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Clinical Review

BRASH SYNDROME: BRADYCARDIA, RENAL FAILURE, AV BLOCKADE, SHOCK, AND HYPERKALEMIA

Joshua D. Farkas, MD, MS,* Brit Long, MD,† Alex Koyfman, MD,‡ and Katherine Menson, DO*

*Pulmonary and Critical Care Medicine, Larner College of Medicine at the University of Vermont, Burlington, Vermont, †Department of Emergency Medicine, San Antonio Uniformed Services Health Education Consortium (SAUSHEC), Brooke Army Medical Center, Fort Sam Houston, Texas, and ‡Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, Texas

Reprint Address: Brit Long, MD, Department of Emergency Medicine, SAUSHEC, Brooke Army Medical Center, 3841 Roger Brooke Drive, Fort Sam Houston, TX 78234

☐ **Abstract—Background: BRASH syndrome, or Bradycardia, Renal Failure, AV blockade, Shock, and Hyperkalemia, has recently become recognized as a collection of objective findings in a specific clinical context pertaining to emergency medicine and critical care. However, there is little emergency medicine and critical care literature specifically evaluating this condition. Objective: We sought to define and review BRASH syndrome and identify specific management techniques that differ from the syndromes as they present individually. Discussion: BRASH syndrome is initiated by synergistic bradycardia due to the combination of hyperkalemia and medications that block the atrioventricular (AV) node. The most common precipitant is hypovolemia or medications promoting hyperkalemia or renal injury. Left untreated, this may result in deteriorating renal function, worsening hyperkalemia, and hemodynamic instability. Patients can present with a variety of symptoms ranging from asymptomatic bradycardia to multiorgan failure. BRASH syndrome should be differentiated from isolated hyperkalemia and overdose of AV-nodal blocking medications. Treatment includes fluid resuscitation, hyperkalemia therapies (intravenous calcium, insulin/glucose, beta agonists, diuresis), management of bradycardia (which may necessitate epinephrine infusion), and more advanced therapies if needed (lipid emulsion, glucagon, or high-dose insulin infusion). Understanding and recognizing the pathophysiology of BRASH syndrome as a distinct entity may improve patient outcomes. Conclusions: BRASH syndrome can be a difficult diagnosis and is due to a combination of hyperkalemia and medications that block the AV node. Knowledge of this condition may assist emergency and critical care providers.**

☐ **Keywords—BRASH syndrome; bradycardia; renal failure; AV blockade; shock; hyperkalemia**

INTRODUCTION

It is well established that both hyperkalemia and medications blocking the atrioventricular (AV) node may cause bradycardia. Animal studies and multiple case reports indicate that these two factors may function synergistically to produce more dramatic bradycardia than would be expected from either factor alone (1–23). Bradycardia may cause or worsen renal dysfunction, in turn exacerbating hyperkalemia. This vicious cycle of hyperkalemia, bradycardia, renal dysfunction, and worsening hyperkalemia can evolve into multiorgan dysfunction (BRASH syndrome, i.e., Bradycardia, Renal failure, AV blockade, Shock, and Hyperkalemia) (7).

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Most experienced clinicians have treated patients with BRASH syndrome successfully, without conscious recognition of this specific pathophysiology. Indeed, most patients with BRASH syndrome will improve with basic supportive therapy. Nonetheless, defining this syndrome and exploring its pathophysiology may optimize diagnosis and management. Consequently, this disorder was codified as BRASH syndrome in 2016 and subsequently explored in numerous conferences and publications (1–23). We provide emergency and critical care providers with an evaluation of BRASH syndrome diagnosis and management in this narrative review.

METHODS

We conducted a literature review of PubMed, Google Scholar, and Google FOAM for topics evaluating bradycardia, renal failure, AV blockade, shock, and hyperkalemia from database inception to September 2019. Search terms included "bradycardia," "atrioventricular block," "renal injury," "kidney injury," "renal dysfunction," "hyperkalemia." We included case reports, case controls, cohort studies, randomized clinical trials, meta-analyses and systematic reviews, peer-reviewed free open access medical education resources, guidelines, and narrative reviews. We decided on inclusion of 36 resources through consensus, with 18 case reports/series detailing patients with BRASH syndrome.

DISCUSSION

BRASH syndrome is typically due to the synergy between hyperkalemia and AV-nodal blocking medications, which leads to bradycardia. Because bradycardia directly reduces the cardiac output, this may impair renal perfusion, thereby causing renal failure, which exacerbates hyperkalemia. Left unchecked, this cycle may progress to multiorgan failure with shock, bradycardia, and renal failure (7). Figure 1 illustrates the pathophysiologic cycle that causes BRASH syndrome (7).

