2-1-2022

Acute Lung Injury Associated With Perioperative Amiodarone Therapy-Navigating the Challenges in Diagnosis and Management

Mark W. Fegley

Alessandra Cardi

John G. Augoustides

Jiri Horak

Jacob T. Gutsche

See next page for additional authors

Recommended Citation

Fegley MW, Cardi A, Augoustides JG, Horak J, Gutsche JT, Nanda S, Kornfield ZN, Saluja A, Sanders J, Marchant BE, and Fernando RJ. Acute Lung Injury Associated With Perioperative Amiodarone Therapy-Navigating the Challenges in Diagnosis and Management. J Cardiothorac Vasc Anesth 2022; 36(2):608-615.

Authors

Mark W. Fegley, Alessandra Cardi, John G. Augoustides, Jiri Horak, Jacob T. Gutsche, Sudip Nanda, Zev N. Kornfield, Abhishek Saluja, Joseph A. Sanders, Bryan E. Marchant, and Rohesh J. Fernando

Journal of Cardiothoracic and Vascular Anesthesia 36 (2022) 608–615

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Case Conference

Acute Lung Injury Associated With Perioperative Amiodarone Therapy—Navigating the Challenges in Diagnosis and Management

Mark W. Fegley, MD[*], Alessandra Cardi, MD[†], John G. Augoustides, MD, FASE, FAHA[†,1], Jiri Horak, MD[†], Jacob T. Gutsche, MD, FASE, FCCM[†], Sudip Nanda, MD[‡], Zev N. Kornfield, MD[*,†], Abhishek Saluja, DO[§], Joseph Sanders, MD[§], Bryan E. Marchant, MD[‖], Rohesh J. Fernando, MD, FASE[¶]

[*]*Critical Care Division, Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

[†]*Cardiovascular and Thoracic Division, Department of Anesthesiology and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

[‡]*Clinical Electrophysiology, Cardiology Associates, St. Luke's University Health Network, Bethlehem, PA*

[§]*Department of Anesthesiology, Pain Management, and Perioperative Medicine, School of Medicine, Wayne State University, Henry Ford Health System, Detroit, MI*

[‖]*Division of Cardiothoracic Anesthesia and Critical Care, Department of Anesthesiology, Wake Forest School of Medicine, Winston Salem, NC*

[¶]*Division of Cardiothoracic Anesthesia, Department of Anesthesiology, Wake Forest School of Medicine, Winston Salem, NC*

Key Words: amiodarone; pulmonary toxicity; acute lung injury; steroid trial; bronchoscopy; acute respiratory distress syndrome

AMIODARONE IS an antiarrhythmic that commonly is indicated in the cardiothoracic surgical intensive care unit for the management of atrial fibrillation.[1,2] Acute lung injury associated with amiodarone exposure is a rare but life-threatening syndrome that may complicate perioperative management.[3] This case conference presents a complex clinical scenario that included acute pulmonary toxicity in the setting of amiodarone therapy for atrial fibrillation. The subsequent expert commentaries explore the diagnostic and management options for this pharmacologic complication in light of the recent literature.

Case Presentation

An 89-year-old woman with severe, symptomatic aortic stenosis presented to the authors' institution for a transcatheter aortic valve replacement via a percutaneous femoral approach. The patient had multiple comorbidities including mild diastolic dysfunction, paroxysmal atrial fibrillation stabilized with sotalol therapy, and sick sinus syndrome that had required a dual-chamber pacemaker. The aortic valve replacement was complicated intraoperatively by an injury to the vertebral artery that required clinical rescue with emergent tracheal intubation, mechanical ventilation, massive transfusion, titrated vasopressor therapy, and endovascular stenting for repair of the vertebral artery.

The patient was admitted to the cardiothoracic surgery intensive care unit for further management. Her postoperative

The project was supported by institutional funding.

[1]Address correspondence to John G.T. Augoustides, MD, FASE, FAHA, Cardiovascular and Thoracic Section, Anesthesiology and Critical Care, Dulles 680, HUP, 3400 Spruce St, Philadelphia, PA, 19104-4283.

E-mail address: yiandoc@hotmail.com (J.G. Augoustides).

https://doi.org/10.1053/j.jvca.2021.05.026

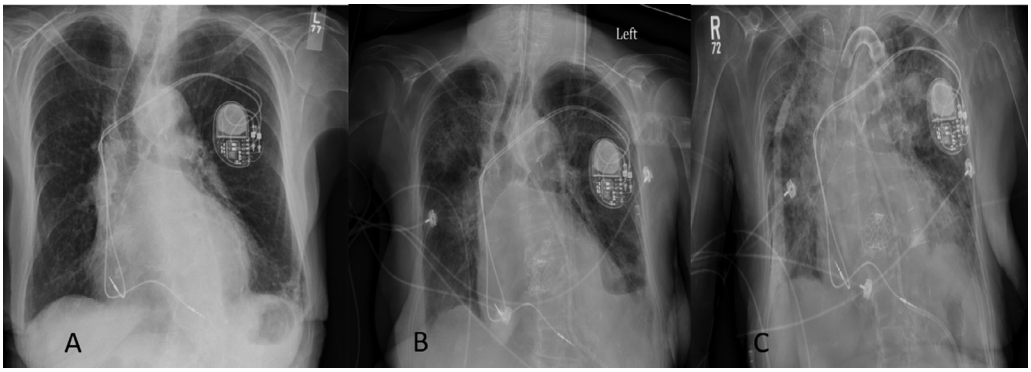

Fig 1. Progression of acute lung injury by chest radiograph. Panel A: Preoperative chest radiograph serves as a clinical baseline. Panel B: Chest radiograph on the 10th postoperative day revealed new diffuse alveolar infiltrates occurring within 24 hours of amiodarone. Panel C: Chest radiograph on the 12th postoperative day has documented progression of the acute lung injury pattern.

