Man with Syncope

Emily Lai MD, PGY-2 and Anita Mehrotra MD, PGY-1

Mr. K, a 57 year-old Caucasian male with a history of coronary artery disease, dilated ischemic cardiomyopathy, ventricular fibrillation arrest status post implantable cardioverter defibrillator (ICD) placement was admitted to telemetry for two syncopal episodes. The patient described multiple episodes of dizziness with fatigue over the week prior to admission, the last two episodes resulting in loss of consciousness with bladder incontinence. He was home alone when these episodes occurred and was unsure of how long he had been unconscious. Mr. K was not aware of any recent firing of his ICD. He denied any shortness of breath, chest pain, diaphoresis, recent fevers or chills.

His medical history was significant for hypertension, coronary artery disease status post two vessel coronary artery bypass grafting, dilated cardiomyopathy, and ventricular fibrillation arrest with subsequent ICD placement four years ago. His most recent echocardiogram was four years ago, showing an ejection fraction of 15%. The patient's medications included enalapril, carvedilol, amiodarone, warfarin, ezetimibe, digoxin, atorvastatin, furosemide, aspirin and niacin. He had no known drug allergies. Mr. K was a retired train conductor. He smoked half of a pack of cigarettes a day and had an 80 pack-year smoking history. He had a history of alcohol, cocaine, and amphetamine abuse, but he quit these drugs 15 years prior. He denied any history of intravenous drug use.

Physical examination on admission was significant for elevated jugular venous pressure, a grade II/VI systolic ejection murmur over the left sternal border, diffuse wheezes on lung exam, and 2+ lower extremity edema. Laboratory results showed a B-type natriuretic peptide level of 662 pg/ml, a creatinine of 1.0 mg/dL, and a digoxin level of 1.6 ng/mL. Chest X-ray showed moderate pulmonary edema. His electrocardiogram (ECG) is shown in Figure 1.

The patient was admitted to telemetry and ruled out for myocardial infarction by serial enzymes. His ICD was interrogated on hospital day 1, revealing three episodes of ventricular tachycardia, which correlated with his

