Correlation Study of Pulmonary Embolism and High-density Lipoprotein Cholesterol

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ABSTRACT

Background: It is currently thought that pulmonary embolism and deep vein thrombosis are different manifestations of the same pathological process of venous thromboembolism. Venous thromboembolism has a negative correlation with high-density lipoprotein cholesterol.

Hypothesis: Pulmonary embolism has a negative correlation with the level of high-density lipoprotein cholesterol.

Methods: A total of 90 patients with pulmonary embolism, diagnosed and treated at a single center, were retrospectively analyzed for the present study. Among them were 57 cases of pulmonary arterial trunk embolism in group A and 33 cases of pulmonary arterial non-trunk embolism in group B.

Results: The results showed that the level of high-density lipoprotein cholesterol decreased markedly in patients with pulmonary arterial trunk embolism as compared to those with pulmonary arterial non-trunk embolism. A stepwise logistic regression analysis was performed upon the relationship between pulmonary arterial trunk embolism and multiple factors. The results showed that a pulmonary arterial trunk embolism had a negative correlation with the level of high-density lipoprotein cholesterol and a positive correlation with triglyceride and high sensitivity C-reactive protein.

Conclusions: Pulmonary arterial trunk embolism is negatively correlated with the level of high-density lipoprotein cholesterol.

Introduction

As one of the more commonly encountered diseases in medicine, pulmonary embolism (PE) is a major cause of mortality and disability in clinical practice. A higher rate of mortality and disability is found for pulmonary arterial trunk embolism. But PE (including pulmonary arterial trunk embolism) has no characteristic clinical symptoms so it is often misdiagnosed or under-diagnosed. As a result, patients lose an optimal therapeutic opportunity and ultimately can become untreatable. Currently blood gas analysis and the D-dimer are 2 parameters for a preliminary screen of PE. The diagnosis can be confirmed by either pulmonary vascular contrast computed tomography (CT) or a ventilation/perfusion (V/Q) scan; but we cannot say we really understood it. Deep vein thrombosis (DVT) is one major risk factor of PE. The modern consensus is to treat PE and DVT as different manifestations of the same pathological process of venous thromboembolism (VTE). Some studies reported a negative correlation between VTE and high-density lipoprotein (HDL).¹⁻³ During clinical practice, the authors have noticed a declining trend of high-density lipoprotein cholesterol (HDL-C) in patients with pulmonary arterial trunk embolism. It was surmised that there was some correlation between the level of HDL-C and the clinical characteristics of PE. The clinical profiles and laboratory testing parameters (including HDL-C) of patients

with acute PE were retrospectively analyzed to ascertain this correlation.

Design and Methods

Study Subjects

A total of 90 patients with acute PE were admitted into the Beijing Friendship Hospital affiliated to Capital Medical University during the period of January 2002 to August 2008. Inclusion criteria included: age 25 to 80 years old of either gender, onset of PE-related symptoms (dyspnea, short breath palpitation, etc.) within 14 days, pulmonary vascular contrast CT demonstrating the presence of pulmonary arterial thrombus, and an above-normal level of D-dimer. Exclusion criteria included: medications of lipid-lowering, antiplatelet, and anticoagulant agents, hormones, pregnancy, recent trauma and surgery, long-term bedridden for various causes, cancer, coronary heart disease, myocardiopathy, rheumatic heart disease, heart failure, chronic lung diseases, hepatic and renal diseases, and immune diseases.

Study Parameters

Demographic data of enrolled patients (age, gender, and smoking status), concurrent basal diseases (including hypertension, diabetes mellitus, DVT, and ischemic cerebrovascular disease), HDL-C, low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol

(TC), white blood cell (WBC) count, blood platelet count, hemoglobin, fasting blood glucose (FBG), random blood glucose, high sensitivity C-reactive protein (hs-CRP), P_{aO_2} and S_{pO_2} under non-oxygen inhalation, and D-dimer. All of the above testing parameters were the results of blood samples at day 1 of hospitalization. Triglycerides and TC are measured by enzymatic methods (CHOD-PAP and GPO-PAP). High-density lipoprotein cholesterol and LDL-C are measured by catalase HDL-C assay and catalase LDL-C assay methods. High sensitivity C-reactive protein is measured by the latex increasing immunity nephelometry method.

Statistical Processing

The statistic software pack SPSS 11.5 (SPSS, Chicago, IL) was employed for statistical processing. The qualitative data were analyzed with an χ^2 test and expressed as mean $\pm$ SD. A *t* test was performed for the intergroup difference.

