Scientific Research Publishing

Open Journal of Anesthesiology, 2024, 14, 145-149
https://www.scirp.org/journal/ojanes
ISSN Online: 2164-5558
ISSN Print: 2164-5531

# Abnormal ACT in a Patient with Prekallikrein Deficiency Undergoing Cardiopulmonary Bypass

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**How to cite this paper:** Fuertes, M.R., Ahmad, N., Perez-Franco, O., Oster, A., Svendrowski, M. and Yue, P. (2024) Abnormal ACT in a Patient with Prekallikrein Deficiency Undergoing Cardiopulmonary Bypass. *Open Journal of Anesthesiology*, **14**, 145-149.
https://doi.org/10.4236/ojanes.2024.145013

**Received:** March 25, 2024
**Accepted:** May 21, 2024
**Published:** May 24, 2024



## Abstract

Prekallikrein deficiency is a disorder that often remains undiagnosed. Prekallikrein activates factor XII, which initiates the intrinsic coagulation pathway. Prekallikrein deficiency results in prolonged Partial Thromboplastin Time and Activated Clotting Time in absence of anticoagulants or active bleeding. This case report describes the anesthesia management of a patient with Prekallikrein deficiency who underwent cardiac surgery with Cardiopulmonary Bypass for correction of a congenital cardiac malformation. We highlight the importance of understanding the different tests available for the diagnosis of coagulation factors deficiency during administration of heparin in the setting of cardiovascular procedures under general anesthesia.

## Keywords

Prekallikrein Deficiency, Fletcher Factor Deficiency, Cardiopulmonary Bypass, Congenital Cardiac Malformation

## 1. Introduction

Activated Clotting Time (ACT) is a common test to guide the administration and reversal of heparin during invasive intravascular procedures, such as cardiopulmonary bypass and cardiovascular surgeries. It has a strong linear correlation with blood heparin concentration. Prolongation of ACT in absence of heparin administration may indicate a deficiency in coagulation factors, thrombocytopenia, or platelet dysfunction [1]. However, the presence of abnormal ACT is not necessarily associated with bleeding disorders [2]. Congenital Prekallikrein (PK) deficiency, also known as Fletcher Factor (FF) deficiency, is a rare autosomal

recessive defect usually diagnosed incidentally during routine coagulation tests demonstrating substantially prolonged activated Partial Thromboplastin Time (aPTT) and normal Prothrombin Time (PT) without associated bleeding abnormalities [3]. Since this condition is rare, and exact prevalence is possibly unknown as it is not associated with bleeding, thrombosis or any other severe clinical symptoms [4], thus, the characterization of its phenotype is not well elucidated. Here, we report anesthesia management of a pediatric patient with PK deficiency on cardiopulmonary bypass with abnormal ACT, but does not demonstrate abnormal coagulation issues.

## 2. Case Report

We present a 6-year-old patient with Secundum Atrial Septal Defect (ASD) who underwent cardiac catheterization for closure of the ASD with device. Patient was mostly asymptomatic presenting only with occasional palpitations and chest pains with exercise. The condition was an incidental finding during physical exam for acute illness when his primary care physician identified a soft systolic murmur along the left upper sternal border. He had tonsillectomy and open fixation of upper extremity fracture in the past without any complications. During cardiac catheterization, the procedure was aborted because it was found that he also had partial anomalous pulmonary venous return (left pulmonary vein to innominate vein) and would need open heart surgery with cardiopulmonary bypass. After heparin was reversed, ACT remained elevated (400 seconds) while heparin assay was zero, activated Partial Thromboplastin Time (aPTT) was 152 seconds, Prothrombin Time (PT) was 12.6 seconds, and International Normalized Ratio (INR) was 1.2. With no bleeding complication was observed, the patient was extubated and admitted overnight for observation and further evaluation.

Hematology was consulted for further evaluation and management. Main differential diagnosis with prolonged ACT and aPTT is L*upus* anticoagulant or coagulation factor deficiency (XII, XI, IX and VII) which were found to be all normal in our patient. A notable finding was deficiency of Prekallikrein. Since the patient did not have a history of bleeding problems in the past the recommendation was to proceed with surgery and manage possible bleeding with Fresh Frozen Plasma (FFP) that usually corrects ACT and PTT prolongation.

