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Clinical Communications: Adult

SYNERGISTIC BRADYCARDIA FROM BETA BLOCKERS, HYPERKALEMIA, AND RENAL FAILURE

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☐ **Abstract—Background: Bradycardia is a common vital sign encountered in the emergency department. These patients are often hemodynamically stable and require no emergent intervention. On occasion, bradycardia can cause hemodynamic instability, and there are established treatment pathways involving atropine, ionotropic and vasopressive infusions, and eventual mechanical pacing, if necessary. However, these pathways fail to account for the many and varied causes of bradycardia and their treatment. Case Report: A 24-year-old man presented to our emergency department with syncope caused by symptomatic bradycardia. This was caused by a largely unrecognized synergistic bradycardia resulting from renal failure, AV nodal blocker use, and hyperkalemia. Our patient's worsening renal failure caused accumulation of both potassium and beta blocker, which resulted in bradycardia and hypotension, in turn worsening renal failure secondary to poor renal perfusion and potentiating his hyperkalemia and beta blocker toxicity. Why Should an Emergency Physician Be Aware of This?: There is a growing number of cases that suggest this is an underrecognized synergistic and potentially lethal mechanism of hemodynamically unstable bradycardia and the treatment falls outside of typical algorithms for handling bradycardia. Understanding the multiple causes of these patients' hemodynamically unstable bradycardia allows for maximal medical management and can prevent unnecessary invasive management for these patients. © 2019 Elsevier Inc. All rights reserved.**

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☐ **Key words—beta blocker; bradycardia; hyperkalemia; renal failure; shock**

INTRODUCTION

The traditional teaching regarding symptomatic bradycardia recommends atropine sulfate redosed ≤3 mg followed by either dopamine or epinephrine infusion and mechanical pacing for refractory cases. There are many and varied causes of bradycardia that are not necessarily addressed by this algorithm (1–3).

Hyperkalemia is known to cause cardiac irritability by increased resting membrane potential in the cardiac myocytes, impaired depolarization, and accelerated repolarization, resulting in a wide variety of dysrhythmias, including bradydysrhythmia, and ultimately resulting in cardiac arrest (1–3). Commonly cited causes for hyperkalemia are beta blockers because of beta 2 antagonism and extracellular shift and renal failure because of decreased excretion (1–3). It is taught that cardiac abnormalities do not develop until severe hyperkalemia, which is defined as levels >7.0 mg/dL. Treatment of this disorder with the use of beta-adrenergic inhalants, insulin, dextrose, calcium, and bicarbonate are well known to emergency physicians. However, given laboratory delays, this might not be immediately recognized in a patient with hemodynamically unstable bradycardia, and an electrocardiogram might not exhibit the hallmark signs of hyperkalemia (1–3).

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It is also known that a common side effect of beta blockers is bradycardia, which can occur even at low doses. Beta blockers inhibit catecholamines at beta-adrenergic receptors leading to negative inotropy and chronotropy and slowed conduction through the atrioventricular (AV) node. Traditionally, beta blocker toxicity has been treated with glucagon, but other therapies are being discussed (1–3). We present a novel case of a young patient with multifactorial hemodynamically unstable bradycardia resulting in syncope. We also review a set of cases over the past 18 years that suggest that this is an unrecognized synergistic mechanism that results in significant bradycardia.

CASE REPORT

A 24-year-old man with history of hypertension and a now failed renal transplant who was restarted on hemodialysis presented to our emergency department (ED) after a brief resolved syncopal episode. Our patient stated that he came home from his manual labor job and felt ill, so he took 1 extra tablet of his metoprolol. He then proceeded to have a seconds-long syncopal episode witnessed by a family member. He also noted that he was anuric for several days, which was abnormal for him. He had never had similar episodes and was fully compliant with his dialysis. It was noted that the patient had an age-normal electrocardiogram (ECG) at our hospital several months earlier.