course in the first week was complicated by paroxysmal atrial fibrillation requiring electrical cardioversion and titrated sotalol therapy. Furthermore, she was diagnosed with ventilator-associated pneumonia that resolved with aggressive antibiotic therapy. The sotalol therapy was discontinued due to associated hypotension. Her trial of tracheal intubation was unsuccessful due to vocal cord dysfunction. In the second week, she underwent successful percutaneous tracheostomy. She was challenged with amiodarone for control of ongoing paroxysmal atrial fibrillation.

Her radiographic imaging series subsequently developed diffuse ground-glass opacities that were concerning for acute lung injury (refer to Fig 1). Although her infectious workup including bronchoscopy with bronchoalveolar lavage was negative at this juncture, her antibiotic therapy was broadened empirically for an extended course. A chest computed tomography scan was obtained on the 12th postoperative day to evaluate the full extent of the alveolar process that was apparent on chest radiograph. This detailed cross-sectional imaging revealed diffuse alveolar infiltrates with areas of consolidation throughout the lung fields (refer to Fig 2).

Given these findings on detailed chest imaging and the recent exposure to amiodarone, the diagnosis of acute amiodarone pulmonary toxicity was entertained. The amiodarone was discontinued promptly and an empirical course of steroids was commenced. Her subsequent clinical course improved gradually, her chest radiograph cleared, and she was removed from the ventilator. She ultimately was discharged from the intensive care unit on the 37th postoperative day and after further recovery was transferred to a skilled nursing facility in fair condition.

Case Discussion

Amiodarone is a benzofuran derivative with potent class III antiarrhythmic activity.[1-3] The medication was developed and marketed in the 1960s as a coronary dilator and antianginal medication. In the 1970s, amiodarone was discovered to have antiarrhythmic properties and its popularity as an effective antiarrhythmic rapidly became established.[3,4] This enthusiasm was dampened subsequently by the emergence of clinical toxicity, including to the eye, thyroid, lung, and liver.[3-8]

Despite the side-effect profile, amiodarone has regained popularity for rhythm control after cardiothoracic procedures due to its efficacy and hemodynamic tolerance in this setting.[1-3] Furthermore, its toxic effects are uncommon in the postoperative period due to the short-term exposure that typically is required.[1-8] The pharmacokinetics and pharmacodynamics of amiodarone, as well as its clinical applications, already have been reviewed in the *Journal*.[3,9] The further discussion is focused on the pulmonary toxicity associated with amiodarone.

The spectrum of amiodarone-induced pulmonary toxicity can vary in clinical presentation and time course, including acute, subacute, and chronic syndromes.[3-10] The clinical phenotype for this complication includes diffuse alveolar hemorrhage, acute respiratory distress syndrome (ARDS), and diffuse interstitial pneumonitis.[10,11] The acute presentation of ARDS may occur in the postoperative period, as illustrated in this case conference.[3] The diagnosis of this entity is challenging, because clinicians primarily must rely on clinical suspicion with a paucity of reliable tests to suggest the diagnosis. The pattern of acute lung injury on cross-sectional imaging often can be an important diagnostic clue.[12]

Adult cardiac surgical patients often experience a pronounced systemic inflammatory response due to factors such as the operative stress response and infection. The clinical diagnosis of amiodarone as a possible cause for diffuse alveolar injury is suggested in the setting of amiodarone exposure without any other overt etiology.[3,12] Cross-sectional imaging in drug-induced alveolar injury typically will reveal a diffuse alveolar pattern throughout the lung fields; whereas the alveolar injury pattern in infectious etiologies often is concentrated in the gravity-dependent lung regions such as the bases (refer to Fig 2).[3,13]

Bronchoscopy with alveolar lavage in patients with amiodarone-induced pulmonary toxicity may reveal macrophages with foamy cytoplasm.[11,13] Although this histologic finding is sensitive for acute lung injury due to amiodarone, it also is found in other pulmonary diseases and is not specific for amiodarone-induced lung toxicity. The presence of foamy