In the operating room after induction of general anesthesia and prior to heparinization, we evaluated baseline coagulation status with the following results: ACT 339, aPTT 44.2, PT 12.0, INR 1.1, Fibrinogen 230, D dimer less than 200 mg/ml, platelets 227 and Thromboelastogram (TEG) was normal. A bolus of FFP was given at 10 ml/kg and continued throughout the case at a rate of 5 ml/kg/hour, 5500 Units of Heparin were administered before cannulation, ACT was 286; patient received a second dose of 4000 Units of Heparin, ACT was 519 and we proceeded with cardiopulmonary bypass. The surgery was uneventful with no bleeding complications. At the end, heparin was reversed with protamine, ACT was 134, Heparin assay zero, aPTT 21, and all other labs were within normal limits

including TEG. The patient received 60 ml of Modified Ultra Filtrated blood, 280 ml of blood from cell saver and 180 ml of platelets. Total FFP infused was 470 ml throughout the case.

The patient was extubated in the operating room and transported to the Pediatric Intensive Care Unit (PICU) with spontaneous ventilation on $O_2$ by simple face mask. He remained stable and was discharged from the PICU 48 hours later.

## 3. Discussion

Prekallikrein deficiency is a rare blood disorder that shows prolonged ACT and PTT; however, bleeding problems do not always occur [3]. A few patients with PK deficiency do experience problems related to blood clotting, such as heart attack, stroke, deep vein thrombosis, epistaxis or excessive bleeding after surgery [5]. However, those are common problems in the general population, and most affected individuals have other risk factors for developing them, so it is unclear whether their occurrence is related to PK deficiency. Prekallikrein, when converted to its active form in plasma, plays a role in the intrinsic coagulation pathway. Researchers suggest that this lack of functional plasma protein does not cause symptoms because the extrinsic coagulation pathway can compensate for this impairment [6].

Our case demonstrates that despite abnormal prolongation of the PTT and ACT, patients with PK deficiency do not show signs or symptoms of abnormal bleeding and are not at increased risk for bleeding compared to the general population when undergoing an extensive surgical intervention such as open heart surgery. However, proper tests should be warranted to ensure safety. Coagulation tests during cardiac surgery under CPB are critical assurance of normal coagulation status postoperatively. Routine ACT could not distinguish between prolonged blood clotting due to heparin effect or acquired abnormalities of the coagulation system after a loading dose of heparin such as the case we report here. Other tests like aPTT and Heparin Assay should be used for differential diagnosis [7]. PTT and ACT reflect the integrity of the intrinsic coagulation pathways, while ACT is the test performed at patient bed site, PTT is analyzed in the laboratory by a medical technologist. The main difference between two of those tests is that PTT prolongation does not correlate with heparin concentration when high doses are administered in the cardiovascular procedure setting, and for that reason, ACT is used intraoperatively [8]. However, PTT is more accurate for the diagnosis of coagulopathy. Short PTT is considered to have little clinical relevance, but some research studies state that it might increase risk of thromboembolism [9]. Prolonged PTT also may indicate antiphospholipid antibody (lupus anticoagulant) and sepsis [10].

At the end of the surgical procedure, ACT is done right after administration of Protamine; a value below 150 is reassurance of adequate heparin reversal. Heparin Assay is used in conjunction with ACT to determine the presence of Heparin

in the blood stream [7]. A value of zero indicates no heparin residual. This test is also named Anti-Xa Assay and is designed to measure plasma heparin, unfractionated and Low Molecular Weight (LMW) as well to monitor anticoagulation therapy [11]. However, Thromboelastography (TEG) is still the gold standard to diagnose coagulation abnormalities during cardiovascular surgery, which was normal in our case. Our case demonstrates the importance of understanding the different tests available for the diagnosis of coagulation factors deficiency during administration of heparin in the setting of cardiovascular procedures under general anesthesia.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

## Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

## Informed Consent

Verbal informed consent was obtained from the parents of the patient for her anonymized information to be published in this article.

## Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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