This cycle may be initiated by relatively mild clinical events. In one study, BRASH patients presenting with the most severe bradydysrhythmias requiring transvenous pacing presented in summer months, with laboratory markers supporting dehydration (9). Other potential triggers may include medication up-titration or any event promoting hyperkalemia or renal failure (e.g., nephrotoxins or potassium-sparing diuretics such as spironolactone). The clinical presentation of BRASH syndrome is usually dominated by manifestations of BRASH syndrome itself, rather than a precipitating event (7).

Some additional medication interactions might facilitate BRASH syndrome, although these medications are not required for its development. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can increase risk of both hyperkalemia and renal dysfunction, as does digitalis. Several beta-blockers are renally excreted (e.g., atenolol, nadolol), causing their levels to accumulate during BRASH syndrome. Finally, nonspecific beta-blockers (e.g., labetalol) may promote hyperkalemia (7).

Clinical Presentation

Patients may present with a variety of symptoms and severity, ranging from asymptomatic bradycardia to multiorgan failure. The most salient aspect of the presentation is generally either the hyperkalemia or the bradycardia, though these may occur concurrently (7). This dominant abnormality, including hyperkalemia, may cause clinicians to overlook other problems. Patients generally appear nontoxic (better than might be expected based on their vital signs and laboratory derangements).

Differentiation from Related Disorders

BRASH syndrome is fundamentally a synergistic process created by a combination of hyperkalemia and medications blocking the AV node. As such, BRASH syndrome lies at the center of a continuum ranging from isolated hyperkalemia to an isolated overdose of an AV nodal-blocking medication (e.g., beta-blocker intoxication), demonstrated in Figure 2. It is not always possible to determine precisely where these boundaries lie. However, it is useful to attempt to draw some distinctions between these three disease states.

BRASH syndrome versus isolated hyperkalemia. Isolated hyperkalemia may precipitate bradycardia, which, in turn, leads to renal failure. However, hyperkalemia does not generally cause bradycardia until the degree of hyperkalemia is severe (e.g., potassium over ~7 mEq/L) (1,10). This may differentiate it from BRASH syndrome, wherein patients often have more moderate hyperkalemia. However, concurrent severe hyperkalemia can occur with BRASH syndrome. Another differentiating feature is the presence of drugs that suppress the AV node, which is invariably a feature of BRASH syndrome. An electrocardiogram demonstrating bradycardia *without* other electrocardiographic features of hyperkalemia is another important clue to BRASH syndrome (11).

BRASH syndrome vs. intoxication with AV-nodal blocking agents. Intoxication with beta-blockers or calcium channel-blockers can lead to bradycardia and shock. Perhaps the single most important differentiating factor compared with BRASH syndrome is the clinical history.

