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Review Article

Lipoprotein(a) and Coronary Heart Disease

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ABSTRACT

The physiological role of lipoprotein(a) (Lp[a]) has yet to be established, though its structure is well known; it is a low density lipoprotein-like particle with structural homology to plasminogen. It is considered to be linked to atherosclerotic vascular disease, associated with atherothrombotic lesions and an acute phase reactant. The purpose of this paper is to review these three aspects of Lp(a), and to discuss recent observations of Lp(a) in the patient with coronary heart disease. Of particular interest is the application of lipoprotein removal.

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INTRODUCTION

The relationship between lipoprotein(a) (Lp[a]) and atherosclerosis has been appreciated for many years (1,2). Increased levels of Lp(a) have been associated with premature coronary artery disease (CAD) and have been implicated as predictors of restenosis after percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) surgery. The structural homology of Lp(a) to plasminogen has prompted studies on the effect of this plasma lipoprotein on fibrinolysis. Lp(a) is believed to profoundly affect fibrinolysis (3). Interestingly, cardiopulmonary bypass (CPB), which is necessary for CABG surgery, is also believed to activate the fibrinolytic system. Recent findings of increased levels of Lp(a) during extracorporeal circulation suggest a paradoxical response of this plasma lipoprotein, since plasma lipids are known to decrease after major surgery and blood components are diluted due to CPB pump prime (4).

Lp(a) is also known to be an acute-phase reactant (5). The acute-phase reaction is a response to a homeostasis disturbed by tissue injury, an infection, neoplastic growth or immunological disorders. As an acute-phase reactant, Lp(a) elevations associated with CPB could have significant clinical implications. Since this particle is both atherogenic and thrombogenic (1), significant increases of Lp(a) could impact coagulation and possibly reperfusion.

REVIEW OF LITERATURE

Lp(a)

Lp(a), first identified by Berg in 1963, is a remarkable low density lipoprotein (LDL)-like protein that transports cholesterol. It is a spherical lipid found predominantly in the 1.05 to 1.21 g/ml density range (data from Macra Lp(a) EIA kit insert, SDI, Newark, DE 19713). Lp(a) is comprised of two cross-linked proteins, apolipoprotein B-100 (molecular mass 513 kD) and apolipoprotein (a) (molecular mass ranges from 200 to 700 kD) (2). The apo(a) contains the lysine binding domains, called kringles, found in plasminogen and other coagulation and fibrinolytic serine proteinases, such as tissue-type plasminogen activator (t-PA), urinary-type plasminogen activator (u-PA), and prothrombin (6). The level of serum Lp(a) is believed to be genetically controlled. In fact, Lp(a) demonstrates the highest heritability of all the plasma lipoproteins (7).

Lp(a) is present in all human plasma, varying considerably among individuals in concentrations ranging from under 0.5 to over 100 mg/dl (5). Increased levels of Lp(a) have been linked to cardiovascular and cerebral vascular disease (1,2).

ATHEROSCLEROSIS

Elevated levels of Lp(a) have been associated with premature coronary heart disease (CHD) (8). Lipids accumulate in the intimal extracellular space, and in subendothelial monocyte-derived macrophages (foam cells) (9). Brown, et al, in a discussion of lipid lowering and plaque regression, reviewed pathological processes in preventing progression of coronary artery disease. Lipid accumulation, plaque fissures and vascular tone are all considered clinically critical aspects of plaque biology (9). The abnormal physiology of vascular spasm, lipid accumulation, and lesion rupture with thrombosis is dependent on the plasma lipoproteins and fibrinogen, not only in the chronic setting, but also over a relatively short period of time (10). Atherosclerosis and thrombosis may represent the remote and immediate consequences of, respectively, the same disease (11). The molecular connection between these two pathologic processes of the vascular endothelium certainly would include Lp(a). Cytotoxic and atherogenic oxidized LDL have been known to cause endothelial dysfunction (12). Lp(a), fibrinogen and various vasoregulatory molecules have been implicated.

We have long known of the association of elevated cholesterol levels and atherosclerotic disease. Cholesterol lowering has been associated with regression or no progression of focal coronary artery stenoses, a decrease in cardiac events, and improved endothelial-mediated coronary vasodilation (13). Recently, Gould, et al, observed that short-term cholesterol lowering (over 90 days) improves myocardial perfusion capacity, as demonstrated by decreases in size and severity of perfusion abnormalities by positive emission tomography (PET) after intravenous dipyridamole in patients with CAD. That study showed beneficial short-term effects of vigorous cholesterol lowering through control of exogenous fat intake (dietary fats) and cholesterol lowering medication (13). Though extracorporeal lipoprotein removal methods were not utilized, it is quite apparent that relatively short-term cholesterol lowering improves myocardial perfusion capacity.