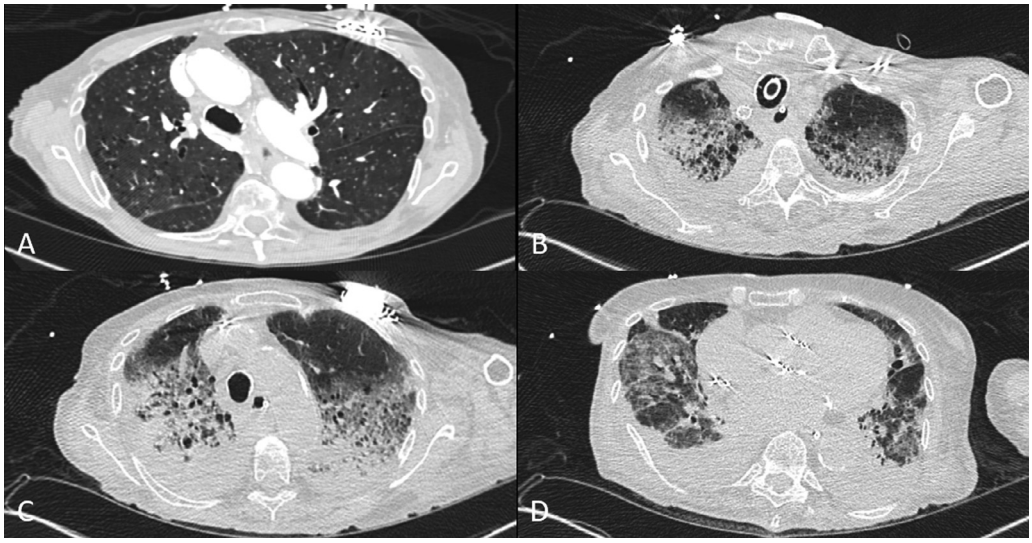

Fig 2. Progression of acute lung injury by serial computed tomography (CT) scans. Panel A: Preoperative chest CT scan serves as a clinical baseline. Panels B-D: Chest CT scan on the 12th postoperative day shows the lung fields in a cross-sectional fashion. There are extensive alveolar infiltrates with areas of consolidation throughout the lung fields.

macrophages in patients exposed to amiodarone is postulated to be due to the creation of oxygen free radicals and increase of phospholipids in lung tissue secondary to the cytotoxic effects of amiodarone.[12,14,15] Clinical trials have suggested the diagnostic role of measuring glycoproteins released into the alveoli and serum by type II pneumocytes in acute alveolar injury.[16-18] Although these markers may be elevated in amiodarone toxicity, their role has remained limited due to their presence in many forms of alveolar injury and so they are not specific for amiodarone-induced lung injury.

The literature regarding the pathogenesis and presentation of acute lung injury due to amiodarone is limited, and, thus, there are still major gaps in the evidence.[3] This literature is confounded by variations in definitions, dosing schedules, drug formulations, routes of administration, and duration of therapy, and has been reviewed recently in the *Journal*.[3,19] The diagnosis and management of the subacute and chronic presentations may not necessarily dictate the clinical approach to acute pulmonary toxicity from amiodarone.[3]

The mainstay of therapy for acute lung injury from amiodarone is immediate cessation of this drug.[3,19] Although there is limited consensus, empirical steroid therapy may be indicated to dampen the acute inflammatory response and to encourage clinical resolution. The clinical guidance for dose and duration of this steroid therapy remains to be determined. The duration of amiodarone-induced acute lung injury is variable. There may be prompt resolution or recovery can be extended due to the long half-life of amiodarone and its propensity to concentrate in lung tissue, especially in type II pneumocytes.[19-21] In one particular patient, it took 60 days after amiodarone cessation for pulmonary infiltrates to clear with full clinical resolution and a good clinical outcome.[20] These considerations are important to consider when advising the patient and family about the expected clinical course and goals of care.

In summary, amiodarone remains a popular and effective choice for pharmacologic control of arrhythmias in adult cardiac surgical patients. Although rare, the risk of acute lung injury must be considered in this setting, especially in patients who manifest new lung infiltrates with no overt etiology. The care team should continue to use amiodarone as indicated but must be aware that acute lung injury is a rare and serious adverse drug reaction.

Expert Commentary (Dr. Saluja/Dr. Sanders)

This case conference highlights a rare side effect of amiodarone in the postoperative period. Briefly, an 89-year-old woman with severe, symptomatic stenosis presented for transcatheter aortic valve replacement that was complicated by vertebral artery injury requiring massive transfusion, tracheal intubation, and a trial of mechanical ventilation. The patient required cardioversion and subsequent amiodarone dosing because of repeated episodes of atrial fibrillation. Thereafter, she developed an acute alveolar pattern of lung injury days after amiodarone therapy was initiated. Once the amiodarone was stopped and steroids were administered, the patient's condition improved.

Amiodarone, a class III antiarrhythmic drug that blocks voltage-gated potassium channels, first was used as an antianginal medication, and then as an effective therapy for various ventricular and supraventricular tachyarrhythmias.[22-25] Furthermore, amiodarone frequently is administered for perioperative prophylaxis for atrial arrhythmias.[3,26] The drug can maintain a sinus rhythm in patients with paroxysmal atrial fibrillation and potentially can assist in conversion of atrial fibrillation to a sinus rhythm.[1-3;22-25]

In the presented case, the patient developed intermittent atrial fibrillation with rapid ventricular response. Therefore, an intravenous load of amiodarone was administered followed by

ongoing oral loading. The perioperative literature has suggested that there is no clear correlation between acute amiodarone therapy at recommended levels and the development of acute lung injury.[3] In the outpatient setting, lower-dosage regimens may be associated with a reduced risk of amiodarone-induced pulmonary toxicity.[10,27,29-31] Over the years, tailored doses of amiodarone have been selected to minimize the risk of lung toxicity, although there is no safe dose.[20,31-35] Indeed, toxicity has been reported at commonly prescribed maintenance dosages of amiodarone, even at ultra-low exposure levels.[20,34-36] Therefore, in this patient, it is likely that pulmonary injury still would have developed, signifying the complicated nature of her hospital course.

