

Sudden Post-Coital Hemopericardium with Cardiac Tamponade on Apixaban



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History

74 year old male with past medical history of nonvalvular A-fib-on Eliquis, HTN, HLD, BPH, OSA, B12 deficiency, OSA, presents SJMC ED as code 3 traffic with chief complaint of “I can’t breathe” triggered during sexual intercourse with partner 60 minutes prior to arrival.

Dyspnea is described acute onset, constant, and present at rest. Symptoms associated with dizziness and lightheadedness. Denies productive cough, wheezing, fevers, chills, chest pain, hemoptysis, recent trauma, or recent falls.

Per EMS, patient was hypotensive at 51/31 and exhibiting afib on the monitor en-route. En route spO2 = 99% prompting EMS to place patient on 2L O2 increase spO2 to 100%.

Physical Exam

Vital Signs:

HR 94

BP 108/95

RR 36

SP02 100 on 3L/min NC

Temp: 34.8 C

GENERAL: Alert and oriented x 4, **patient in moderate to severe respiratory distress. Uncomfortable appearing.**

HEENT: No facial asymmetry. NCAT. Pupils equal, round, reactive to light at 4 mm. Extraocular movements are normal. Conjunctiva pink bilaterally. Oropharynx is moist and clear.

NECK: Supple. No meningeal signs. **No JVD.**

CHEST WALL: Symmetrical movement on inspiration. No retractions or crepitus.

CARDIOVASCULAR: Regular rate, **irregular** rhythm, I do not hear a murmur. **Weak and thready pulses in all limbs.**

LUNGS: Clear to auscultation. No wheezes, rales, rhonchi. **1-2 words with each breath. Increase work of breathing.**

Physical Exam (continued)

ABDOMEN: Soft, nontender, nondistended, normal-active bowel sounds. There are no pulsatile masses. No involuntary or voluntary guarding present. No Peritoneal signs.

EXTREMITIES: No calf swelling. There is no peripheral edema.

BACK: On visual inspection, no erythema or induration to the midline. On palpation, no tenderness to palpation.

SKIN: No jaundice, rash or petechiae. **Mottling of skin seen in lower extremities.**

NEUROLOGIC: Patient is alert. GCS is normal at 15. Patients strength and sensory exams are normal and symmetrical against resistance.

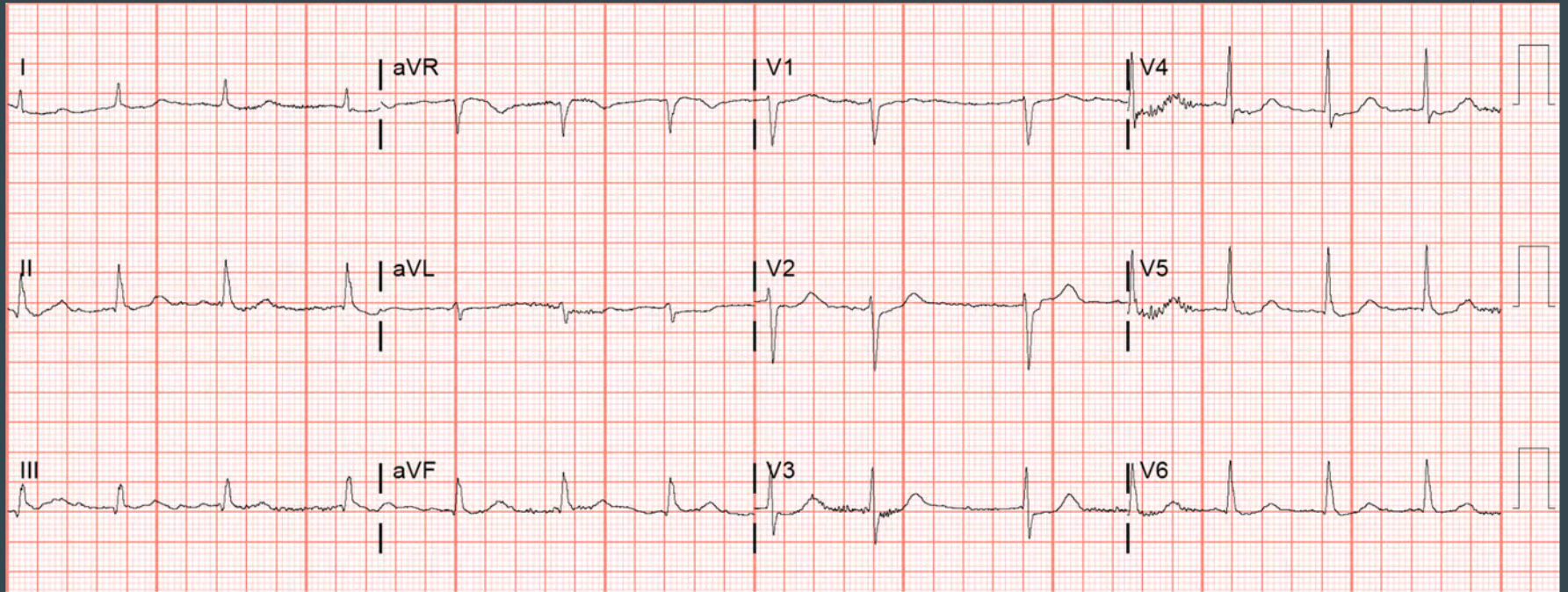
PSYCH: **Anxious appearing.** Mood and affect appropriate.