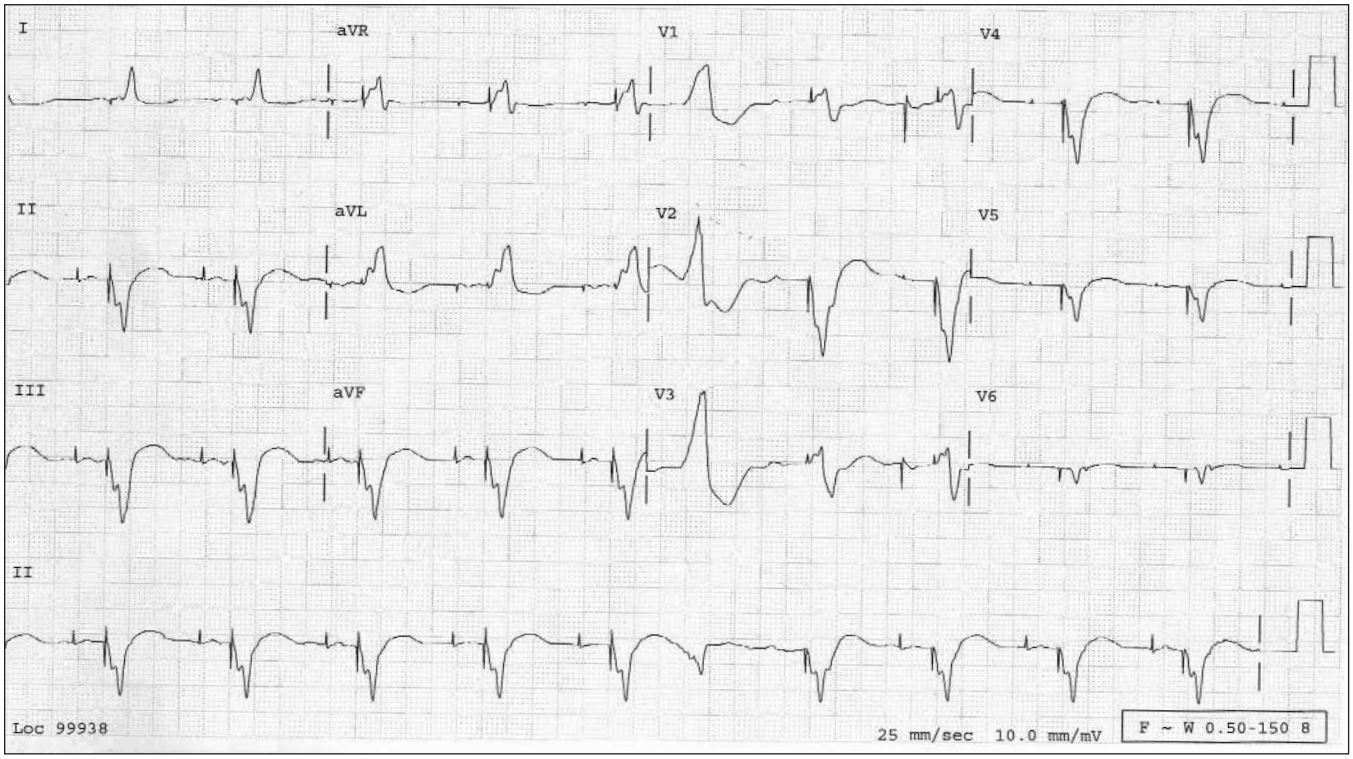

Figure 1

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symptoms. The settings of his ICD were adjusted, and the electrophysiology service recommended reloading the patient with oral amiodarone. The patient was started on amiodarone 400 mg three times a day for the next five days. For treatment of his congestive heart failure exacerbation, the patient was diuresed with intravenous furosemide with a goal negative balance of one to two liters per day. The patient was also started on nebulizers for suspected chronic obstructive pulmonary disease and spironolactone to optimize his heart failure regimen. The patient reported feeling improvement over the next four days.

On the morning of hospital day #5, Mr. K complained of feeling very uncomfortable with a sensation of fullness and bloating in his abdomen, which the patient attributed to being constipated. He reported no bowel movements in the past few days. He also complained of increased weakness, shortness of breath and an episode of chills, nausea and emesis overnight. On physical exam, he was afebrile, heart rate was 60 beats per minute and blood pressure was 124/77 mmHg. His abdomen was distended but nontender with active bowel sounds. No rebound or guarding was present. An arterial blood gas was attempted but was felt to be venous. The pH of the venous blood gas was 7.37. Stool softeners and laxatives were ordered and an extra dose of furosemide was given.

A few hours later, the patient called the nurse complaining of feeling poorly. The nurse noted the patient to be diaphoretic and cyanotic. She attempted to take his blood pressure and could not detect a pressure by manual cuff. The primary team was called to evaluate the patient and detected a systolic blood pressure of 54 mmHg by doppler. A fluid bolus of one liter of normal saline was given with improvement of the systolic blood pressure to 82 mmHg by doppler. The patient complained of an uncontrollable gasping for air but denied any chest pain. Central venous access was obtained, and the critical care unit team was called to evaluate the patient for hypotension and cyanosis.

Physical examination revealed the patient to be alert in moderate distress with cyanotic lips. After a one liter fluid bolus, the patient had a heart rate of 70 beats per minute and respirations were 30 breaths per minute. A pulse oximetry reading was unobtainable due to cyanotic extremities. Jugular venous pressure was estimated at 10mmHg. The systolic murmur was unchanged from prior exams. Lung exam demonstrated wheezes diffusely with 1+ lower extremity edema. A stat echocardiogram was ordered to evaluate the possibility of cardiac tamponade given the patient's hypotension. Echocardiogram showed an ejection fraction of 10%, severe left ventricular enlargement with global dysfunction, mild to moderate mitral regurgitation, but no pericardial effusion.

An electrocardiogram was obtained and is shown in Figure 2. Compared to his previous ECG on admission which showed mostly ventricular paced beats, the patient now had a sinus rhythm with widened QRS complexes (duration 640ms) and peaked T waves. Hyperkalemia was suspected, and the patient was given two ampules of calcium gluconate and 10 units of insulin intravenously with one ampule of dextrose 50%. The patient's blood pressure fell to the 70s/40s mmHg and continous dopamine infusion was started. The patient was placed on a 100% non-rebreather mask and urgently transferred to the cardiac intensive care unit.

Stat laboratory results returned showing the serum potassium to be 6.8 meq/L (compared to 4.0 meq/L the day before), serum bicarbonate of 19 meq/L (previously 31 meq/L), calcium 2.0 mg/dL (from 4.2 mg/dL) and creatinine of 1.7 mg/dL (from 1.0 mg/dL). The patient was given three more ampules of calcium gluconate and two ampules of sodium bicarbonate for his hyperkalemia.