The pathogenesis of amiodarone lung toxicity also has been linked to supplementary oxygen, especially when the concentration is high.[30,37,38] Notably, the risk may be potentiated whether the exposure is to isolated oxygen or to oxygen combined with mechanical ventilation.[20,36] In the presented case, the patient received, at times, higher oxygen concentrations that were indicated clinically in the perioperative period. Furthermore, amiodarone itself may induce production of oxygen radicals, which are toxic and can cause cellular damage.[30,31] The evidence linking oxygen concentration as an etiologic factor in this acute setting is limited and far from conclusive.[3]

Multiple mechanisms have been proposed to explain the pathogenesis of amiodarone lung, including the impairment of lipid metabolism leading to increased cellular phospholipid content.[20,28,29] This phospholipid accumulation results in endothelium damage. Additionally, production of oxygen radicals may lead to direct damage of alveolar cell membranes, eventually resulting in acute alveolar injury. [20,28,29] However, because the etiology and pathogenesis still are being investigated, perhaps this diagnosis is one of exclusion with a high index of clinical suspicion.[3] Ultimately, the diagnosis was cemented in this patient after clinical improvement followed the cessation of amiodarone and a steroid trial.

In amiodarone-induced pulmonary toxicity, the lung parenchyma often is remarkable for ground-glass opacities, which often are peripheral in location and may be found early.[39] Furthermore, alveolar and/or interstitial infiltrates often are apparent in both lung fields.[39,40] In this case, the patient's clinical course had failed to improve in the second postoperative week, prompting consideration of a wide differential diagnosis. Subsequent detailed cross-sectional chest imaging showed diffuse alveolar infiltrates with consolidation and ground-glass opacities throughout both lung fields (refer to Fig 2). Overall, high-resolution scanning with computed tomography can reveal the extent of a pulmonary disease process to a greater extent than plain chest radiography (refer to Fig. 1 and 2).[39-42] This detailed chest imaging, coupled with appropriate clinical suspicion, suggested the diagnosis in this patient.

The histology of amiodarone lung often will include injured alveoli with lipid-laden foamy macrophages.[41,42] The thorough workup in this patient included bronchoscopy with titrated lavage. Although these histologic findings are suggestive of amiodarone-induced alveolar injury, they are not specific to this disease process.[43] Therefore, the presence of foamy macrophages can suggest the diagnosis, but does not definitively make the diagnosis. A high index of clinical suspicion, combined with the appropriate clinical setting and chest imaging, are more important in the diagnostic process for amiodarone-induced pulmonary toxicity.[3]

Furthermore, a search for possible serum markers has been ongoing. Select glycoproteins secreted by type II alveolar pneumocytes have been evaluated as possible biomarkers for pneumonitis.[16-18] Because proliferation of type II pneumocytes has been observed during the pathogenesis of amiodarone lung, this approach may yield promising serum markers for this pathologic process.[44] But although this type of biomarker has been shown to be elevated significantly in alveolitis, it remains at this juncture a nonspecific marker for amiodarone-induced lung injury.[16-18, 44]

The diagnosis of amiodarone lung requires a high clinical suspicion and ultimately is a diagnosis of exclusion, as illustrated in this patient.[45,46] Therefore, once this diagnosis has been established, amiodarone administration immediately should be ceased.[45-47] Furthermore, although steroids commonly are prescribed in this setting, there is no general agreement on what the prescribed dose should be, and there appears to be some variance as to the correct dosing regimen.[3,45-47] However, it is reasonable to consider a steroid trial when substantial involvement of the lung parenchyma is apparent in chest imaging.[45-47]

There is variability in the resolution phase of acute lung injury associated with amiodarone therapy. The resolution may be substantial but gradual, as in this patient. The patient eventually was weaned from the ventilator and discharged from the hospital. Therapy varies by patient, as each patient responds differently to treatment. Furthermore, the concentration of amiodarone present in the lung tissue varies from patient to patient, and this likely affects the duration of required treatment.[44-46] The steroid trial also can be titrated according to the clinical trajectory.

There are several concluding comments to be made from this excellent case presentation. The rare diagnosis of amiodarone-induced pulmonary toxicity should be considered whenever therapy is initiated. If atrial fibrillation is identified, alternative medications should be considered**.** If amiodarone use is deemed most appropriate, the lowest effective dose should be considered. The oxygen concentration should be minimized whenever clinically possible. Detailed cross-sectional chest imaging plays an important diagnostic role in this setting. Clinical suspicion of this diagnosis should lead to cessation of amiodarone therapy, followed by steroid therapy. Finally, the clinical trajectory also can be affected by serial chest imaging.