Differential Diagnosis

- Acute Coronary Syndrome
- Massive Pulmonary Embolism
- Ruptured Aortic Aneurysm
- Aortic Dissection
- Tension Pneumothorax
- Pleural Effusion
- Acute Heart Failure
- Cardiac Tamponade
- Pulmonary Hemorrhage

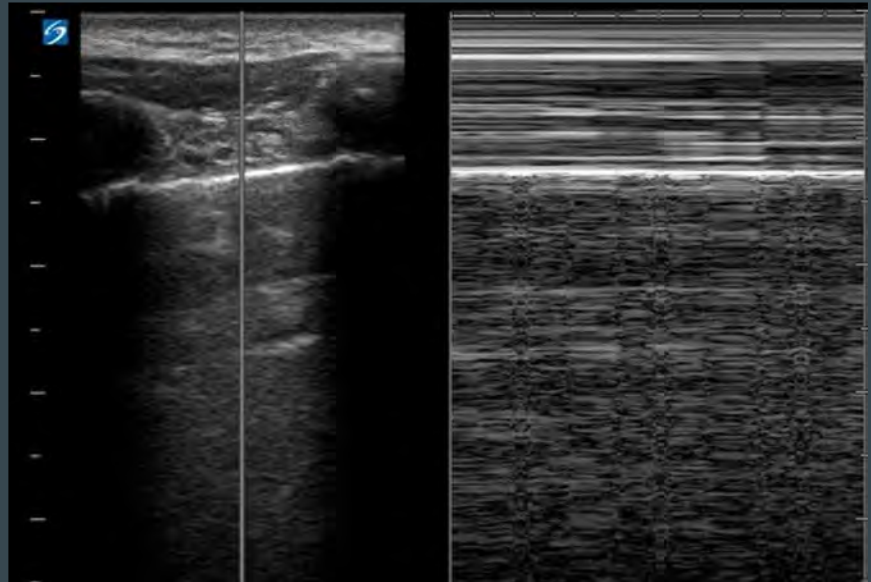
ED Course

0940 - Patient spO2 = 100 on #L of oxygen. Patient continuously repeating "I cant breathe." EKG in progress.



ED Course

0942 - Bedside **pulmonary US** in progress.