Approximately 10 minutes after arrival to the CCU, the patient began to complain of extreme shortness of breath. His heart rate rapidly decreased to the 50s, and the patient became unresponsive and pulseless. Cardiopulmonary resuscitation was initiated for pulseless electrical activity and three doses of epinephrine were given. The patient's rhythm converted to pulseless ventricular fibrillation, and defibrillation was attempted three times without change in rhythm or recovery of pulse. An intravenous bolus of amiodarone was also given without any response. Resuscitative efforts were continued for 20 minutes before the patient was pronounced dead.

Discussion

Post-mortem, a serum digoxin level sent earlier that morning showed a level of 5.8 ng/ml. This level was well above the upper limit of therapeutic (0.5 to 2 ng/ml).

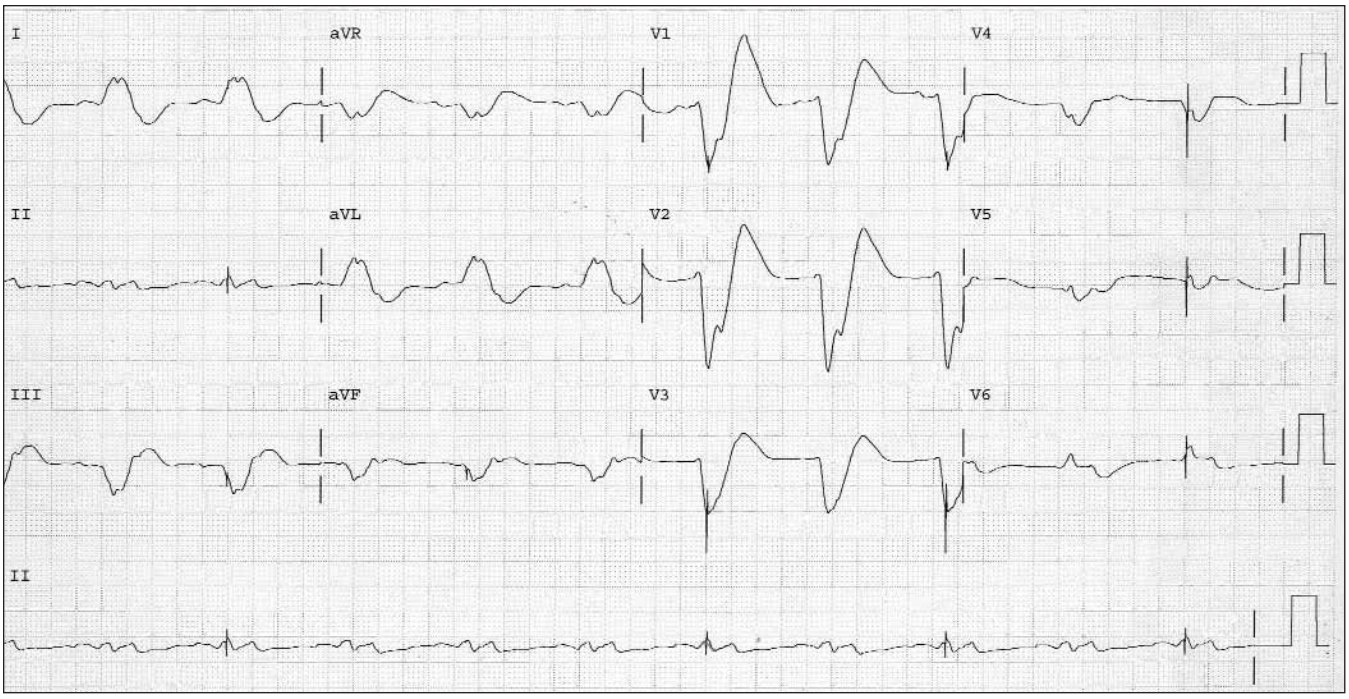

Figure 2

Digoxin toxicity was likely a contributing factor in this unfortunate case. The patient had multiple known risk factors for digoxin toxicity, including cardiac disease, potential electrolyte abnormalities from diuresis, acute renal insufficiency, and the addition of medications that interfere with digoxin metabolism.

Digoxin acts by inhibiting the sodium-potassium adenosine triphosphatase (ATP-ase) pump in myocytes. With each action potential, sodium enters but a decreased amount of sodium exits leading to an increase in intracellular sodium and a decrease in intracellular potassium. Through the sodium-calcium exchange, the increase in sodium results in increased intracellular calcium. This increases myocardial contractility and enhances automaticity while slowing conduction through the atrioventricular node. The decrease in intracellular potassium may cause a relative increase in extracellular potassium leading to elevated serum potassium levels.