Results

There were 57 cases of pulmonary arterial trunk embolism in group A and 33 cases of pulmonary arterial non-trunk embolism in group B.

A comparison of the demographic data and the basal diseases in group A vs group B is presented in Table 1. The mean HDL-C was 34.5 ± 8.5 mg/dL in group A and 44.1 ± 6.4 mg/dL in group B. The former was significantly lower than the latter ($P = 0.000$; Table 2). The logistic regression analyses were performed upon the relationship between the pulmonary arterial trunk embolism and the following variables: age, gender, smoking, history of hypertension, diabetes mellitus, DVT, HDL-C (lower than normal if male <40 mg/dL or female <50 mg/dL), LDL, TC, TG, body mass index (BMI; above normal if BMI >25 kg/m²), WBC count, blood platelet count, FBG (impaired FBG if FBG >108 mg/dL), and hs-CRP (above normal if hs-CRP >3 mg/L). The results showed

Table 1. Comparison of Demographic Data and Basal Diseases in Group A vs Group B

	Group A	Group B	P Value
Demographic data			
Age	65.00 ± 11.94	59.21 ± 13.76	0.039
Gender (M/F)	26/31	16/17	0.792
Smoking (Y/N)	17/40	8/25	0.569
Complicated with basal diseases			
Hypertension (Y/N)	35/22	18/15	0.524
DM (Y/N)	12/45	3/30	0.142
DVT (Y/N)	24/33	9/24	0.159
Ischemic cerebrovascular disease (Y/N)	15/42	2/31	0.018
Presentation to symptom onset time	6.00 ± 4.99	5.00 ± 4.54	0.36

Table 2. Comparison of Parameters Between Group A and Group B

	Group A	Group B	P Value
HDL-C (mg/dL)	34.50 ± 8.51	44.13 ± 6.44	0.000
LDL-C (mg/dL)	107.63 ± 50.90	128.99 ± 57.06	0.004
TG (mg/dL)	130.49 ± 58.69	119.72 ± 49.86	0.379
TC (mg/dL)	175.59 ± 41.09	198.85 ± 33.24	0.007
BMI (kg/m ²)	25.30 ± 3.86	26.49 ± 4.25	0.233
FBG (mg/dL)	105.91 ± 35.40	97.14 ± 20.17	...
Log FBG (mg/dL)	2.00 ± 0.13	1.98 ± 0.09	0.376
hs-CRP (mg/L)	9.58 ± 4.65	7.98 ± 7.45	0.249

Table 3. Logistic Regression Analyses of the Relationship Between Pulmonary Arterial Trunk Embolism and Several Variables

		B	SE	Wald	df	Sig	Exp(B)
Step 1 ^a	HDL11	−2.257	0.642	12.369	1	0.000	0.105
	TG11	2.117	0.902	5.508	1	0.019	8.309
	CRP11	2.191	0.799	7.514	1	0.006	8.945
	Constant	−3.760	2.242	2.812	1	0.094	0.023

^a Variable(s) entered on step 1: HDL11, TG11, CRP11.

Figure 1. Receiver-operating characteristics curve demonstrating concordance of HDL-C level and the patients with pulmonary arterial non-trunk embolism.

that there was a correlation between pulmonary arterial trunk embolism and the levels of HDL-C, TG, and hs-CRP; a negative correlation between pulmonary arterial trunk embolism and the levels of HDL-C; and a positive correlation between TG and hs-CRP (Table 3). An HDL-C >38.4 mg/dL was taken as the exclusion criterion for pulmonary arterial trunk embolism with a sensitivity of 88% and specificity of 74% (Figure 1).

Discussion

As demonstrated by the present study, patients with new-onset pulmonary arterial trunk embolism had a lower level of HDL-C. For patients with new-onset pulmonary arterial non-trunk embolism with HDL-C >38.4 mg/dL, the sensitivity was 88% and specificity 74%. The study results also suggested that, after excluding the influences of other factors, the patients with new-onset pulmonary arterial trunk embolism had a higher level of TG. It implied that there was a correlation between dyslipidemia and pulmonary embolism.

The levels of HDL-C correlated with the new-onset cases of pulmonary arterial trunk embolism. The previous meta-analytic results showed that the patients with a high TG and a low HDL-C were likely to suffer VTE.¹ There was correlation between VTE and metabolic syndrome (including a low-level of HDL-C).^{2–4} The level of HDL-C was also lower in patients with recurrent venous embolism.⁵ All these suggested that the VTE patients had a lower level of HDL. The results of the present study served to further confirm those of previous studies. It was simultaneously found that the patients with new-onset pulmonary arterial trunk embolism had a lower level of HDL-C.