Expert Commentary (Dr. Marchant/Dr. Fernando)

Amiodarone is one of the most common medications for arrhythmias.[4-8] Although it has many potential benefits, it is accompanied by a host of possible side effects, including amiodarone pulmonary toxicity.[22-24, 33-35] In this case conference, the authors discuss an uncommon but very serious

scenario, wherein a patient being treated with amiodarone for unstable atrial fibrillation developed ARDS. Ultimately, this conferred significant morbidity and contributed to a prolonged hospitalization.

The association of amiodarone and pulmonary toxicity is not new, and has an incidence in the range of 1%-to-10% in prior studies, depending on variables such as definitions and clinical setting.[48] Older patients and those with prior pulmonary disease may be at elevated risk.[49] Further possible risk factors include male sex, delivery of high oxygen levels, and previous cardiac or thoracic surgery.[10,28-31,49] The daily and cumulative treatment doses, as well as treatment duration, also may play a role.[20,32-38] Unfortunately, the clinical efforts to minimize the risks of this lung toxicity have been limited due to its ongoing prevalence despite smaller doses of amiodarone, shorter durations of treatment, and even after discontinuation of the drug.[10,20,28-36]

Classically, a patient would develop subacute interstitial pneumonitis after being treated with amiodarone over a long period.[3] Symptoms often are nonspecific, such as cough and shortness of breath. Infiltrates may be present bilaterally on chest radiography.[39,40] Computed tomography further highlights the extensive nature of the disease process, and pulmonary function tests demonstrate a restrictive defect, with a low diffusing capacity of the lung for carbon monoxide.[10,28-31,30,40]

In contrast to this classic presentation, an acute lung injury also has been described in association with amiodarone therapy.[3] The clinical spectrum includes diffuse interstitial pneumonitis, diffuse interstitial hemorrhage, and acute respiratory distress syndrome with diffuse alveolar injury.[3] Clinical retrospective trials in the 1990s documented an incidence as high as 10% of acute lung injury with the use of amiodarone therapy in the perioperative setting.[50,51] Subsequent randomized clinical trials with amiodarone have documented a very low incidence, below 1%.[3,52,53] Overall, these conflicting results have suggested to some investigators that the extent to which amiodarone is associated with acute lung injury may be limited, perhaps playing a role in a vulnerable patient, rather than solely being the cause.[3]

The relationship between acute pulmonary toxicity and cardiothoracic surgery is particularly concerning because atrial fibrillation is a common occurrence in the postoperative period.[1,2,5,6,54,55] To guide management of perioperative atrial fibrillation in this setting, the Society of Cardiac Anesthesiologists and European Association of Cardiothoracic Anesthetists recently have developed and published a practice advisory.[9] Amiodarone therapy has been given a class IIa recommendation for the prevention of atrial fibrillation in patients in sinus rhythm and at high risk for this arrhythmia. Furthermore, in this practice advisory, amiodarone therapy was designated a class IIa recommendation for rhythm control in episodes of atrial fibrillation. Interestingly, although greater than 90% of members from these two professional societies indicated that they routinely chose amiodarone to treat atrial fibrillation, only 30%-to-40% of members routinely chose it for prophylaxis.[9] When queried further, the respondents indicated that the adverse effects of amiodarone posed a significant barrier for routine prophylaxis against perioperative atrial fibrillation.[9] Although the authors of the practice advisory acknowledged the possibility of acute lung injury with amiodarone, they reaffirmed that this typically results after longer exposure. This likely explains, in part, the recommendations for amiodarone in both the treatment and prophylaxis of perioperative atrial fibrillation in the cardiothoracic setting. Although its incidence may be lower in transcatheter compared to surgical aortic valve replacement, many patients such as the one presented in this case conference may present for transcatheter aortic valve replacement with a prior history of atrial fibrillation.[56,57] Also, the approach may play a role, with transapical procedures possibly conferring more risk than transfemoral.[56,57]

ARDS is characterized by an immune-mediated damage to alveolar endothelium with subsequent impairment in gas exchange and pulmonary compliance.[58,59] Although in the overall population there are many risk factors, factors such pneumonia, aspiration, sepsis, hemorrhagic shock, and blood transfusion deserve mention as they specifically related to this patient. Although there is conflicting evidence as to risk factors specific to the cardiac surgical population, factors such as prior cardiac surgery, complex procedures, emergency procedures, and transfusion of more than three units of packed red blood cells often are identified.[59,60] Regardless of etiology, this syndrome is a major driver behind postoperative respiratory failure after cardiothoracic procedures. Unfortunately, when it develops, it has been associated with a mortality rate as high as 40%-to-80%.[59,60]

The patient presented in this case conference clearly had a complex perioperative course with significant pulmonary involvement. She required emergent tracheal intubation intraoperatively, with titrated mechanical ventilation and periods of high concentrations of inspired oxygen. Her worsening respiratory status resulted in antibiotic therapy for presumed pneumonia, and intermittent bronchoscopy for pulmonary hygiene and respiratory culture. When radiographic evidence was suggestive of diffuse alveolar injury, a differential diagnosis was considered, with the ultimate diagnosis being amiodarone-induced pulmonary toxicity with an ARDS as its phenotypic manifestation. Because this diagnosis is uncommon and relies on exclusion of more common etiologies, the care team was appropriate in considering a robust differential diagnosis.

