

Received: 2017.06.10  
Accepted: 2017.07.24  
Published: 2017.10.10

## A Case of Diffuse Alveolar Hemorrhage as a Possible Complication of Bivalirudin Therapy

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

ABCDEFG 1 **Htun Latt**  
AEF 2 **Sammy Aung**  
AEF 2 **Kyaw Kyaw**  
EF 3 **Thein Tun Aung**  
ABCDEF 2 **Chanwit Roongsritong**

1 Department of Internal Medicine, University of Nevada-Reno, School of Medicine, Reno, NV, U.S.A.

2 Department of Heart and Vascular Health, Renown Regional Medical Center, Reno, NV, U.S.A.

3 Department of Cardiology, Good Samaritan Hospital, Dayton, OH, U.S.A.

**Corresponding Author:** Htun Latt, e-mail: [htunlatt888@gmail.com](mailto:htunlatt888@gmail.com)

**Conflict of interest:** None declared

**Patient:** Male, 61  
**Final Diagnosis:** Diffuse alveolar hemorrhage  
**Symptoms:** Hemoptysis  
**Medication:** Bivalirudin  
**Clinical Procedure:** Percutaneous coronary intervention  
**Specialty:** Cardiology

**Objective:** Rare complication/disease

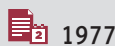
**Background:** Diffuse alveolar hemorrhage (DAH) is a rare but potentially fatal complication of anticoagulant or antiplatelet therapy. Bivalirudin is a specific and reversible direct thrombin inhibitor (DTI).

**Case Report:** We report a case of severe DAH, possibly related to bivalirudin use, in a 61-year-old patient undergoing coronary intervention. The patient had presented with an out-of-hospital cardiac arrest due to acute ST elevation myocardial infarction (STEMI). During the coronary intervention, shortly after receiving bivalirudin, the patient started having frank bleeding from the endotracheal tube and developed hemodynamic compromise. Despite aggressive intervention and intensive care, the patient died.

**Conclusions:** At this time, to our knowledge, there have been no reports of DAH associated with the use of bivalirudin.

**MeSH Keywords:** Acute Coronary Syndrome • Hemorrhage • Percutaneous Coronary Intervention

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/905721>



1977



—



4



18



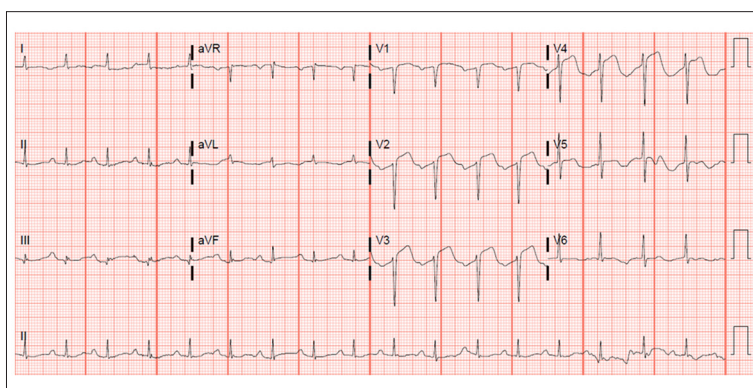
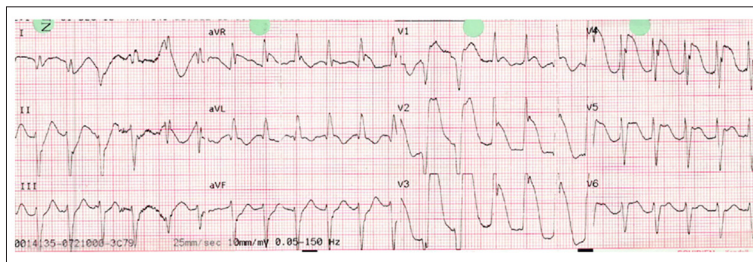
## Background

Diffuse alveolar hemorrhage (DAH) is observed in patients who receive concomitant platelet glycoprotein (Gp) IIb/IIIa inhibitors and unfractionated heparin during the coronary intervention [1–4]. However, DAH has also been reported in patients who receive dual antiplatelet therapy and low molecular weight heparin [5–8]. Bivalirudin is a specific and reversible direct thrombin inhibitor (DTI). We describe a case of DAH, possibly triggered by bivalirudin therapy.

