Cholesterol in pleural exudates depends mainly on increased capillary permeability

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Pleural fluid (PF) cholesterol is a useful parameter to differentiate between pleural transudates and exudates, although the pathophysiologic mechanisms for its increase in exudates are not fully understood. We aim to elucidate the cause of this increase by analyzing the levels of cholesterol—high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), apolipoprotein A (ApoA), and apolipoprotein B (ApoB)—in PF and blood as well as the number of leucocytes and red cells in the PF. We studied 259 patients with pleural effusion (57 transudates and 202 exudates). The correlations of the pleural and serum (S) levels of these parameters were analyzed, with the pleural cholesterol fractions as the dependent variables and their levels in blood and the pleural/serum protein ratio (P/S prot ratio) as the independent variables. The pleural fluid cholesterol levels (PFCHOL) correlated with their blood levels and the capillary permeability ($r = 0.885$). No significant differences were found between the percentage of LDL, with regard to total cholesterol in the serum (SCHOL), and the same percentage in the exudates, between the PF/S LDL ratio (0.46) and the PF/S CHOL ratio (0.48), or between the PF/S ApoB ratio and the PF/S LDL ratio. The percentage of PF cholesterol bound to HDL and LDL was significantly higher (91.9%) than in the blood (90%). No significant correlations were found between any of the lipids studied and the number of erythrocytes and leucocytes. In conclusion, the PFCHOL may be predicted from the SCHOL, and the capillary permeability may be reflected by the PF/S prot ratio. (Translational Research 2010;155:178–184)

Abbreviations: ApoA = apolipoprotein A; ApoB = apolipoprotein B; HDL = high density lipoprotein; LDL = low density lipoprotein; PFCHOL = concentration of cholesterol in pleural fluid; PF = pleural fluid; PFLDL = PF low-density lipoprotein; PF/S prot ratio = PF total protein and S total protein ratio; S = serum; SCHOL = concentration of cholesterol in the serum; SD = standard deviation; SLDL = LDL cholesterol level in blood

Pleural effusion is a common finding in clinical practice. The first step in the diagnosis of the causative pathology is to determine whether the effusion is a transudate or an exudate. The concentration of cholesterol in pleural fluid (PFCHOL) is useful to distinguish between the two,[1-10] but the reason why it is higher in exudates has not been totally clear. One possibility is that the main source of cholesterol in pleural fluid (PF) is the degeneration of extravasated leucocytes and erythrocytes, which are more numerous in exudates

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AT A GLANCE COMMENTARY

Valdés L, et al.

Background

Pleural fluid (PF) cholesterol is a useful parameter to differentiate between pleural transudates and exudates, although the pathophysiologic mechanisms for its increase in exudates are not fully understood. Furthermore, the reason why it is higher in exudates is not totally clear.

Translational Significance

Until now, few works have studied the role that the apolipoprotein might have in the study of this mechanism. From our work, we concluded that PF cholesterol levels depend almost exclusively on their blood levels and the capillary permeability, as measured by the PF-to-serum total protein ratio.

than in transudates; a second possibility is that the passage of circulating cholesterol from the capillaries to the pleural cavity is facilitated, like that of protein,[11] by the increase in capillary permeability, which gives rise to exudates.

The findings in previous studies suggest that the increase in cholesterol levels in pleural exudates is probably caused by the increase in capillary permeability, particularly at the expense of the low-density lipoproteins (LDLs).[2,4,12] The results of other studies seem to support this same pathophysiologic mechanism, but they suggest some metabolic changes in the lipoproteins may play a part once they enter the pleural space.[13] However, until now, few works have studied the role that apolipoprotein might have in the study of this mechanism.[14]

The purpose of this study is to find the origin of the high levels of cholesterol in pleural exudates. For this reason, the determination of the high-density lipoprotein (HDL) ,and LDL-cholesterol fractions as well as apolipoprotein A (ApoA) and apolipoprotein B (ApoB), in both PF and blood (serum [S]), in addition to the number of erythrocytes and leucocytes in the PF, could be useful. Our working hypothesis was that the increase in capillary permeability would entail higher PFCHOL levels.

MATERIAL AND METHODS

All patients admitted to the departments of chest medicine and internal medicine during the last 2.5 years were studied prospectively. Those who had a chylothorax or pseudochylothorax, or who had been treated with diuretics in the previous days, were excluded. Those definitely included were classified into transudates or exudates in accordance with biochemical criteria and their clinical picture.[15] The study protocol was approved by the Human Studies Review Board of our center, and all patients gave informed consent.

The PF and blood samples were drawn at the same time, after the patient fasted for more than 12 h. The PF samples were sent routinely to microbiology, cytology, and biochemistry laboratories for analysis.

The total cholesterol concentration was determined on an Advia 2400 analyzer (BAYER Healthcare, Morristown, NJ) using their Cholesterol method (BAYER Healthcare). Cholesterol esters were hydrolyzed to cholesterol and free fatty acids by cholesterol esterase; in the presence of oxygen, the cholesterol was converted by cholesterol oxidase into 4—cholesten-3-one and hydrogen peroxide, and a peroxidase catalyzed the formation of a colored complex of peroxide, 4—aminophenazone, and phenol determined by measuring the absorbance at 505 nm.

Cholesterol fractions were determined by electrophoresis on a buffered agarose gel using a REP Cholesterol Profile (HELENA Laboratories, Mount Waverly, Australia). Lipoprotein bands were incubated with a mixture of cholesterol esterase, cholesterol dehydrogenase, and diaphorase and were quantified by the determination of optical density at 570 nm in an EDC densitometer (HELENA Laboratories).

ApoA-I and ApoB were determined by immunonephelometry in a BNA-II nephelometer (Dade Behring Marburg Gmbh, Deerfield, Ill), using N antiserum for human ApoA-I and ApoB (Dade Behring Marburg Gmbh).

Statistical analyses. Data are reported as means ± standard deviations (SDs). Kolmogorov–Smirnov tests were used to check distributional normality. The significance of differences between means was estimated by Student *t* tests. PF lipid and apolipoprotein levels were regressed on the corresponding S levels and were analyzed by multivariable linear regression on the corresponding S levels together with the ratio between PF total protein and S total protein (PF/S prot ratio, with similar expressions for other ratios between PF and S parameters). The analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, Ill) and Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, Wash). The criterion for statistical significance was $P < 0.05$.

RESULTS

The study group comprised 57 patients with transudates and 202 patients with exudates (Table I). Total, LDL, and HDL cholesterol levels, as well as ApoA and ApoB concentrations, were all lower in PF than in S, and the levels measured in PF were all lower in transudates than in exudates (Table II). All these PF analytes correlated