MODULATION OF FIBRINOLYSIS

Atherosclerotic cardiovascular disease is associated with decreased fibrinolytic activity. Studies clearly indicate an inverse correlation between fibrinolytic activity and risk of coronary artery disease (14). The relationship between Lp(a) and fibrinolysis has been investigated because of the structural homology of Lp(a) to plasminogen. The increased incidence of atherosclerosis and elevated levels of Lp(a) may be due to suppression of normal fibrinolytic activity (6). Recent literature suggests that oxidized LDL (Ox-LDL) which accumulates in atherosclerotic arteries modulates the endothelial fibrinolytic system (15). Lipid products in Ox-LDL have been shown to impair endothelial fibrinolysis in vitro. Kugiyama and colleagues demonstrated that Ox-LDL stimulated plasminogen activator inhibitor-1 (PAI-1) release while it inhibited t-PA release from cultured human umbilical vein endothelial cells (15).

Lp(a) regulates plasmin generation and inhibition (6). Evidence has supported the theory that Lp(a), by molecular mimicry, competes with plasminogen for receptors (16). Miles, et al, suggest that competition of Lp(a) and plasminogen for cellular binding sites may contribute to the thrombotic and atherosclerotic risks associated with elevated Lp(a) levels (16). Work by Hajjar and colleagues supports this belief that Lp(a) interferes with endothelial cell fibrinolysis by inhibiting plasminogen binding and thereby affecting plasmin generation (3). Plasmin directly affects fibrinolysis (3).

ACUTE-PHASE REACTANT

Immunohistochemical findings demonstrate that plasma levels of Lp(a) can fluctuate as an acute-phase reactant (5). In an effort to clarify the significance of transient increases in Lp(a), investigators have studied patients with myocardial infarction and patients undergoing surgery. Acute-phase proteins, such as C-reactive protein, have been used to demonstrate the presence or absence of an acute-phase reaction. The acute-phase reaction is a response to a homeostasis disturbed by tissue injury, an infection, neoplastic growth, or immunological disorders.

Increased levels of Lp(a) observed during extracorporeal circulation may indicate that this particle is responding in an acute phase response mode (4). This logic is supported by the knowledge that CPB is known to activate a whole body inflammatory response. The purpose of this acute phase reaction is not known; however, future investigations of Lp(a) may provide insight. For example, Lp(a) may be a marker of biocompatability of extracorporeal devices, or provide insight on impaired fibrinolytic capacity of the patient.

Lp(a) AND PTCA

Although the role of serum cholesterol and Lp(a) remains unclear, new information is helping to elucidate several aspects of this LDL-like protein. It is clear that Lp(a) and LDL cholesterol are involved in the cellular mechanisms that contribute to restenosis after PTCA (17). The primary limitation of PTCA continues to be restenosis, which has been reported to occur in approximately 30% of the lesions (7). In 1992 it was reported that serum Lp(a) levels appear to be potent predictors of restenosis in subjects returning for arteriography after PTCA (17). In that report, Hearn and associates found that of several parameters studied, Lp(a) was the only significant independent predictor of restenosis after PTCA (17). Importantly, they documented progressively higher risk of restenosis with each quintile level of Lp(a), and their highest quintile level (40 to 120 mg/dl) correlated with a restenosis rate of 89% (17).

Yamaguchi, et al, investigated the effectiveness of LDL-apheresis in preventing restenosis after PTCA in what is called the LDL-apheresis Angioplasty Restenosis Trial (L-ART) (18). The authors conclude that intensive Lp(a) and LDL-lowering therapy is a practical method for preventing restenosis after PTCA. Furthermore, they found that when plasma Lp(a) reduction is insufficient, restenosis rates can be improved by more frequent and adequate LDL-apheresis (18).

Lp(a) AND CABG SURGERY

Serum Lp(a) is significantly associated with the degree of stenosis of saphenous vein grafts (19). At levels of 31.6 mg/dl or above, Hoff and associates found that 92% of the patients studied demonstrated vein graft stenosis (19).

Recently a group from Japan found that aggressive use of arterial grafts, intensive cholesterol-lowering drug therapy, and LDL-apheresis may be useful in patients with familial hypercholesterolemia. (20)

Lipoproteins are clearly involved with the long term patency of bypass grafts. In addition to the long term consequences of changes in lipoproteins and their metabolism (chronic lipid deposition and subsequent stenosis), there most likely exists short term consequences. Lipid molecules have a profound effect on the cellular mechanisms that are integral to atherogenesis. As previously mentioned, Lp(a) may have a regulatory role in thrombogenesis by interfering with the physiological functions of plasminogen.

