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Brief Communication

Relationship of high CH50 level and interruption of cascade reaction of complement mRNA expression in acute venous thromboembolism patients

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Abstract: In patients with pulmonary embolism (PE), forepart components of complements were activated. However there are interruption/decrease of cascade reaction and cytolytic effects in complement system. This study detected CRP, CH50, C3 and C4 levels in patients with venous thromboembolism (VTE) and compare with the imbalance of complement associated gene mRNA expression in PE patients. There was significant increase of CH50 in acute VTE patients. Even though CH50 increased significantly in acute VTE patients and had a relatively high sensitivity, cytolytic effects of complements might decrease, based on the genomics results of complement cascade reactions imbalance/interruption and increased total complements in VTE patients.

Keywords: CH50, complement, pulmonary embolism

Introduction

Venous thromboembolism (VTE) consists of pulmonary embolism (PE) and deep venous thrombosis (DVT). PE included acute pulmonary embolism (APE) and chronic thromboembolic pulmonary hypertension (CTEPH). Among them, APE has become one of the global essential healthy issues all over the world already, due to its high rate of morbidity, mortality, misdiagnosis and missed diagnosis [1]. Since the first guideline of VTE diagnosis, treatment and prophylaxis came out in 1995, nine editions of guideline have been raised by ACCP till 2012. The latest ninth edition brought forward the risk factors of VTE, such as infection, malignant tumor, autoimmune disease, trauma, surgery, advanced age and so on [2]. Smeeth et al have reported that the occurrence of VTE was associated with infection, particularly in the first two weeks after infection [3]. We have reported virus-like microorganisms observed in cytoplasm and intercellular substance of lymphocytes from peripheral venous blood in VTE patients with pulmonary hypertension and T cell immune dysfunction/disorder [4]. We also observed rod-shaped bacteria like microorganisms in apoptotic phagocytes from peripheral venous blood in patients with repeated PE/DVT and T cell immune dysfunction/disorder [5]. Besides, we also found thrombi in veins of multiple organs (such as pulmonary artery, kidney, liver and pancreas) in a patient who died of SARS [6]. All these findings indicated that onset of VTE has an involvement of microorganisms infections. What's more, we discovered natural killer cell dysfunctions in APE patients [7] and CD3+/CD8+ T lymphocyte dysfunctions in APE and CTEPH patients [8, 9], suggesting that decreasing functions of immune cells in innate and adaptive immune systems were associated with occurrence of VTE.

Complements are core molecules of innate immune system, involved in both innate and adaptive immunity. Complements consist of nine components, together with factors associated with complement activities and corresponding regulations, are termed complement system. The activation of complement system renders cascade reaction. The common end of the activation pathway forms membrane attack complex, which exerts cytolytic effect. Complement system contains 30 kinds of proteins, but not all of them are detected routinely in clinical practice. Authors of this article have dete-