ED Course

0950 - Bedside AP CXR

0958 - BP: **58/41**. HR: 83, spO2: 100

0958 - 100 MCG phenyl epinephrine push ordered

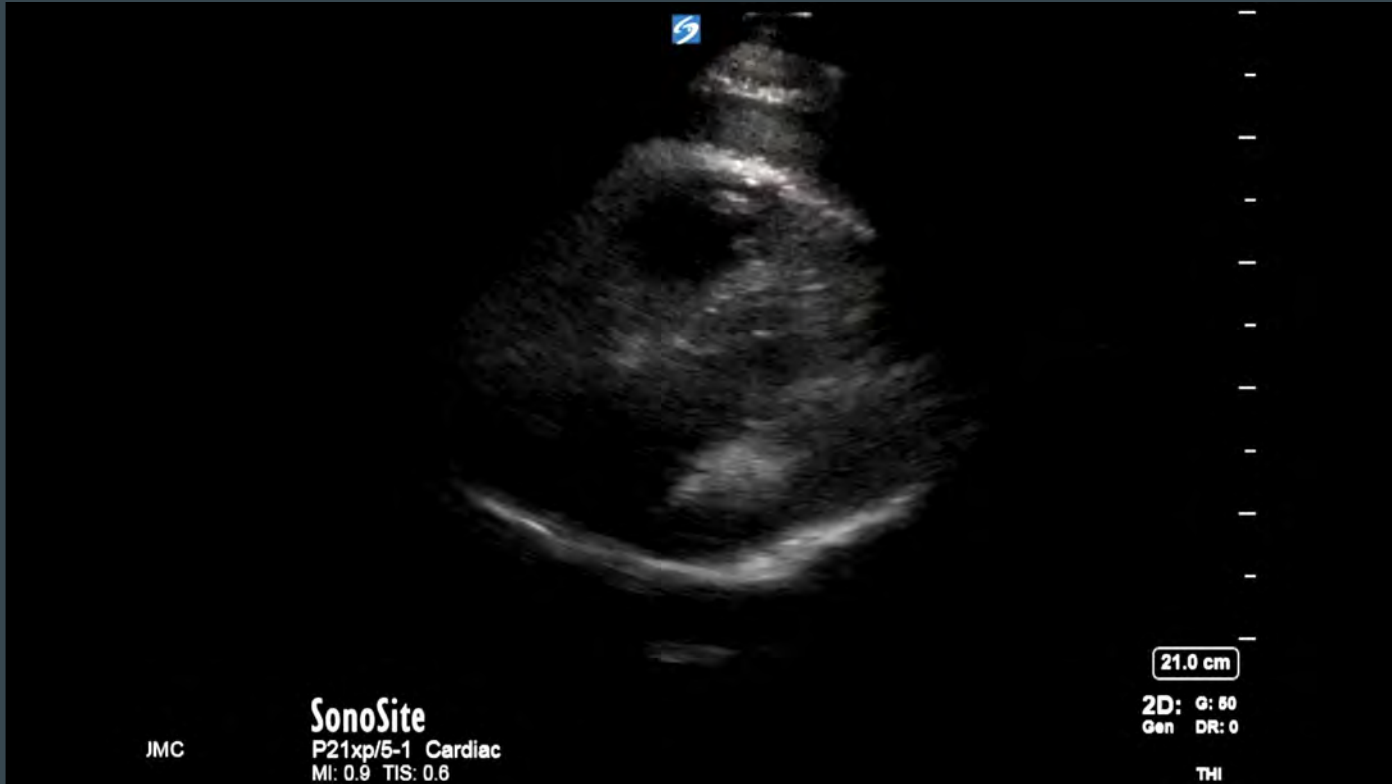
1001 - BP: **55/46**, spO2: 100 on 3L

1009 - 100 MCG phenyl epinephrine IVP

1014 - Bedside **Cardiac Echo** performed...



