A dyspnea patient with abnormal prolonged prothrombin time and activated partial thromboplstin time, but without bleeding symptoms

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ABSTRACT A patient with erythrocytosis secondary to chronic obstructive pulmonary disease (COPD) was admitted to hospital because of dyspnea. The coagulation tests revealed abnormal prolonged prothrombin time (PT) and activated partial thromboplstin time (APTT), however, it could not be explained by the patient's medical history or physical signs of coagulation disorder. High hematocrit (Hct), which leads to reduced plasma-to-anticoagulant rate and increased final plasma anticoagulant concentration, was identified as the reason for false prolongation of PT and APTT.

KEY WORDS PT; APTT; Hct; erythrocytosis; plasma-to-anticoagulant rate

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Case report

A previously 45-year-old patient with established Chronic Obstructive Pulmonary Disease (COPD) ten years ago was admitted to our hospital, complaining of a gradually aggravating dyspnea during the past three years. Instead of abstaining from smoking and receiving any further treatment, he averaged 20 cigarettes a day after COPD establishment, which directly led to his dyspnea three years ago. On admission, physical examination revealed a typical barrel chest with a larger thoracic anterior-posterior diameter and a widen intercostal space.

The laboratory investigations revealed: RBC 8.37×10^{12}/L; WBC 7.21×10^{9}/L; PLT 212×10^{9}/L; Hb 232 g/L; Hct 75.3%; Creatinine (Cr) 152 μmol/L (Reference interval: 44-133 μmol/L), and other indexes in hepatic function examination remained normal; Arterial oxygen saturation (SaO_2) 86%; FEV_1 41%. Based on these findings, the diagnosis of COPD and secondary erythrocytosis were made.

The following test on coagulation function was performed on STA-R Evolution automated coagulation analyzer (Diagnostica-Stago, Inc., Parsippany, New Jersey, USA) with corresponding reagents, and the results revealed a prolongation of PT at 24.7 s (Reference interval: 8-14 s) and APTT at 71.7 s (Reference interval: 31.5-43.5 s). No abnormality was showed in TT, Fib or D-dimer. To our surprise, the patient had neither symptoms nor family history or prior personal history of bleeding during the past three months, and did not receive any anticoagulant therapy in the last month. No hemolytic reaction or lipemia was perceived by the unaided eye. To avoid any detecting error, the tests were run again and showed a similar result with PT 25.3 s and APTT 69.5 s. While the clinicians maintained a high index of suspicion for the result that whether there is anything wrong with the vacuum blood tube or during the process of blood collecting, another sample was collected smoothly on the second day with a similar result of 25.0 s in PT and 70.1 s in APTT.

Discussion

As the screening tests for coagulopathy diseases and monitoring approach for anticoagulants treatment, PT and APTT reflect the integrity of the extrinsic and endogenous pathways of the procoagulant cascade, respectively (1). In this case, the abnormal prolonged PT and APTT seems not attributed to COPD, since previous reports has shown that the coagulation changes were small amount in COPD patients (2). Further investigation revealed that the patient presented no bleeding

