A reversal of fortune: A case of cardiovascular collapse following protamine sulfate infusion

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Introduction

We present the case of an 84-year-old man who developed the acute onset of cardiovascular collapse after protamine infusion at the end of an atrial fibrillation (AF) ablation. Factors associated with presentation and management of this potentially fatal reaction are discussed.

Case report

An 84-year-old man with a history of coronary artery disease and symptomatic paroxysmal AF presented to the hospital for a repeat AF ablation.

He had a history of paroxysmal AF with onset 6 years prior to presentation. He underwent successful electrical cardioversion at that time and was started on dofetilide. He continued to have symptomatic episodes of AF and underwent a pulmonary vein isolation 5 years prior to presentation. He remained asymptomatic until 2 years prior when he was hospitalized for AF and successfully electrically cardioverted. He was seen in clinic 2 months prior to presentation and the decision was made to pursue repeat ablation for symptomatic AF.

Upon presentation his blood pressure was 133/59, heart rate 74, and SpO2 94% on room air. He was well appearing, with lungs clear to auscultation bilaterally and no lower extremity edema. His jugular venous pressure was within normal limits. Auscultation revealed irregularly irregular rhythm without murmurs or gallops. His most recent electrocardiogram (ECG) 3 months prior to presentation showed normal sinus rhythm with a known right bundle branch block and first-degree atrioventricular block (Figure 1). Preprocedural transesophageal echocardiogram showed a normal ejection fraction (EF) and no left atrial appendage thrombus. Transthoracic echocardiogram (TTE) 6 months prior to presentation demonstrated a preserved EF (Video 1).

Radiofrequency ablation was performed with successful bilateral pulmonary vein and left atrial posterior wall isolation. He was anticoagulated with heparin and received a total dose of 15,000 units throughout the case. Anticoagulation was reversed with protamine sulfate. Activated clotting time was 364 ms at time of reversal. A 5 mg test dose was given and after a 5-minute waiting period, an additional 65 mg was given over 10 minutes. The patient then had profound cardiovascular collapse near the end of the infusion requiring hemodynamic support with boluses of epinephrine and phenylephrine and a continuous infusion of dopamine and vasopressin.

TTE performed during this event showed a newly reduced EF to 30% with global hypokinesis (Video 2). He was then given 100 mg hydrocortisone, 25 mg diphenhydramine, and 163.5 mg methylene blue.

Prior to this instance, he had received protamine sulfate 3 separate times without issue. He had received 60 mg of protamine 3 months prior for an abdominal aortic aneurysm repair. He had also received protamine for his coronary artery bypass graft (14 years prior) and his prior AF ablation (5 years prior). He had a remote history of vasectomy. He had no documented history of neutral protamine Hagedorn (NPH) insulin use or fish allergy.

While requiring ionotropic support, he developed sustained atrial tachycardia for which cardioversion was attempted twice at 360 J. He then developed sustained ventricular tachycardia and was given 300 mg intravenous amiodarone and successfully cardioverted. In the following 24 hours he was weaned from norepinephrine and continued on amiodarone owing to continued AF while on inotropes. His ejection fraction 24 hours later had normalized (Video 3). He underwent cardioversion again on postprocedure day 3 and was discharged home the same day.

Given the acute presentation, the differential included cardiac tamponade, malignant arrhythmia, hemorrhagic shock, medication toxicity, anaphylaxis, acute coronary syndrome, intracranial hemorrhage, and air embolus. The TTE showed

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KEY TEACHING POINTS

- Risk factors for anaphylaxis to protamine sulfate include previous exposure to protamine, neutral protamine Hagedorn (NPH) insulin use, fish allergies, and previous vasectomy.
- Protamine sulfate anaphylactic reactions can be distinguished from other acute causes of cardiac decompensation by the timing relative to protamine use, bedside echocardiography, laboratory evaluation, and electrocardiography.
- Little evidence guides the treatment and management of protamine reactions. Pretreatment with steroids and antihistamines in high-risk patients and the use of methylene blue for refractory anaphylaxis are options for management.

no effusion or cardiac tamponade. It demonstrated global hypokinesis without any regional wall motion abnormalities to suggest acute coronary syndrome. ECG during the event initially revealed normal sinus rhythm without evidence of ST- or T-wave abnormalities prior to the development of atrial and ventricular tachycardia. Neurogenic shock secondary to intracranial hemorrhage or air embolus also appeared unlikely, given the evidence of cardiac decompensation on TTE. His hemoglobin was stable, with no clinical signs of hemorrhage. Given the temporal association with protamine administration and global hypokinesis seen on TTE, protamine reaction was felt to be the most likely etiology of his acute decompensation.

At 2-month follow-up he felt well, with no fatigue, chest pain, or symptomatic AF as noted at previous visits. Amiodarone was stopped.

Discussion

We present a case of anaphylaxis and cardiovascular collapse in response to protamine sulfate. Protamine sulfate is derived from salmon sperm and is a commonly used agent for reversal of periprocedural anticoagulation and with apheresis.[1] Many physiologic derangements including hypotension, transient pulmonary hypertension, decreased contractility, and bronchospasm have been described. Descriptions of decreased cardiac contractility as observed in our patient are thought to arise from globally decreased coronary perfusion mediated by leukotriene C_4 and prostaglandin D_2 released from cardiac mast cells.[2] Platelet activating factor, another common mediator of anaphylaxis, has also been shown in animal models to reduce coronary blood flow and, subsequently, myocardial contractility.[3] Although rare, anaphylactic reactions to protamine sulfate have previously been described for decades and are thought to arise via IgG and IgE mechanisms[4,5] in addition to direct mast cell degranulation and complement activation.[6] IgE-mediated mechanisms of anaphylaxis have been studied in the context of diabetics exposed to protamine antigens through insulin preparations, whereas IgG appears implicated in patients with previous exposure to protamine.