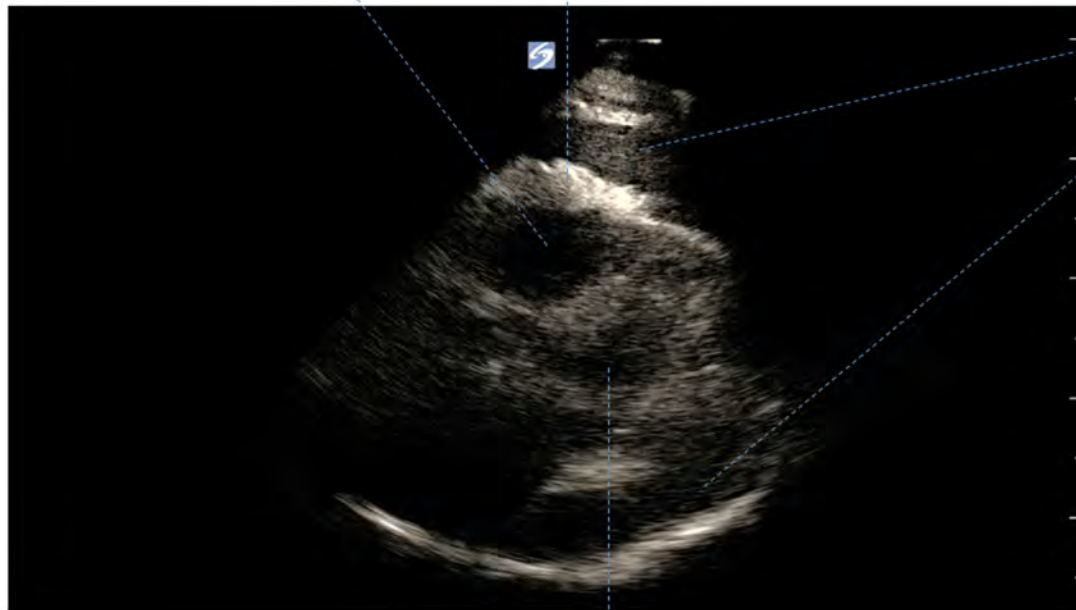
ED Course



Right ventricle

Thrombus

Pericardial
effusion



Left ventricle

ED Course

1017 - phenyl epinephrine 100 MCG IVP

1018 - BP: 93/50, HR: 81, spO2: 99. norepinephrine drip started at 10 MCG/MIN.

1030 - Arterial line placed.

1035 - Cardiology/Cardiothoracic paged.

1037 - HR: 77, BP: 80/58, spO2: 100

1047 - BP: 90/64

1049 - 60mcg/min of phenyl epinephrine gtt

1056 - Phenyl epinephrine drip bumped up to 80mcg/min

1101 - Pericardiocentesis in progress, could not aspirate given amount of clot around heart. BP: 101/60, HR: 80, spO2: 100%

1116 - Informed of pts critical status and concern pt is peri-code.

1123 - Patient heart rate dropped to 54. Lost pulses. CPR started. Phenylepinephrine maxed out.

1125 - 1 AMP of Epi IVP given. CPR continued.

1128 - Rhythm is PEA, 1 AMP of Epi IVP given

1134 - Patient intubated by Anesthesiology/Resident Physician

1136 - pulse check, no pulses. Compressions paused, Patient shocked with 200J, compressions continued immediately after.

ED Course

1146 - CT surgeon bedside. Plan discussed for emergent thoracotomy. Discussed case with wife who is at bedside being supported by staff/clergy.

1148 - Pulse check, compressions paused, no femoral, faint carotid pulses, compressions continued, 1 AMP Epi given. Betadine applied to patient's chest. CT Surgeon performs thoracotomy.

1153 - Pulse check, no pulses.

1156 - Clots and large volume blood being removed from patient's pericardial sac (~800 cc of blood/clot). Pulse check, minimal pulse on right carotid, positive femoral pulse. HR: 89.

1157 - Wide complex perfusing rhythm at 87, BP: 140/86. Patient with bounding carotid and femoral pulses. Bedside US w excellent cardiac activity. Discussed to take patient to OR.