## Case Report

A 61-year-old man with no known cardiac disease collapsed at home. The wife witnessed the event and immediately called the emergency medical service (EMS). Within approximately five minutes, EMS arrived at the field. The patient was found to be pulseless and cardiopulmonary resuscitation (CPR) was immediately performed. He was intubated and successfully resuscitated with the return of spontaneous circulation within 10 minutes. At the field, the resting twelve-lead electrocardiogram (EKG) showed 4–5 mm ST segment elevation in the anterolateral leads (Figure 1). The patient was airlifted in a stable condition to our institution, and arrived within 40 minutes.

On arrival to the emergency room, initial hemodynamic parameters included blood pressure (BP) 137/76 mmHg, heart rate (HR) 105 beats per minute (bpm), respiratory rate (RR) 29/min, and oxygen saturation maintained above 90% on 40%



fraction of inspired oxygen ( $\text{FiO}_2$ ), with a positive end-expiratory pressure (PEEP) of 8 cm  $\text{H}_2\text{O}$ .

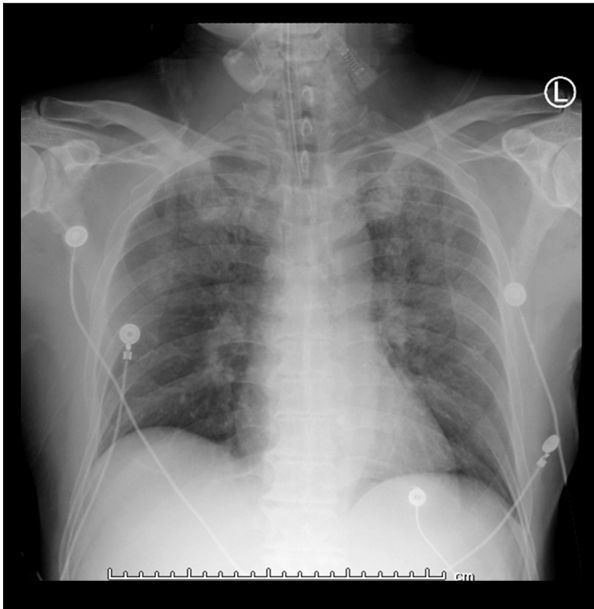
A repeat EKG continued to show 2–3 mm ST segment elevation in the anterolateral leads (Figure 2), and he was diagnosed with ST elevation myocardial infarction (STEMI). Aspirin, 325 mg, was given through a nasogastric tube. Initial troponin was measured at 1.57 ng/ml, and B-natriuretic peptide (BNP) was 25 pg/ml. An initial chest X-ray (CXR) showed bilateral mild, patchy central infiltrates (Figure 3). He was taken as an emergency to the cardiac catheterization laboratory for primary percutaneous coronary intervention (PCI).

After an initial contrast injection for angiography, he developed ventricular tachycardia with hypotension requiring defibrillation. Sinus rhythm was restored after one defibrillation procedure. Intravenous (IV) amiodarone at a loading dose of 150 mg was given, followed by an infusion at 1 mg/minute. An intra-aortic balloon pump (IABP) was placed to maintain the BP, which subsequently normalized with intermittent elevations. Vital signs at that time were BP 103/70 mmHg, HR 92 bpm, RR 28/min, and  $\text{SpO}_2$  of 100% on 40%  $\text{FiO}_2$ .

Coronary angiography showed two sequential 99% stenoses in the proximal and mid portions of the left anterior descending

**Figure 1.** The initial electrocardiogram (EKG) of the patient performed in the field (the patient's home). The resting twelve-lead electrocardiogram (EKG) shows a 4–5 mm ST segment elevation in the anterolateral leads. Ventricular tachycardia (VT), the presence of atrioventricular dissociation, extreme right axis deviation and a different QRS axis from baseline. The differential diagnosis is left bundle branch block (LBBB) or massive anterior myocardial infarction (MI) due to occlusion of left anterior descending (LAD) coronary artery.

**Figure 2.** The electrocardiogram (EKG) of the patient on admission to the emergency room. The resting twelve-lead electrocardiogram (EKG) in the emergency room shows a 2–3 mm ST segment elevation in the anterolateral leads, and he was diagnosed with ST elevation myocardial infarction (STEMI).



**Figure 3.** The initial chest X-ray of the patient on hospital admission. The initial chest X-ray (CXR) shows bilateral, mild, patchy, central lung infiltrates.