REMOVAL OF LIPOPROTEIN(a)

Of the 1.5 million myocardial infarctions that occur in the United States each year, over 500,000 result in death (21). Since Lp(a) contributes so profoundly to CAD and even appears to be a predictor of restenosis after intervention, it would be logical to add extracorporeal lipoprotein removal techniques to current pharmacological and lifestyle modification efforts.

Heparin-induced extracorporeal lipoprotein precipitate (HELP) is an effective apheresis procedure for lowering lipid levels (22). A group in Germany investigated changes in Lp(a) after HELP-LDL-apheresis and concluded that it was an effective procedure for simultaneous reduction of both LDL and Lp(a) levels while retaining protective HDL (7). A single treatment resulted in 62% decrease in concentration of Lp(a) and 60% decrease in LDL-cholesterol (7). Patients were generally treated at intervals of between 7 and 14 days. Repeated elimination of Lp(a) did not lead to an induction in its synthesis (7).

In addition to Help-LDL-apheresis, which involves precipitation of apo B-containing lipoproteins with heparin at a low pH, there also exist several other techniques for lipoprotein removal. Matsuda and associates recently reviewed currently available LDL-apheresis systems, including thermofiltration, double filtration, LDL chemical adsorption (dextran sulfate), plasma exchange, immunoadsorption, and HELP-LDL-apheresis

(23). They concur that applications of these technologies once every two weeks to once a month can reduce LDL, spare HDL, and reduce triglyceride and fibrinogen levels depending on the techniques employed (23). The multiparameter assessment of these six LDL-apheresis systems included the observation that the treatment of hyperlipidemic patients has proven to be effective, safe, and economically feasible, regardless of the system used (23).

CONSIDERATIONS FOR CARDIOVASCULAR PERFUSION

With regards to cardiovascular perfusion, previous studies have documented the effects of CPB on the formed elements of the blood. The non-physiologic state does profoundly affect erythrocytes, leukocytes and thrombocytes. These responses have been investigated for decades and continue to be scrutinized in an effort to improve techniques integral to CPB (i.e., hypothermia, extracorporeal circulation, artificial oxygenation). Studies have recently included information regarding plasma proteins. Serum protein changes during CPB have been implicated to affect host defense mechanisms (24). Despite these recent endeavors to further knowledge on the effects of extracorporeal circulation, only one study to date investigated the specific effects on lipoproteins (4).

What is known of LDL removal during CPB? LDL-apheresis (plasma separator and LDL adsorber) of hypercholesterolemic patients during CPB has been conducted in a group of eight patients in Japan (25). To prevent excessive influx of LDL into subendothelium, Miyawaki and colleagues, successfully lowered LDL levels sufficiently before reperfusion in an effort to counter ischemic-reperfusion injury (25). They observed no significant differences between treatment (n=6) and control groups (n=41) in blood loss and blood coagulation data (25).

CONCLUSION

Lp(a) is an LDL-like particle with a glycoprotein, apo(a), that has structural homology to plasminogen. The physiological role of Lp(a) has yet to be established. Lp(a) is considered to be linked to atherosclerotic vascular disease, associated with atherothrombotic lesions, and involved in acute phase responses.

Lp(a) appears to be a molecular link between the chronic pathologic consequences of increased oxidized LDL (decreased vascular flow from chronic lipid deposition and stenosis) and the acute pathologic consequence of coronary artery disease, thrombogenesis. Though this link has not been clearly identified, it seems logical that the same culprit, Lp(a), would be involved with both phenomena.

There is a well documented high incidence of vascular disease in Western societies. It is clear that lowering lipid levels is associated with a decreased progression of vascular disease and possibly with regression of disease.

Practically speaking, consistent compliance to lifestyle and diet modifications is not *always* likely. Pharmacologic agents, though effective, do have some limitations (i.e., patient compliance, effectiveness on certain individuals, indicated risks). Therefore, it seems appropriate to investigate other methods of lipid reduction, namely lipid apheresis. Extracorporeal lipoprotein removal techniques indeed merit further investigation. In part, investigation is warranted because these techniques would have profound effects on patients with known hyper-cholesterolemia; and, more importantly, these techniques may have a role as *adjunctive therapy* in the treatment of patients in the acute stages of coronary artery disease.

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