Risk factors for anaphylaxis include fish allergies, previous vasectomy, and previous exposures to NPH insulin or protamine sulfate. The patient in our case had multiple previous exposures to protamine and a remote vasectomy.

Protamine is thought to share antigens with fish proteins, resulting in cross reactivity. Various studies have shown an association with fish allergies[7]; however, the absolute risk is extremely small and other studies have disputed this finding.[1]

Protamine is used in insulin formulations to slow the rate of absorption, hence its use in NPH insulin.[8] Use of NPH insulin has been associated with increased IgG or IgE to protamine sulfate and an increased risk of anaphylaxis to protamine.[6] Other

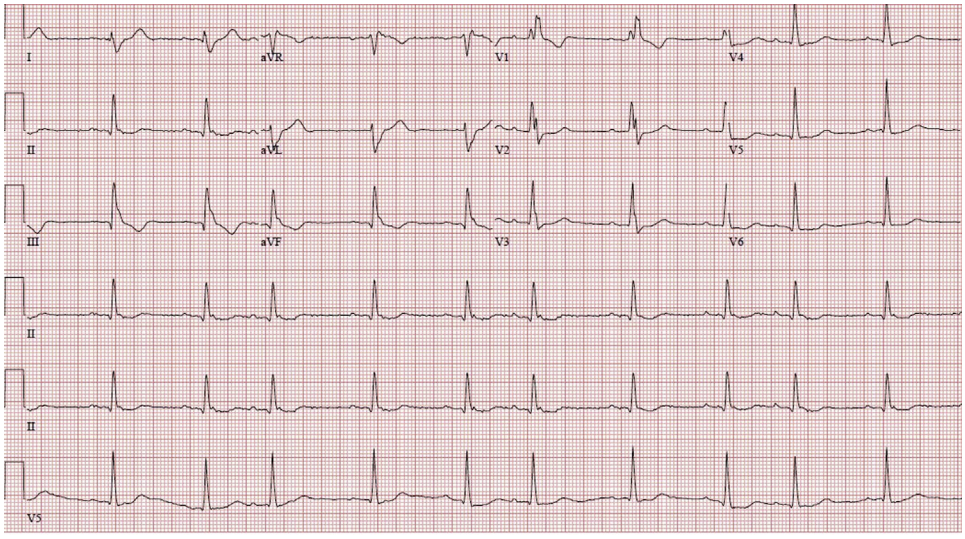

Figure 1 Preprocedural electrocardiogram.

insulin formulations do not show this association. One study showed that only diabetic patients with daily injections of NPH would develop IgE, whereas patients with infrequent or previous injections of NPH would develop IgG antibodies, suggesting previous exposure to protamine sulfate.[5]

Following a vasectomy, the blood-testes barrier is interrupted, resulting in sensitization of the host immune system to antigens common to sperm. It has been postulated that this represents a risk factor for protamine anaphylaxis, given the common antigenic precursor.[9] One study found 29% of men with previous vasectomies had developed a specific IgG against protamine, in comparison with 0% of the control group.[10] The presence of IgG and IgE antibodies to protamine has previously been demonstrated to confer risk of anaphylaxis.[5] Despite this, no causative relationship has been identified.

An additional consideration in our case is the dose of protamine used. Protamine doses of greater than 50 mg over 10 minutes are not recommended in the package insert for protamine.[11,12] Although higher doses likely confer increased risk, no evidence exists that has established protamine dose as a risk factor for anaphylactoid reactions.

For patients with the above risk factors, one must be aware of the risk for anaphylaxis in response to protamine sulfate. One study showed that prophylactic steroids and/or antihistamines in patients using NPH insulin decreased the likelihood of allergic reactions; however, no patient in either group had anaphylaxis.[13] Pretreatment may represent a viable risk-mitigating option.

Identification of an acute protamine anaphylactic reaction necessitates the evaluation for more common causes of cardiac decompensation following ablation. Common etiologies include pericardial tamponade, hemorrhagic shock, and malignant arrhythmia. Time course can help differentiate between the etiologies, given the strong temporal association of protamine administration to anaphylaxis. Initial diagnostics should include a focused echocardiogram, ECG, and laboratory evaluation.

Despite the severity of the reaction observed in this case, anaphylactic reactions to protamine sulfate remain exceedingly rare and, often, case reportable. Reversal of procedural anticoagulation during pulmonary vein isolation with protamine sulfate has been shown to decrease time to vascular hemostasis without a concomitant increase in vascular or thromboembolic complications.[14]

In the case of a suspected protamine anaphylactic reaction, little evidence exists to guide treatment. We recommend standard management of anaphylaxis including steroids, epinephrine, and antihistamines in addition to intravenous fluids and mechanical circulatory support as needed. Several small studies have evaluated the role of methylene blue owing to its nitric oxide synthase inhibition and the known role of nitric oxide in anaphylaxis to protamine.[15] This may represent a viable option for treatment; however, little evidence exists on its efficacy.

Conclusion

Anaphylaxis to protamine sulfate is extremely rare. Risk factors include previous exposure to protamine, NPH insulin use, and previous vasectomy. Pretreatment with steroids and antihistamines and use of methylene blue for refractory anaphylaxis in addition to standard treatment may be associated with better outcomes.

Appendix

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hrcr.2020.02.008.

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