High-density lipoprotein participates in the process of reverse transport of cholesterol. It has a variety of functions, such as anti-inflammation, antioxidation, and protection of the vascular endothelium. As demonstrated by a large body of epidemiological data, there was a negative correlation between the level of HDL-C and the occurrence of coronary heart disease. Some studies showed that the level of HDL-C was probably the manifestation of one kind of pathological state. The patients with pulmonary arterial thrombus had a higher probability of suffering coronary atherosclerosis and acute myocardial infarction.^{6,7} Atherosclerosis is also a risk factor of pulmonary arterial thrombosis.⁸ The patients with atherosclerosis had a higher probability of suffering PE. Atherosclerosis and PE may share some common risk factors.^{6–8} The formation of venous thrombosis is mainly related with the activation of clotting factors and the stasis of venous blood flow. In addition, platelets also play a partial role in the formation of venous thrombosis. The result of current research suggested that the abnormal metabolism of blood lipids, including a reduced level of HDL-C and an elevated level of TG, affected the functions of vascular endothelium and increased the activity of platelets^{9,10} resulting in abnormal coagulatory functions and promoting inflammatory responses.^{11–13} High-density lipoprotein inhibited the apoptosis of endothelial cells through the regulation of their proliferation^{14,15} so as to maintain their structural integrity. In the meantime, HDL could boost the production of eNOS in endothelial cells so as to further increase the release of nitric oxide (NO) and enhance the bioavailability of NO.^{16–18} Thus HDL could not only improve the vasodilatory function, but also inhibit the initiator of an

extrinsic pathway of blood coagulation—tissue factor^{19,20} and suppress the activity of clotting factors, Va and VIIIa.²¹

Animal experiments have confirmed that HDL could inhibit the in vivo activity of platelets both directly and indirectly. It inhibits the platelet function through suppressing the release of platelet activating factor. Studies of HDL infusions into cholesterol-fed rabbits indicate that HDL upregulates endothelial cell thrombomodulin, which is an additional anticoagulant factor.²² Therefore the reduction of HDL maybe one of the initiating factors for pulmonary arterial trunk embolism. As reported by Yang et al,²³ the level of HDL became elevated in VTE patients after heparin therapy. It suggested that the level of HDL-C increased somewhat when the body thrombus load improved. Pulmonary arterial trunk embolism may trigger a series of body stress responses that result in an abnormal metabolism of lipid metabolism, including a reduced level of HDL-C. Currently it is not known which of the 2, the pulmonary arterial trunk embolism or HDL-C, comes first. Moreover, HDL inhibits thrombus formation in vivo within a time frame relevant to acute thrombosis.²⁴ But patients with pulmonary arterial trunk embolism who had an HDL-C >38.4 mg/dL were relatively few. It has been suggested that patients with high HDL-C levels could have active anticoagulation factors when a massive PE occurred, so that some embolus autolyzed and only obstructed subsegmental pulmonary artery branches. Therefore, the levels of HDL-C are likely to help screen for pulmonary arterial trunk embolism in another way.

Within the present study, the *t* test results of 2 independent samples revealed that the patients with pulmonary arterial trunk embolism tended to be of an advanced age. But the regression analysis demonstrated no correlation between age and pulmonary arterial trunk embolism. This aspect may be explained by the fact that a correlation exists between age and thrombosis. On the other hand, it probably has something to do with the fact that elderly patients are more likely to have dyslipidemia. The *t* test results of 2 independent samples revealed that a higher percentage of patients with pulmonary arterial trunk embolism had ischemic cerebral disease. But the regression analysis demonstrated no direct correlation between ischemic cerebral disease and pulmonary arterial trunk embolism. This is probably related to ischemic cerebral disease and dyslipidemia.^{25,26} Dyslipidemia, including a reduced level of HDL-C, is involved in both the pathological processes of pulmonary arterial thrombosis and atherosclerosis. And there is some correlation between pulmonary arterial thrombosis and atherosclerosis.

Meanwhile, previous studies have demonstrated a negative correlation between the level of HDL-C and the occurrence of coronary heart disease. The present study also revealed that the patients with pulmonary arterial trunk

embolism had a higher tendency of death, and the HDL-C levels tended to be lower than it is in the survivor. Further studies are needed to confirm whether the elevation of HDL-C is able to prevent a second venous thrombosis in VTE patients and whether the elevation of HDL-C is able to improve prognosis in PE patients. We may have only observed a vague phenomenon between HDL-C and pulmonary embolism, but we think more studies are needed to reveal a substantial relationship.

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