The response in the first postoperative week was clinically consistent with ventilator-associated pneumonia that typically develops about 48-to-72 hours after intubation.[61] Although this chest infection may occur in up to 25% of mechanically ventilated patients, the risk is highest during the first five days of endotracheal intubation.[61] Indeed, this was addressed by the critical care team as evidenced by the initiation of levofloxacin. The emergent nature of endotracheal intubation also opens up the possibility of pulmonary aspiration. In emergency medicine, witnessed aspiration during endotracheal intubation has an incidence of approximately 5%, whereas occult aspiration (as assessed by pepsin analysis in tracheal aspirates) may occur in up to 50% of emergent endotracheal intubations.[62] Although there certainly are differences between urgent perioperative and emergency department intubations, especially regarding

fasting status, this nevertheless does raise concern for the risk of aspiration, particularly in patients requiring bag mask ventilation. Overall, these two aspects of the case are important because a recent review noted that among all established risk factors for ARDS, the preponderance of occurrence (upward of 85%) can be attributed to pneumonia, aspiration, and sepsis.[63]

The possibility of transfusion-associated acute lung injury also was considered as a potential culprit for the patient's respiratory compromise.[64] This form of alveolar injury has been defined as new acute-onset lung injury with radiographic evidence of bilateral infiltrates that occurs within six hours of administration of blood products in a patient without other risk factors for acute lung injury.[64] Sometimes this syndrome may follow exposure to just one unit of blood.[64] These criteria have come into question recently as critically ill patients, who have additional risk factors for acute lung injury, also seem to sustain lung injuries with blood transfusions, albeit on a different timeline.[65,66] A recent cohort study of critically ill patients found that the odds ratio for developing ARDS after blood transfusion was 2.74 compared to controls who did not receive blood.[65] In light of this type of data, leaders have proposed a delayed syndrome to describe lung injury manifesting after blood transfusion over an extended timeline (six-72 hours after transfusion) and independent of additional risk factors.[65,66] This delayed acute lung injury occurred in up to a quarter of transfused critically ill patients in a dose-dependent manner, with additional units of blood increasing risk.[66] Notably, although this type of delayed acute lung injury is certainly a consideration, this patient also experienced hemorrhagic shock and massive blood transfusion, which are both independent risk factors for ARDS, though whether this is a separate mechanism remains unclear.[59,60,63-66]

As outlined in this case conference, this patient had multiple etiologies to explain the development of ARDS. However, the timeline did not strongly support some of these factors. In fact, after exposure to these insults, the patient's respiratory status improved substantially to the point that she had a brief trial of tracheal extubation, with her failure in this setting being attributed to vocal cord dysfunction. The onset of the diffuse alveolar injury after resolution of known instigators makes the diagnosis of amiodarone lung all the more likely. However, perhaps amiodarone is only partially to blame. A recent comprehensive narrative review of this topic in the *Journal* has questioned its prevalence, and highlighted the scant recent literature, but did point out that amiodarone may play a contributory role in the pathogenesis of postoperative ARDS.[3]

Regardless of the postulated mechanisms, exposure to high-oxygen concentrations, as well as cardiothoracic procedures, seem to be risk factors for the development of amiodarone-induced lung injury.[10,28-31] These multiple associations suggest that this type of lung injury does not exist in a vacuum; rather, its development occurs in already stressed lungs.[36-38] Indeed, theories surrounding its pathogenesis involve a two-stage phenomenon, with the first stage being a perioperative stressor damaging the lungs enough for the second stage of amiodarone toxicity to result in ARDS.[3] Could this have been what happened in this patient? Perhaps this patient sustained an initial lung injury that did not progress until exposed to the added insult of amiodarone. On the other hand, did her initial recovery suggest that amiodarone alone was the culprit? Regardless, this case serves to raise awareness about the potential serious complications of this widely used medication.

In summary, although pulmonary toxicity classically is a consequence of long-term amiodarone therapy, this case conference raises suspicion for the possibility of acute toxicity as well. Unfortunately, the exact nature of the relationship between amiodarone and acute alveolar injury is not completely clear in the literature due to mixed findings. Until additional evidence is available, recent clinical guidelines have recommended amiodarone for the treatment and prophylaxis of atrial fibrillation complicating cardiac surgery. Nevertheless, despite the potential for acute lung injury, amiodarone should be kept in mind, particularly when respiratory failure persists and the etiology remains elusive despite comprehensive clinical investigation.

Conflict of Interest

None.

References

1 Boons J, Van Biesen S, Fivez T, et al. Mechanisms, prevention and treatment of atrial fibrillation after cardiac surgery: A narrative review [epub ahead of print]. J Cardiothorac Vasc Anesth 2021. https://doi.org/10.1053/j.jvca.2020.11.030; Accessed June 14th 2021.

2 Zimetbaum P. Antiarrhythmic drug therapy for atrial fibrillation. Circulation 2012;125:381–9.

3 Feduska ET, Thoma BN, Torjman MC, et al. Acute amiodarone pulmonary toxicity. J Cardiothorac Vasc Anesth 2021;35:1485–94.