(LAD) coronary artery, along with 90% stenosis in the distal portion of the dominant left circumflex artery (LCA). Then, IV bivalirudin was administered at a standard dose of 0.75 mg/kg bolus followed by an infusion at 1.75 mg/kg/hour. About 15 minutes after initiation of bivalirudin, the patient was noted to have tachycardia (HR 140–150 bpm), tachypnea (RR 40–45/min), and  $O_2$  desaturation (70%) on ventilator support requiring an increase in  $FiO_2$ . After a stent had been placed at the distal LAD lesion, no reflow was noted. The interventional cardiologist decided to add a standard dose of IV eptifibatid with a 180 mcg/kg bolus. Another stent was deployed at the proximal LAD lesion, and it resulted in no residual stenosis in LAD with a good antegrade flow.

About 15 minutes after IV eptifibatid was given, and 35 minutes following the IV bivalirudin bolus and 55 minutes after the IV amiodarone bolus, active bleeding from the endotracheal tube was observed, along with desaturation down to 70% despite 100%  $FiO_2$ . The patient also became much more tachypneic. A bivalirudin drip was immediately discontinued. Only a single bolus dose of IV eptifibatid was given, and eptifibatid infusion was never initiated, nor did the patient receive any heparin products. Continuous suction was required in an attempt to maintain his oxygen saturation. The pulmonologist was immediately consulted, and flexible bronchoscopy was performed in the cardiac catheterization laboratory. Active bleeding was observed from the lower lobe of the right lung and upper lobe of the left lung, but no obvious source was identified. Left ventriculography showed hypokinesis of the anterior wall and moderately reduced left ventricular (LV)



**Figure 4.** A repeat chest X-ray following right heart catheterization. Repeat chest X-ray (CXR) after right heart catheterization showed a new finding of diffuse bilateral dense consolidation with air bronchograms and sparing of the lower lobes.

systolic function, but no mitral regurgitation was observed. The LV end-diastolic pressure (LVEDP) was elevated at 25 mmHg. Right heart catheterization showed pulmonary capillary wedge pressure (PCWP) of 35 mmHg. Multiple doses of intravenous furosemide and nitroglycerine were administered. We also decided not to give any additional antiplatelet agent. He was subsequently admitted to the intensive care unit (ICU), and the IV amiodarone drip was continued. Six hours later, repeat troponin was 137 ng/ml and BNP was 799 pg/ml.

On admission to the ICU, initial laboratory results showed normal hemoglobin (Hb) of 16.0 g/dl, platelet count of 238 K/uL, prothrombin time with international normalized ratio (INR) of 1.0 and activated partial thromboplastin time (PTT) of 32.6 seconds. Platelet counts continued to be normal (223 K/uL), but his Hb dropped to 12 g/dl. Repeat CXR showed a new finding of diffuse bilateral dense consolidation with the sparing of lower lobes (Figure 4). Activated clotting time was not tested since no heparin was used. His oxygen saturation remained very difficult to maintain, and he subsequently became more hypotensive despite treatment with multiple vasopressors. The IABP was replaced with an Impella CP® heart pump device, but he continued to deteriorate and unfortunately died within 36 hours after his initial presentation.

## Discussion

The concomitant use of platelet Gp IIb/IIIa inhibitors and unfractionated heparin is a documented risk factor for diffuse alveolar hemorrhage (DAH) with an estimated incidence of 0.14% for abciximab and 0.33% for eptifibatid [1–4]. DAH has also been associated with the use of antiplatelet agents (aspirin, ticlopidine, ticagrelor) [5–7], low molecular weight heparin [5,8], amiodarone [9] and rivaroxaban [10]. Also, a rare case of DAH related to the use of hyaluronic acid dermal fillers (cosmetic product) was reported by Basora et al. [11]. The results of the ACUITY trial have shown similar rates of bleeding and ischemic events with the use of either bivalirudin or heparin when combined with a platelet Gp IIb/IIIa inhibitor in patients with acute coronary syndrome who were undergoing invasive treatment [12]. The same trial showed similar rates of ischemia and significantly lower rates of bleeding with bivalirudin monotherapy [12]. To the best of our knowledge, there has been no report of severe alveolar hemorrhage associated with bivalirudin use and our report is perhaps the first case describing a possible association between bivalirudin use and DAH.

DAH is a potentially life-threatening clinical syndrome, characterized by hemoptysis, anemia, radiographic signs of diffuse pulmonary hemorrhage, and hypoxic respiratory failure. Histologically, DAH can show pulmonary capillaritis, pulmonary hemorrhage, and diffuse alveolar damage (DAD). Pulmonary capillaritis, the most common underlying pathology for DAH, is often caused by systemic vasculitis (microscopic polyangiitis, Wegener's granulomatosis) and rheumatologic diseases (rheumatoid arthritis, systemic lupus erythematosus). Antithrombotic agent-related DAH is often attributable to pulmonary hemorrhage, whereas DAD is a common pathology associated with amiodarone-induced alveolar hemorrhage and acute respiratory distress syndrome (ARDS) [13,14].