1200 - OR 15 is ready for patient. Patient prepped for transport to OR.

1207 - Patient transported to OR via gurney

Hospital Course

- Patient went to OR where **median sternotomy** was performed which revealed **ongoing active bleeding**.
- The pericardium was marsupialized and additional blood clot evaluated.
- Complete exploration of the heart revealed there was **no evidence of** aortic or coronary dissection, no cardiac chamber bleeding, no epicardial inflammation and normal pericardial thickness
- It did appear, however, that there was a surface of epicardium around the coronary sinus that had **muscle and epicardial bleeding without a vessel**. This was repaired with **pledgeted sutures and bioglue**.

Hospital Course

- After being transferred to the intensive care unit, patient required up to **4 vasoactive medications** and was transfused with multiple units of **blood products, cryoprecipitate, factor 7 and 9 and activated prothrombin complex concentrate**.
- It was understood that these interventions would likely not reverse the effects of apixaban, but **Andexanet alfa was not available for administration**.
- The patient developed cardiogenic and hypovolemic shock, upper gastrointestinal hemorrhage, oliguria, severe acidosis and right sided hemiparesis.
- Patient ultimately **expired 24 hours** after initial presentation.

Discussion

- Research studies show DOACs are associated with lower risk of major bleeding when compared with warfarin, which has made DOACs a leading first line medication for nonvalvular atrial fibrillation patients.
- However, in the past few years, there have been several case reports of DOACs such as direct factor Xa inhibitors and direct thrombin inhibitors causing **spontaneous bleeds, including in the pericardium**¹⁻⁴.
- Many of these case reports cite drug-interactions such as **common CYP450 medication inhibitors**⁴, **herbal products**², and **renal failure**⁵ as likely causes.
- A medication review of our case reveals our patient was on 180 mg of extended-release **diltiazem** and 20 mg **sildenafil**, both notable **CYP450 inhibitors**.
- A recent in vitro study shows sildenafil may significantly block apixaban and rivaroxaban cell efflux via p-glycoprotein inhibition thereby increasing DOAC intestinal absorption potentially resulting in increased bioavailability and subsequent bleeding risk⁵.
- We postulate **regular sildenafil use** prior to sexual intercourse in patients taking DOACs may be a risk factor for spontaneous serious post coital bleeding.

Discussion

- Currently, it is **unclear** whether exertional activity such sexual intercourse is a risk factor for cardiac bleeding in patients on DOACs.
- We propose a theory where **exertional activity** such as coitus may cause **myocardial ischemia** in older, vasculopathic patients and subsequent reperfusion injury.
- During **reperfusion injury**, increased intracellular calcium, increased supply of oxygen free radicals, and subsequent inflammatory response may trigger **bleeding** in patients taking DOACs.
- However, recent studies have shown exercise as a potential protective factor via heat shock proteins, extracellular vesicles containing antioxidants, and improved mitochondrial function¹²⁻¹⁵.
- In our patient, it is **unclear** if the exertional activity itself played a role in his spontaneous muscle and epicardial bleeding.
- Our case could present a **potential refutation** of exercise as a potential protective factor in preventing reperfusion injury.