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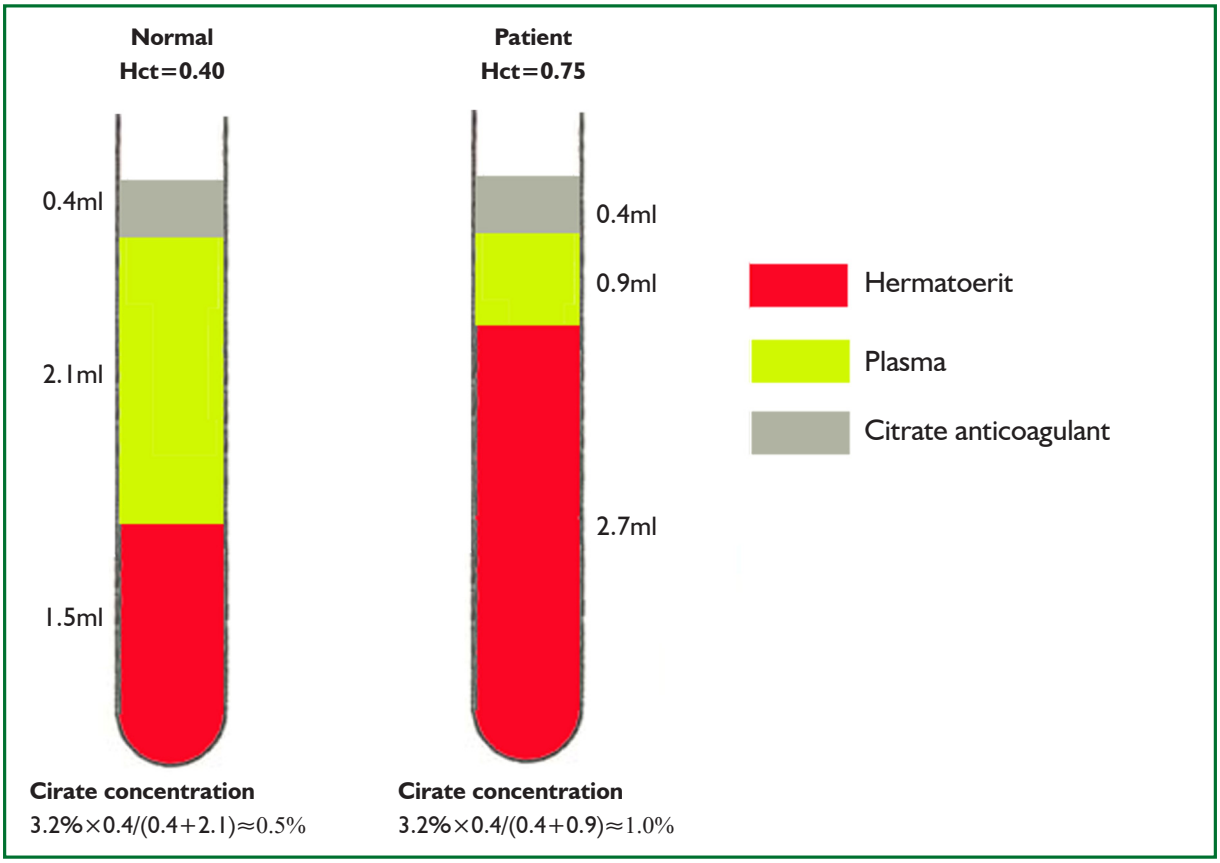

Figure 1. The effect of hematocrit on relative volume of citrate anticoagulant in blood collection tube

symptoms, had no family history of bleeding disorder, as well as anticoagulants treatment histories. Therefore, we speculated the abnormalities of PT and APTT were attributed to analytical errors or pre-analytical errors. The former was excluded soon after we seriously analyzed the same specimen again, since both PT and APTT were similar with previous test results. To exclude the pre-analytical errors, such as test tubes' quality, blood collection, specimen transportation and storage condition (3), a new sample test was asked. According to the quality control requirements of blood coagulation experiment (4), a new sample with serious collection, transportation and storage was analyzed, however, consistent with previous results; abnormal PT and APTT were observed. In summary, the tests results were insignificant regardless of the same specimen or new ones. Further, we hypothesis that the preexisting hematologic conditions, including hyperbilirubinemia, hyperlipidemia and hemolysis (5), may explained the prolonged PT and APTT. However, this possibility was easily excluded, as for no visible hemolysis, hyperbilirubinemia, hyperlipidemia to naked eye was seen, and the laboratory test found neither hyperbilirubinemia nor hyperlipidemia.

The main cause of the false prolongation was of the significantly increased hematocrit (Hct). In normal circumstances, a 3.2% citrate solution was used in the vacuum blood tubes prevent the activation. The mechanism under the anticoagulation effect of citrate was acted by their irreversible binding ability to plasma calcium, an essential element of procoagulant cascade (6). For patients with typical hematocrits (35%-50%), the volume of anticoagulant to whole blood will be in the proper 1:9, and to plasma will be approximately 1:5 ratios (suppose the hematocrit was 40%) (Figure 1, left). Thus, the final citrate concentration under this condition is approximately 0.5%. During PT and APTT testing, an additional calcium, often contain in the analytical reagent, is added to plasma to neutralize the anticoagulation effects of citrate, thus allowed plasma to clot in the present of extrinsic (phospholipids) or intrinsic (thromboplastin) pathway activator. In this case, due to impaired lung function caused by COPD, the patient's hematocrit was 75.3%, which markedly exceeded its upper reference limits. The volume ratio of anticoagulant to plasma was approximately 1:2, failed to fall into the proper 1:5 ratio (Figure 1, right). Under such condition, the citrate sodium would be 1.0%. Obviously, the excessive citrate sodium in plasma will weaken the procoagulant activity of PT and APTT reagent by reducing the availability of

assay-added calcium and consequently result in an artifactual prolongation of PT and APTT.

According to CLSI guidelines, for patients with hematocrits of more than 55%, the ratio of anticoagulant and the plasma should be adjusted to yield more reliable results (7). To correct the ratio, 0.20 ml of citrate was discarded from collection tube (the total volume of citrate in collection tube was 0.4 ml) before blood collection, and the results showed that PT and APTT values were 11.3 s and 35.7 s, respectively.

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