The diagnosis of DAH is made clinically in an appropriate clinical context and may be supported by radiography, bronchoscopy, and pathologic examination. Occasionally, the diagnosis is made by exclusion. DAH may be mistaken clinically as acute pulmonary edema, which is a common complication of acute coronary syndrome (ACS). Therefore, a low threshold of clinical suspicion should be maintained to initiate proper management of this potentially fatal condition.

The appropriate treatment of DAH depends on the underlying cause. Immunosuppressive therapy is the mainstay of treatment in patients with DAH associated with systemic vasculitis and rheumatologic diseases [14,15]. However, no definitive therapy has been established for DAH due to anticoagulants, antiplatelet agents, or amiodarone at this time, possibly due to the scarcity of the incidences of occurrence. Rather, the treatment is mainly limited to removal of the offending agents, reversal

of anticoagulant or antiplatelet activity, and supportive care. Corticosteroids may play a role in the management of DAH.

In this patient, the initial EKG at the field (Figure 1) revealed ventricular tachycardia (VT), supported by the presence of atrioventricular dissociation, extreme right axis deviation and a different QRS axis from baseline. The main differential diagnosis was left bundle branch block from massive anterior myocardial infarction due to occlusion of LAD. The repeat EKG (Figure 2) showed persistent ST elevation in  $V_{2-4}$  precordial leads. The decision was made to pursue primary PCI in the setting of ongoing myocardial ischemia or infarction. On the other hand, the initial CXR (Figure 3) showed nonspecific patchy infiltrates, not convincing for pulmonary edema. Bronchoscopy also reported active bleeding from both lungs, which could not be explained solely by pulmonary edema from STEMI. Furthermore, the repeat CXR (Figure 4), after the bleeding episode, showed a new finding of diffuse dense consolidation in the upper two-thirds of both lungs, supporting a diagnosis of a new onset hemorrhagic event during PCI. Although chest compressions provided by EMS may have contributed to a certain degree of lung injury, it cannot explain the evolution of changes from the first CXR to the second one. CPR lasted less than 10 minutes, and no rib fractures were noted on the images to indicate any significant trauma to the lungs. Moreover, no clear association had been documented between CPR and DAH in the literature. Additionally, no mitral regurgitation was noted during left ventriculography, and so there was a low possibility of flash pulmonary edema due to rupture of mitral valve chordae tendineae.

Our patient received a standard dose of bivalirudin after he received 325 mg of aspirin without any P2Y<sub>12</sub> receptor inhibitor or heparin products. Although he did receive a standard bolus dose of eptifibatid, no subsequent dose or infusion was given afterward. Our patient also received a total of 200 mg of IV amiodarone prior to the onset of hemorrhage. Literature reports that signs of DAH occur on an average of 5–72 hours after the initiation of eptifibatid and 6.5 months after the use of amiodarone with the shortest onset for DAH being 5 hours for the former and 15 days for the latter [4,9,16]. On this basis, neither the timing nor the dosing would likely be in support of eptifibatid and amiodarone being the major contributors of the severe alveolar hemorrhage in our patient. Furthermore, his baseline and immediate post-procedure platelet counts were in normal ranges, thus, implying that eptifibatid's role in DAH disease process may have been minimal. The clinical deterioration (hypoxemia and tachycardia) started prior to administration of eptifibatid. Therefore, we concluded that bivalirudin might have been the main culprit in triggering DAH in our patient.

There have been limited data about risk factors for the development of DAH due to antithrombotic agent use. Literature suggests that history of acute myocardial infarction, older age, prolonged or complicated angioplasty, underlying chronic lung disease, pulmonary hypertension or elevated PCWP in patients treated with platelet Gp IIb/IIIa inhibitors may be associated with a higher risk of developing DAH [2,17,18]. Our patient has an acute anterior wall STEMI, CPR for pulseless electrical activity (PEA) arrest, complicated angioplasty with the use of IABP, bivalirudin and eptifibatide, ventricular arrhythmia requiring defibrillation and amiodarone, high PCWP and possibly baseline pulmonary hypertension or chronic lung disease as noted in the initial CXR. A combination of these risk factors may have contributed to the development of DAH to a certain extent. However, we believe bivalirudin is the most likely precipitating factor for the development of DAH in our patient.