4 Pollak PT. Oral amiodarone: Historical overview and development. Pharmacotherapy 1998;18:121S–6S.

5 January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014;130:e199–267.

6 January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:104–32.

7 Zimetbaum P. Amiodarone for atrial fibrillation. New Engl J Med 2007;356:935–41.

8 Waks JW, Zimetbaum P. Antiarrhythmic drug therapy for rhythm control in atrial fibrillation. J Cardiovasc Pharmacol Therapeut 2017;22:3–19.

9 O'Brien B, Burrager PS, Ngai JY, et al. Society of Cardiovasclar Anesthesiologists/European Association of Cardiothoracic Anaesthetists practice advisory for the perioperative atrial fibrillation in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2019;33:12–26.

10 Wolkove N, Baltzan M. Amiodarone pulmonary toxicity. Can Respir J 2009;16:43–8.

11 Skeoch S, Waetherley N, Swift AJ, et al. Drug-induced interstitial lung disease: A systematic review. J Clim Med 2018;7:356.

12 Watts MM, Grammer LG. Hypersensitivity pneumonitis. Allergy Asthma Proc 2019;40:425–8.

13 Pesenti A, Musch G, Lichtenstein D, et al. Imaging in acute respiratory distress syndrome. Intensive Care Med 2016;42:686–98.
14 Rossi G, Cavazza A, Spagnolo P, et al. The role of macrophages in interstitial lung diseases. Eur Resp Rev 2017;261:170009.
15 Bedrossian CW, Warren CJ, Char J, et al. Amiodarone pulmonary toxicity: Cytopathology, ultrastructure, and immunocytochemistry. Ann Diagn Pathol 1997;1:47–56.
16 Endoh Y, Hanai R, Uto K, et al. KL-6 as a potential new marker for amiodarone-induced pulmonary toxicity. Am J Cardiol 2000;86:229–31.
17 Endoh Y, Hanai R, Uto K, et al. Diagnostic accuracy of KL-6 as a marker of amiodarone-induced pulmonary toxicity. Pac Clin Electrophysiol 2000;23:2010–3.
18 Kobayashi J, Kitamura S. KL-6: A serum marker for interstitial pneumonia. Chest 1995;108:311–5.
19 Teerakanok J, Tantrachoti P, Chariyawong P, et al. Acute amiodarone pulmonary toxicity after surgical procedures. Am J Medical Sci 2016;352:646–51.
20 Kaushik S, Hussain A, Clarke P, et al. Acute pulmonary toxicity after low-dose amiodarone therapy. Ann Thorac Surg 2001;72:1760–1.
21 Brien JF, Jimmo S, Brennan FJ, et al. Distribution of amiodarone and its metabolite, desethylamiodarone, in human tissues. Can J Physiol Pharmacol 1987;65:360–4.
22 Vassallo P, Trohman RG. Prescribing amiodarone: An evidence-based review of clinical indications. JAMA 2007;298:1312–22.
23 Siddoway LA. Amiodarone: Guidelines for use and monitoring. Am Fam Physician 2003;68:2189–96.
24 Primeau R, Agha A, Giorgi C, et al. Long-term efficacy and toxicity of amiodarone in the treatment of refractory cardiac arrhythmias. Can J Cardiol 1989;5:98–104.
25 Soar J, Perkins GD, Maconochie I, et al. European Resuscitation Council Guidelines for Resuscitation: 2018 Update – antiarrhythmic drugs for cardiac arrest. Resuscitation 2019;134:99–103.
26 Aasbo JD, Lawrence AT, Krishnan K, et al. Amiodarone prophylaxis reduces major cardiovascular morbidity and length of stay after cardiac surgery: A meta-analysis. Ann Intern Med 2005;143:327–36.
27 Voulgareli I, Chronaiou A, Tsoukalas D, et al. A rare case of lipoid pneumonia attributed to amiodarone. Pneumonia (Nathan) 2018;10:12.
28 Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity: Recognition and pathogenesis (Part I). Chest 1988;93:1067–75.
29 Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity: Recognition and pathogenesis (Part 2). Chest 1988;93:1242–8.
30 Camus P, Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Clin Chest Med 2004;25:65–75.
31 Jessurun GA, Crijns HJ. Amiodarone pulmonary toxicity. BMJ 1997;314:619–20.
32 Polkey MI, Wilson PO, Rees PJ. Amiodarone pneumonitis: No safe dose. Respir Med 1995;89:233–5.
33 Goldschlager N, Epstein AE, Naccarelli GV, et al. A practical guide for clinicians who treat patients with amiodarone. Heart Rhythm 2007;4:1250–9.
34 Sunderji R, Kanji Z, Gin K. Pulmonary effects of low dose amiodarone: A review of the risks and recommendations for surveillance. Can J Cardiol 2000;16:1435–40.
35 Ott MC, Khoor A, Leventhal JP, et al. Pulmonary toxicity in patients receiving low-dose amiodarone. Chest 2003;123:646–51.
36 Baron E, Mok WC, Jayawardena M, et al. Amiodarone lung: Under recognized but not forgotten. J R Coll Physicians Edinb 2021;51:61–4.
37 Ashrafian H, Davey P. Is amiodarone an underrecognized cause of acute respiratory failure in the ICU? Chest 2001;120:275–82.