The initial vital signs and the physical examination were unremarkable. However, shortly into his ED stay, a member of our staff was called to the room to evaluate the patient. The patient was noted to be markedly bradycardic on telemetry, unresponsive, and hypotensive. An ECG revealed the patient to be in a junctional bradycardia with a rate of 40 beats/min (Figure 1). The patient received 1 mg of atropine sulfate, after which his heart rate normalized, and his mental status improved. He was also given 1 amp of calcium gluconate empirically because of his history of renal failure. Point-of-care laboratory values revealed a serum potassium of 7.4 mEq/L. The patient was then treated with sodium bicarbonate and intravenous fluids. However, over the next 30 min the patient continued to have recurrent bradycardia requiring multiple doses of atropine sulfate and worsening mental status. He also had multiple asystole pauses, lasting as long as 10 seconds. At this point, the patient was intubated, started on an epinephrine infusion, and a transvenous pacemaker was placed, which successfully stabilized the patient's heart rate and blood pressure.

The patient was admitted to the intensive care unit where he was emergently dialyzed, and his heart rate returned to normal by the following day. Further evaluation for causes of his bradycardia were all unremarkable. He was later extubated and transferred to the floor. An ECG several days later was again age-normal.

DISCUSSION

It was felt that this patient's life-threatening bradycardia was related to a synergistic effect of his hyperkalemia, kidney failure, and beta blocker overload. This patient had worsening renal failure as evidenced by his recent

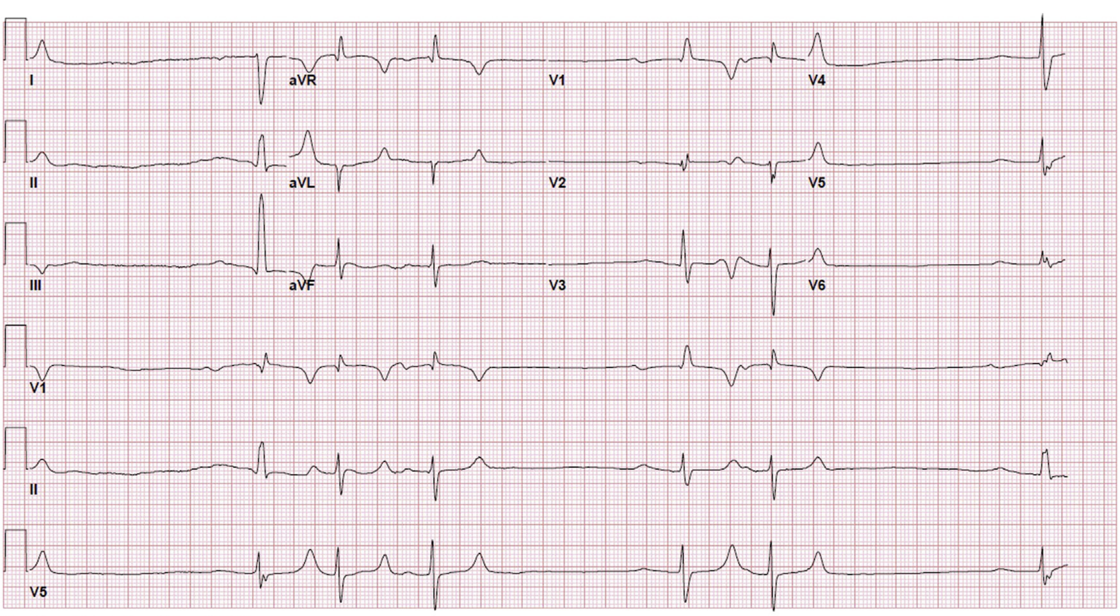

Figure 1. The electrocardiographic results from our patient immediately upon his sudden onset of bradycardia and altered mentation.