The most important method of diagnosing digoxin toxicity is to maintain a high level of suspicion. Signs and symptoms of digoxin toxicity are often subtle and nonspecific. Patients may experience nausea, vomiting, abdominal pain, fatigue, blurred vision, headache, dizziness, confusion, delirium, and altered color vision (classically described as seeing yellow halos around lights). No single ECG abnormality is pathognomonic of digoxin excess. However, the combination of enhanced automaticity and impaired conduction (e.g., atrioventricular (AV) block accompanied by an accelerated junctional pacemaker) is highly suggestive of toxicity even when serum levels are within the "accepted" therapeutic range. The first presenting sign of digoxin toxicity may be a cardiac arrhythmia. Almost any arrhythmia may be associated with digoxin toxicity, though the most frequent is ventricular ectopy. Sinus bradycardia, sinus arrest, paroxysmal atrial tachycardia, heart block, junctional rhythms, ventricular tachycardia and fibrillation are also commonly seen.

Digoxin is excreted through the kidneys proportional to the glomerular filtration rate and is therefore dependent on creatinine clearance. Renal insufficiency is then a predisposing factor for digoxin toxicity. In our patient, the acute renal insufficiency was likely secondary to aggressive diuresis.

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Table 1. Commonly Used Medications that Affect Digoxin Level

Drug	Effect	Mechanism
Amiodarone	Increases	↓ renal clearance
Verapamil	Increases	↓ renal clearance
Diltiazem	Increases	↓ renal clearance
Spironolactone	Increases	↓ renal clearance
Indomethacin	Increases	↓ renal clearance
Cyclosporine	Increases	↓ renal clearance
Tetracycline	Increases	Altered gut flora
Cholestyramine	Decreases	↓ gut absorption
Rifampin	Decreases	Induction of gut P-glycoprotein

Amiodarone, among many other drugs, is known to increase serum digoxin levels though decreased renal excretion at the tubular level and may also displace bound digoxin from tissue. (See Table 1 for a list of other commonly used medications that affect digoxin levels.) It is recommended that patients being started on amiodarone should have their maintenance doses of digoxin decreased by 50 percent with close monitoring of serum digoxin levels. In our patient, his maintenance digoxin dose while on amiodarone 200 mg daily was 0.25 mg with a digoxin level within therapeutic range (1.6 ng/mL). He was also started on spironolactone during his hospitalization, which like amiodarone, increases digoxin levels by decreasing renal clearance. The patient's rapid increase in serum digoxin level was likely due to decreased renal excretion from the combination of the oral amiodarone load, the addition of spironolactone, and acute renal failure.

As previously mentioned, digoxin toxicity may also be associated with hyperkalemia by inhibiting sodium-potassium exchange into the myocyte. In this case, Mr. K had three potential causes of hyperkalemia: acute renal failure, spironolactone use, and digoxin toxicity. The treatment he received for his hyperkalemia included multiple ampules of calcium gluconate which may have further potentiated the effects of digoxin.

Elevated serum calcium levels increase ventricular automaticity and this effect is at least additive to, and may be synergistic with, the effects of digoxin. Administration of intravenous calcium to patients taking digoxin may provoke lethal ventricular arrhythmias, in particular, refractory ventricular tachycardia and fibrillation. Thus, calcium gluconate administration is problematic in hyperkalemia if digoxin toxicity is suspected and generally not recommended. In Mr. K's case, the cause of his cardiac arrest may have been primarily hyperkalemia which would correlate with his rhythm of pulseless electrical activity. However, his rhythm then converted to ventricular fibrillation that was unchanged after multiple attempts at defibrillation. This may have been the effect of the five ampules of calcium gluconate that were unknowingly administered in the context of digoxin toxicity.

In severe cases of digoxin toxicity, digoxin-specific antibody fragments (Digibind) may be used to treat patients. Digibind rapidly binds circulating digoxin (as digoxin has an increased affinity for the antibody fragment over the sodium-potassium pumps) thus inactivating the drug. Indications for use of Digibind include an acute ingestion of greater than 10 mg of digoxin, plasma digoxin levels greater than 10ng/ml, and potassium levels greater than 5meq/L in the presence of a life-threatening arrhythmia, as in this case. The antibody fragments are given intravenously over 30 minutes, unless cardiac arrest has occurred, in which case the solution is given as a bolus. Side effects are few with Digibind but include worsening congestive heart failure and hypokalemia.

Would the outcome of Mr. K's case have been different if digoxin toxicity had been suspected and Digibind administered? We hope that by highlighting this case of digoxin toxicity with associated hyperkalemia, we will heighten awareness for the diagnosis and never have to ask ourselves this question in the future.

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