## References:

1. Ali A, Patil S, Grady K, Schreiber T: Diffuse alveolar hemorrhage following administration of tirofiban or abciximab: A nemesis of platelet glycoprotein IIb/IIIa inhibitors. *Catheter Cardiovasc Interv*, 2000; 49(2): 181–84
2. Guo J, Xu M, Xi Y: Tirofiban-induced diffuse alveolar hemorrhage: After primary angioplasty. *Texas Heart Inst J*, 2012; 39(1): 99–103
3. Zhou X, Peng H, Yin Y et al: Diffused alveolar hemorrhage: A rare and severe complication of tirofiban-induced thrombocytopenia. *Int J Cardiol*, 2016; 206: 93–94
4. Iskandar SB, Kasasbeh ES, Mechleb BK et al: Alveolar hemorrhage: An underdiagnosed complication of treatment with glycoprotein IIb/IIIa inhibitors. *J Intervent Cardiol*, 2006; 19(4): 356–63
5. Yildirim F, Kara I, Okuyan H et al: Diffuse alveolar hemorrhage associated with low molecular weight heparin and dual anti-platelet therapy after percutaneous coronary intervention. *Clin Respir J*, 2016 [Epub ahead of print]
6. Ikeda M, Tanaka H, Sadamatsu K: Diffuse alveolar hemorrhage as a complication of dual antiplatelet therapy for acute coronary syndrome. *Cardiovasc Med*, 2011; 12(6): 407–11
7. Whitmore TJ, O'Shea JP, Starac D et al: A case of pulmonary hemorrhage due to drug-induced pneumonitis secondary to ticagrelor therapy. *Chest J*, 2014; 145(3): 639–41
8. Hayashi S, Maruoka S, Nakagawa Y et al: Diffuse alveolar hemorrhage associated with low molecular weight heparin. *Respirol Case Rep*, 2013; 1(1): 2–4
9. Iskandar SB, Abi-Saleh B, Keith RL et al: Amiodarone-induced alveolar hemorrhage. *Southern Med J*, 2006; 99(4): 383–88
10. Hammar SP: Fatal pulmonary hemorrhage after taking anticoagulation medication. *Respir Med Case Rep*, 2015; 15: 66–70
11. Basora JF, Fernandez R, Gonzalez M, Adorno J: A case of diffuse alveolar hemorrhage associated with hyaluronic acid dermal fillers. *Am J Case Rep*, 2014; 15: 199–202
12. Stone GW, McLaurin BT, Cox DA et al: Bivalirudin for patients with acute coronary syndromes. *New Engl J Med*, 2006; 355: 2203–16
13. Borders CW III, Bennett S, Mount C, Claassen SL: A rare case of acute diffuse alveolar hemorrhage following initiation of amiodarone: A case report. *Military Med*, 2012; 177(1): 118–20
14. Lara AR, Schwarz MI: Diffuse alveolar hemorrhage. *Chest J*, 2010; 137(5): 1164–71
15. Kazzaz NM, Coit P, Lewis EE et al: Systemic lupus erythematosus complicated by diffuse alveolar haemorrhage: risk factors, therapy and survival. *Lupus Sci Med*, 2015; 2(1): e000117
16. Mikkilineni H, Bruhl SR, Colyer WR, Pandya U: A retrospective analysis and case series of glycoprotein IIb/IIIa inhibitor associated diffuse alveolar hemorrhage: Two case reports. *Cases Journal* 2009; 2(1): 8553
17. Khanlou H, Eiger G, Yazdanfar S: Abciximab and alveolar hemorrhage. *New Engl J Med*, 1998; 339(25): 1861–63
18. Aguirre FV, Topol EJ, Ferguson JJ et al: Bleeding complications with the chimeric antibody to platelet glycoprotein IIb/IIIa integrin in patients undergoing percutaneous coronary intervention. *Circulation*, 1995; 91(12): 2882–90

## Conclusions

DAH is a rare, but often fatal, complication of an antithrombotic agent use. We report a case of fatal DAH that we believe to have been as a result of bivalirudin therapy during primary PCI. DAH may easily be confused with acute pulmonary edema, which is a common complication of acute coronary syndrome. Therefore a clinical suspicion must be maintained to initiate proper management of the potentially fatal disease. However, no definitive therapy has been established for DAH induced by anticoagulation, which warrants further study.

## Conflict of interests

None.