Table 1. Cases of Synergistic Bradycardia Reported Since 2000

Year	Patient Age, Years	HR, Beats/Min	MAP, mm Hg	AV Nodal Blocker	K^+, mEq/L	Cr, mg/dL	Treatment	Reference
2002	78	40	80	Metoprolol	7.4	8.5	Calcium, emergent permanent pacer	Zimmers and Patel (5)
2002	81	52	131	Atenolol	6.0	2.1	Lasix and bicarbonate	Zimmers and Patel (5)
2004	57	48	73	Carvedilol	6.8	2.7	Not specified	Vuckovic and Richlin (6)
2006	70	48	71	Metoprolol	6.5	3.3	Albuterol, calcium, sodium polystyrene sulfonate, transcutaneous pacing, and hemodialysis	Isabel and Champion (7)
2006	54	22	40	Diltiazem and atenolol	6.4	1.8	Atropine, transcutaneous pacing, insulin, and calcium	Bonvini et al. (8)
2006	63	—	—	Verapamil	6.8	Dialysis	Not specified	Letavernier et al. (9)
2006	57	—	—	Verapamil	6.4	Dialysis	Atropine, held verapamil	Letavernier et al. (9)
2006	58	—	—	Verapamil	6.7	Dialysis	Emergent dialysis, held verapamil	Letavernier et al. (9)
2008	78	33	—	Unspecified beta and calcium channel blocker	7.9	2.1	Calcium, insulin, lasix, and sodium polystyrene sulfonate	Unterman and Moscavitch (10)
2008	77	30	53	Propranolol and diltiazem	6.7	2.7	Dopamine, Foley, calcium, insulin, and sodium polystyrene sulfonate	Mirandi et al. (11)
2009	79	28	79	Metoprolol and amlodipine	6.4	4.4	Calcium, bicarbonate, and sodium polystyrene sulfonate	Argulian (12)
2010	76	28	79	Carvedilol	9.2	1.3	Transcutaneous pacing, insulin, and bicarbonate	Erden et al. (13)
2011	97	56	75	Amlodipine	6.3	1.6	Calcium and insulin	Aziz et al. (14)
2011	70	38	62	Carvedilol	6.1	2.1	Calcium and insulin	Aziz et al. (14)
2012	65	48	85	Verapamil	5.6	3.0	Calcium and insulin	Hegazi et al. (15)
2012	57	44	67	Verapamil	5.1	1.7	Calcium and albuterol	Hegazi et al. (15)
2013	85	33	61	Sotalol	10.1	2.5	Calcium, bicarbonate, insulin, albuterol, and hemodialysis	Juvet et al. (16)
2017	81	33	104	Bisoprolol and amlodipine	5.8	2.8	Atropine and isoproterenol	Ahmad and Tan (17)

AV = atrioventricular; HR = heart rate; MAP = mean arterial pressure.

sudden cessation of urine output. This led to accumulation of potassium and beta blockade, both requiring renal clearance, causing a synergistic symptomatic bradycardia. His worsening renal failure caused the accumulation of both potassium and beta blocker, resulting in his bradycardia and hypotension, in turn worsening renal failure because of poor renal perfusion and potentiating his hyperkalemia and beta blocker toxicity.

This mechanism was initially suggested in a 1984 randomized controlled trial using a canine model. Researchers found that acutely hyperkalemic dogs with therapeutic levels of verapamil had significantly lower mean arterial pressures and decreased heart rate compared with the control group without calcium channel blockage. This hemodynamic instability also occurred at lower levels of potassium infusion than in the control group and did not respond as well to calcium therapy. This study suggested a synergistic effect between the AV nodal blockers, such as calcium channel and beta blockers, and hyperkalemia in contributing to hemodynamic instability (4).

This phenomenon is a novel cause of bradycardia in the ED that has only been described clinically at a case report level thus far. However, there has been an accumulating number of cases that suggest that this mechanism is a prevalent, underrecognized, and clinically significant cause of symptomatic bradycardia and hemodynamic instability that are summarized in Table 1 (5–17).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

When reviewing the reported causes of this synergistic bradycardia, it is noteworthy that 14 of 18 cases occurred at relatively low levels of hyperkalemia, below the 7.0 mEq/L serum potassium level commonly taught as a threshold for severe hyperkalemia and cardiac disturbance. Most compelling about the cases summarized is that most resolved with aggressive medical management, only 4 of 18 required pacing, and only 1 resulted in a permanent pacemaker. Calcium and insulin were the most commonly used treatments, which appeared to result in marked improvement for many patients. Calcium is a known membrane stabilization agent for hyperkalemia, and insulin has indications in both hyperkalemia and beta blocker toxicity (1–3). Most of the reported patients did well over the long term after emergent treatment and adjustment of their outpatient medications. In retrospect, more aggressive early treatment of the hyperkalemia with albuterol and aggressive reversal of the beta blockade with glucagon may have temporized this patient to dialysis and prevented the patient's need for epinephrine and transvenous pacing. If this phenomenon becomes more widely known, it might be possible to treat these patients more effectively. It is our hope that early recognition of this synergistic bradycardia and aggressive medical management in the ED of the 3 contributing factors—renal failure, AV nodal blocking agents, and hyperkalemia—can result in less invasive treatment of these patients in the future.

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