglyceride-rich lipoproteins and progression of atherosclerosis. *Eur Heart J*. 1998;19:A40–A44.
- Stroes E, de Bruin TWA, de Valk H, et al. No activity in familial combined hyperlipidemia: potential role of cholesterol remnants. *Cardiovasc Res*. 1997;36:445–452.
- Yokoyama I, Ohtake T, Momomura S-I, et al. Altered myocardial vasodilation in patients with hypertriglyceridemia in anatomically normal coronary disease. *Arterioscler Thromb Vasc Biol*. 1998;18:294–299.
- Cohen JC, Noakes TD, Spinnler Benade AJ. Postprandial lipemia and chylomicron clearance in athletes and in sedentary men. *Am J Clin Nutr*. 1998;49:443–447.
- Pimstone SN, Clee SM, Gagné SE, et al. A frequently occurring mutation in the lipoprotein lipase gene (Asn291Ser) results in altered postprandial chylomicron triglyceride and retinyl palmitate response in normolipidemic carriers. *J Lipid Res*. 1996;37:1675–1684.
- Wilcox JN, Subramanian RR, Sundell CL, et al. Expression of multiple isoforms of nitric oxide synthase in normal and atherosclerotic vessels. *Arterioscler Thromb Vasc Biol*. 1997;17:2479–2488.
- Reinier G, Lambert A. Lipoprotein synergizes with interferon gamma to induce macrophage nitric oxide synthetase mRNA expression and nitric oxide production. *Arterioscler Thromb Vasc Biol*. 1995;15:392–399.
- Mochizuki S, Murase T, Yamaoka H, et al. Lipoprotein lipase activity in ischemic and anoxic myocardium. *Res Cardiol*. 1987;82(suppl 1):45–52.
- Chiba T, Miura S, Sawamura F, et al. Antiatherogenic effects of a novel lipoprotein lipase-enhancing agent in cholesterol-fed New Zealand white rabbits. *Arterioscler Thromb Vasc Biol*. 1997;17:2601–2608.
- Tsutsumi K, Inoue Y, Shima A, et al. The novel compound NO-1886 increases lipoprotein activity with resulting elevation of high density lipoprotein cholesterol, and long-term administration inhibits atherogenesis in the coronary arteries of rats with experimental atherosclerosis. *J Clin Invest*. 1992;92:414–417.
- Kobayashi J, Nagashima I, Hikita M, et al. Effect of troglitazone on plasma lipid metabolism and lipoprotein lipase. *Br J Clin Pharmacol*. 1999;47:433–439.