38 Saussine M, Colson P, Alauzen M, et al. Postoperative acute respiratory distress syndrome. A complication of amiodarone associated with 100 percent oxygen ventilation. Chest 1992;102:980–1.
39 Oyama N, Oyama N, Yokoshiki H, et al. Detection of amiodarone-induced pulmonary toxicity in supine and prone positions: High-resolution computed tomography study. Circ J 2005;69:466–70.
40 Kuhlman JE, Teigen C, Ren H, et al. Amiodarone pulmonary toxicity: CT findings in symptomatic patients. Radiology 1990;177:121–5.
41 Malhotra A, Muse VV, Mark EJ. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 12-2003. An 82-year-old man with dyspnea and pulmonary abnormalities. N Engl J Med 2003;348:1574–85.
42 Kennedy JI, Myers JL, Plumb VJ, et al. Amiodarone pulmonary toxicity. Clinical, radiologic, and pathologic correlations. Arch Intern Med 1987;147:50–5.
43 Myers JL, Kennedy JI, Plumb VJ. Amiodarone lung: Pathologic findings in clinically toxic patients. Hum Pathol 1987;18:349–54.
44 Nakajima M, Kawahara Y, Yoshida K, et al. Serum KL-6 as a possible marker for amiodarone-induced pulmonary toxicity. Intern Med 2000;39:1097–100.
45 Schwaiblmair M, Berghaus T, Haeckel T, et al. Amiodarone-induced pulmonary toxicity: An under-recognized and severe adverse effect? Clin Res Cardiol 2010;99:693–700.
46 Terzo F, Ricci A, D'Ascanio M, et al. Amiodarone-induced pulmonary toxicity with an excellent response to treatment: A case report. Respir Med Case Rep 2020;29:100974.
47 Nacca N, Bhamidipati CM, Yuhico LS, et al. Severe amiodarone induced pulmonary toxicity. J Thorac Dis 2012;4:667–70.
48 Jackevicius CA, Tom A, Essebag V, et al. Population-level incidence and risk factors for pulmonary toxicity associated with amiodarone. Am J Cardiol 2011;108:705–10.
49 Abuzaid A, Saad M, Ayan M, et al. Acute amiodarone pulmonary toxicity after drug holiday: A case report and review of the literature. Case Rep Cardiol 1993;2015:927438.
50 Van Mieghem W, Coolen L, Malysse I, et al. Amiodarone and the development of ARDS after lung surgery. Chest 1994;105:1642–5.
51 Hawthorne HR, Wood MA, Stambler BS, et al. Can amiodarone pulmonary toxicity be predicted in patients undergoing implantable cardioverter defibrillator implantation? Pacing Clin Electrophysiol 2021;16:2241–9.
52 Mitchell LB, Exner DV, Wyse DG, et al. Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPABEAR: A randomized controlled trial. JAMA 2005;294:3093–100.
53 Crystal E, Kahn S, Roberts R, et al. Long-term amiodarone therapy and the risk of complications after cardiac surgery: Results from the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT). J Thorac Cardiovasc Surg 2013;125:633–7.
54 Van Cott TE, Yehle KS, DeCrane SK, et al. Amiodarone-induced pulmonary toxicity: Case study with syndrome analysis. Heart Lung 2021;42:262–6.
55 Gillinov AM, Bagiella E, Moskowitz AJ, et al. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. N Engl J Med 2016;374:1911–21.
56 Motloch LJ, Reda S, Rottlaender D, et al. Postprocedural atrial fibrillation after transcatheter aortic valve implantation versus surgical aortic valve replacement. Ann Thorac Surg 2012;93:124–31.
57 Tarantini G, Mojoli M, Urena M, et al. Atrial fibrillation in patients undergoing transcatheter aortic valve implantation: Epidemiology, timing, predictors, and outcome. Eur Heart J 2017;38:1285–93.
58 Kogan A, Segel MJ, Ram E, et al. Acute respiratory distress syndrome following cardiac surgery: Comparison of the American-European Consensus Conference definition versus the Berlin definition. Respiration 2019;97:518–24.
59 Rong LQ, Di Franco A, Gaudino M. Acute respiratory distress syndrome after cardiac surgery. J Thorac Dis 2016;8:E1177–86.
60 Stephens RS, Shah AS, Whitman GJR. Lung injury and acute respiratory distress syndrome after cardiac surgery. Ann Thorac Surg 2013;95:1122–9.
61 Kalanuria AA, Ziai W, Mirski M. Ventilator-associated pneumonia in the ICU. Crit Care 2014;18:208.
62 Driver BE, Klein LR, Schick AL, et al. The occurrence of aspiration pneumonia after emergency endotracheal intubation. Am J Emerg Med 2018;36:193–6.

63 Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562–72.
64 McVey MJ, Kapur R, Cserti-Gazdewich C, et al. Transfusion-related acute lung injury in the perioperative patient. Anesthesiology 2019;131:693–715.
65 Zilberberg MD, Carter C, Lefebvre P, et al. Red blood cell transfusions and the risk of acute respiratory distress syndrome among the critically ill: A cohort study. Crit Care 2007;11:R63.
66 Marik PE, Corwin HL. Acute lung injury following blood transfusion: Expanding the definition. Crit Care Med 2008;36:3080–4.