References

- Zain Ul Abideen, A et. al. (2009). Hemorrhagic Cardiac Tamponade Associated with Apixaban: A Case Report and Systematic Review of Literature. *Cardiovascular Revascularization Medicine*, 20(11), 15–20. Retrieved from <https://www.sciencedirect.com/science/article/pii/S1553838919302283>
- Shivamurthy, P., Brar, N., & Therrien, M. L. (n.d.). Isolated Hemopericardium Associated With Rivaroxaban: First Case Report. *Pharmacotherapy*, 34(9), 169–172. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/25074401/>
- Menendez, D., & Michel, J. (n.d.). Hemopericardium with tamponade following rivaroxaban administration and its attenuation by CYP3A4 inhibitors. *Baylor University Medical Center Proceedings*, 4, 414–415. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5023303/>
- Oladiran, O., Segal, J., Nwosu, I., & Nazir, S. (n.d.). A Rare Case of Spontaneous Cardiac Tamponade Induced by Concomitant Use of Rivaroxaban and Amiodarone. *Case Reports Cardiology*. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/30159173/>
- Jelani, Q.-ul-ain, Gordon, R., & Schussheim, A. (n.d.). Dabigatran-Induced Spontaneous Hemopericardium and Cardiac Tamponade. *Texas Heart Institute Journal*, 44(5), 370–372. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5731597/>
- Margelidon-Cozzolino, V., Hodin, S., Jacqueroux, E., Delezay, O., Bertoletti, L., & Delavenne, X. (2015). In Vitro Assessment of Pharmacokinetic Drug-Drug Interactions of Direct Oral Anticoagulants: Type 5-Phosphodiesterase Inhibitors Are Inhibitors of Rivaroxaban and Apixaban Efflux by P-Glycoprotein. *Journal of Pharmacology and Experimental Therapeutics*, 365(5), 519–525. Retrieved from <http://jpet.aspetjournals.org/content/365/3/519>
- Christeresson, C., Wallentin, L., & Andersson, U et al. (2019). Effect of apixaban compared with warfarin on coagulation markers in atrial fibrillation . *Heart*, 105, 235–242. Retrieved from <https://heart.bmj.com/content/heartjnl/105/3/235.full.pdf>

References

- Bahit, M. C., Lopes, R. D., & Wojdyla, D. M. et al. (2017). Non-major bleeding with apixaban versus warfarin in patients with atrial fibrillation. *Heart*, 103, 623–628. Retrieved from <https://heart.bmj.com/content/heartjnl/103/8/623.full.pdf>
- Eisho, S., Salem, N. M., Hoffman, J. L., Koerber, J. M., & Smythe, M. A. (2018). Major Bleeding With Apixaban in Atrial Fibrillation: Patient Characteristics, Management, and Outcomes. *Hospital Practice*, 46(4), 165–169. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/30058431/>
- Sigawy C., Apter S., Vine J., Grossman E. Spontaneous hemopericardium in a patient receiving apixaban therapy: first case report. *Pharmacotherapy*. 2015;35:e115–e117.
- Borges, J. P., & Verdoom, K. D. S. (2017). Cardiac Ischemia/Reperfusion Injury: The Beneficial Effects of Exercise. *Advanced Exporative Medical Biology*, 999, 155–179. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/29022263/>
- Bei, Y., Xu, T., & Lv, D. et al. (2017). Exercise-induced circulating extracellular vesicles protect against cardiac ischemia-reperfusion injury. *Basic Res Cardiol*, 112(4), 38. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5748384/pdf/nihms926571.pdf>
- Kavazis, A. N. (2009). Exercise Preconditioning of the Myocardium. *Sports Medicine*, 39, 923–935. Retrieved from <https://link.springer.com/article/10.2165/11317870-000000000-00000>
- Levine, G. N., Steinke, E. E., & Bakaeen, F. G. (2012). Sexual Activity and Cardiovascular Disease. *Circulation*, 125(8), 1052–1072. Retrieved from <https://www.ahajournals.org/doi/full/10.1161/CIR.0b013e3182447787>
- Vishwakarma, V. K., Upadhyay, P. K., Gupta, J. K., & Yadav, H. N. (1995). Pathophysiologic role of ischemia reperfusion injury: A review. *Journal of Indian College of Cardiology*, 7(3), 97–104. Retrieved from <https://www.sciencedirect.com/science/article/abs/pii/S1561881116301365>
- Apixaban: Drug information. (n.d.). Retrieved April 5, 2020, from https://www.uptodate.com/contents/apixaban-drug-information?search=apixaban&source=panel_search_result&selectedTitle=1~145&usage_type=panel&kp_tab=drug_general&display_rank=1

Questions?