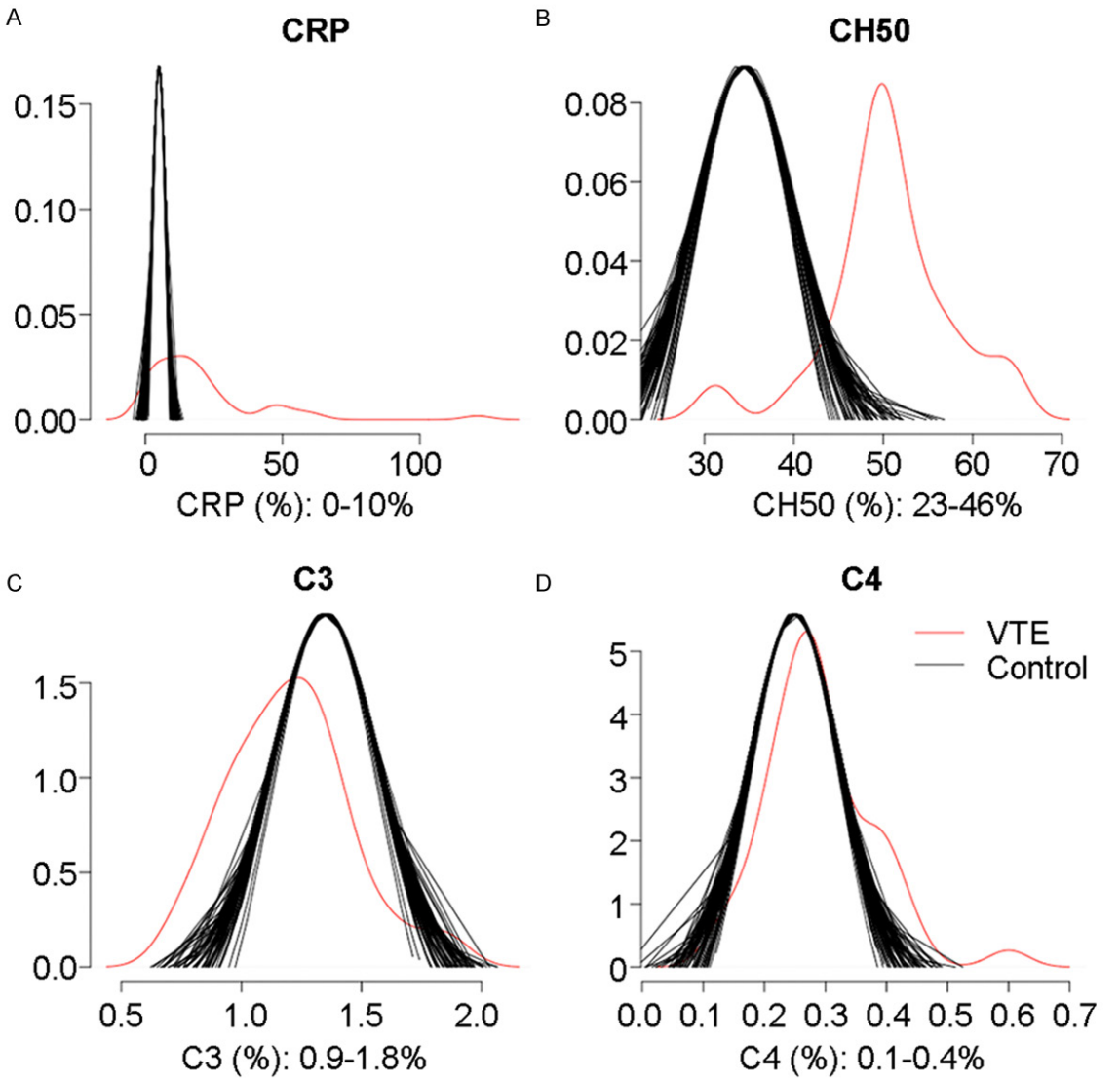

Figure 1. A. Compared with normal range, CRP increased significantly in VTE patients. Density curve of VTE patients was flatter and shifted to the right significantly ($P < 0.01$). B. Compared with normal range, CH50 increased and density curve shifted to the right significantly in VTE patients ($P < 0.01$). C. C3 was almost within the normal range and density curve shifted slightly to the left in VTE patients. D. C4 was almost within the normal range and density curve shifted slightly to the right in VTE patients.

cted the differences of complements associated mRNA expressions between PE group (20 symptomatic PE patients) and control group (20 healthy controls) via human whole genome sequencing technology [10].

In PE patients, mRNA expression of forepart components and complement receptors associated genes was significantly upregulated, which indicated that forepart components of complements were activated. Downregulation of mRNA expressions of backpart components associated genes in the terminal of complement activation pathway and imbalance of mRNA expression of complement regulatory protein associated genes indicated interruption/decrease of cascade reaction and cytolytic effects in complement system.

This study detected CRP, CH50, C3 and C4 levels in VTE patients and compare with the imbalance of complement associated gene mRNA expression in PE patients.

Materials and methods

Fourty-five patients diagnosed with acute VTE (12 PE patients and 33 DVT patients) were

enrolled in this study. Patients were placed in a sitting position, and a morning fasting peripheral blood of 2 ml was collected from median cubital vein. CH50 was detected with liposome immune assay (Beckmann DxC-800 fully automatic biochemical analyzer, USA; Reagents: Wako Pure Chemical Industries, Ltd., Japan). CRP, C3 and C4 were detected with immunonephelometry (BNII system, Siemens AG, Germany; Reagents: Siemens Healthcare Diagnostics Products GmbH). Density curve was delineated with R software.

Results and discussion

The CRP level increased in 31/45 patients, and remained normal in 14/45 patients; the CH50 level increased in 38/45 patients, and remained normal in 7/45 patients; the C3 level decreased in 3/45 patients, increased in 2/45 patients, and remained normal in 40/45 patients; the C4 level increased in 4/45 patients, and remained normal in 40/45 patients. The density curves of CRP, CH50, C3 and C4 were shown in **Figure 1A-D** respectively.

CRP, C3 and C4 are positive acute phase proteins. CRP is synthesized in liver when wound or inflammation cause tissue damages. It increases within 6-8 hours after infection, and peaked within 24-48 hours. CRP can activate complement, and complement activation is an important event in inflammatory response. CH50 reflects the activities of C1-C9 via classic pathway, which needs adaptive immunity after pathogens are recognized by antibodies. CH50 is similar with CRP, with a high sensitivity of inflammation. CH50 and CRP increased significantly in this study, which indicated that VTE patients were at a state of acute inflammatory reactions. C3 and C4 levels in VTE patients had no significant change in this study.

Associated genes mRNA expressions of forepart components and receptors of complements in symptomatic PE patient were significantly upregulated, indicating the activation of forepart components of complements. Downregulation of backpart components associated genes mRNA expressions in terminal of complement activation pathway and imbalance of complement regulatory proteins associated genes mRNA expressions indicated interruption/decrease of cascade reactions and cytolytic effects in complement system. There was significant increase of CH50 in acute VTE patients, indicating increasing synthesis of total complements, which might be associated with activation of forepart components of complements. Even though CH50 increased significantly in acute VTE patients and had a relatively high sensitivity, cytolytic effects of complements might decrease, based on the genomics results of complement cascade reactions imbalance/interruption and increased total complements in VTE patients.

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Disclosure of conflict of interest

None.

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