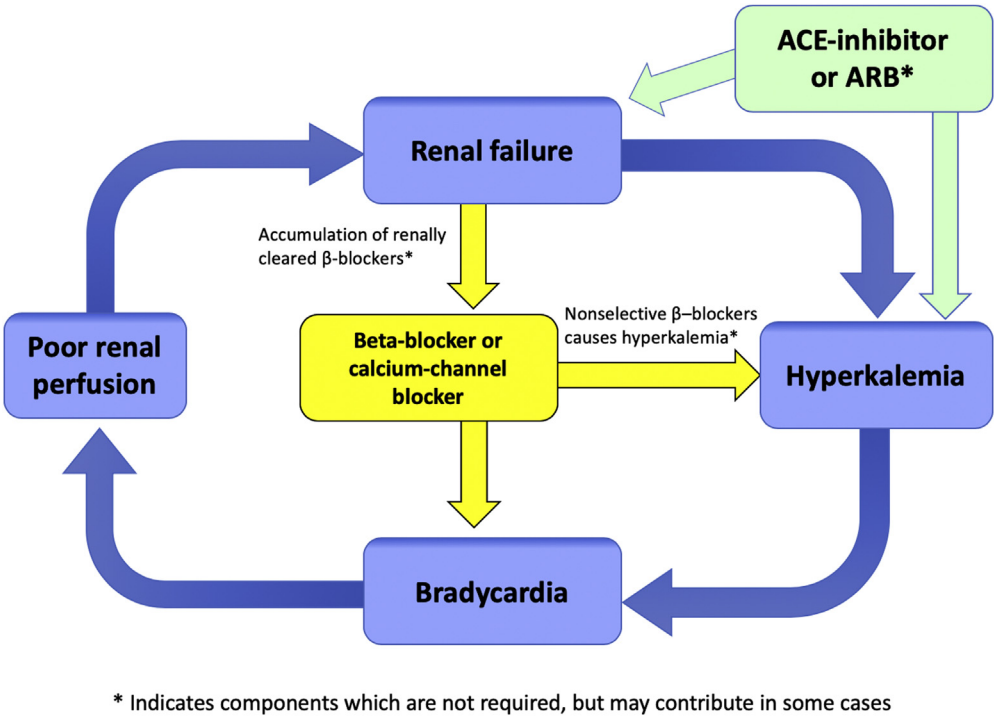

Figure 1. BRASH (Bradycardia, Renal failure, AV blockade, Shock, and Hyperkalemia) pathophysiology (7). ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker.

Patients with BRASH syndrome are typically taking their medications as directed (7). BRASH syndrome does not generally involve supratherapeutic drug levels, but rather the problem arises due to synergy between therapeutic drug levels and hyperkalemia (7). Other features that could favor BRASH syndrome include hyperkalemia and a dramatic clinical response after administration of intravenous (i.v.) calcium.

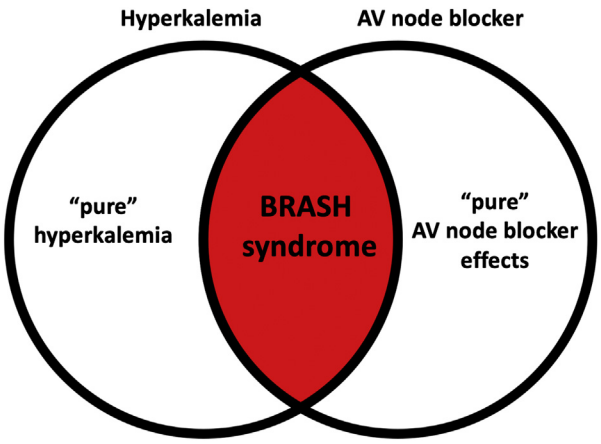

Figure 2. BRASH exists at the nexus of hyperkalemia and AV node blockade. BRASH = Bradycardia, Renal failure, AV blockade, Shock, and Hyperkalemia; AV = atrioventricular.

Epidemiology of BRASH Syndrome

Until recently, BRASH syndrome was not recognized as a specific entity, and little is known regarding its epidemiology. Case reports fitting the definition of BRASH syndrome are listed below in Table 1 (1–3,5,6,11–23). Given the involvement of antihypertensive medications and borderline renal function, this is most common in older patients with cardiac disease and limited renal reserve. The risk may be especially high among patients on multiple different AV-nodal blocking medications for management of atrial fibrillation.

Treatment of BRASH Syndrome

The most common error in managing BRASH syndrome is fixating on a single component of the syndrome (e.g., hyperkalemia) and focusing solely on management of that problem (e.g., emergent dialysis). Meanwhile, other aspects of the syndrome are overlooked (e.g., the patient might remain under-resuscitated, bradycardic, and malperfused) (7). Failure to address these other associated components could result in patient harm.

Understanding the pathophysiology of BRASH syndrome facilitates a coordinated management strategy that addresses all components of the syndrome. The key to treatment of BRASH syndrome is not any single intervention, but rather simultaneously addressing several

Table 1. Reported Cases of BRASH Syndrome (1–3,5,6,11–23)

Patient Age, Years	Medications Involved	Potassium (mEq/L)	Cr (mg/dL)	Initial Vital Signs	Treatments	Reference (First Author, Year)
53	Verapamil 120 mg q.i.d., propranolol 40 mg q.i.d.	6.8	1.6	HR 32 beats/min, BP 70/mm Hg	Isoproterenol, dopamine	Lee 1986 (11)
75	Verapamil 120 mg t.i.d., captopril	6.9	2.4	HR 30 beats/min, BP 70/mm Hg	Atropine, isoproterenol, calcium, pacemaker	Jolly 1991 (5)
66	Verapamil SR 360 mg	7.1	6.1	HR 26 beats/min, MAP 68 mm Hg	Isoproterenol, dopamine, calcium, bicarbonate, insulin/glucose	Váquez 1996 (21)
78	Metoprolol, lisinopril	7.5	8.5	HR 30 beats/min, BP 80 mm Hg	Transvenous pacing, calcium, furosemide, bicarbonate	Zimmers 2002 (20)
81	Atenolol	6.0	2.1	HR 52 beats/min, MAP 131 mm Hg	Lasix, bicarbonate	Zimmers 2002 (20)
57	Carvedilol 50 mg b.i.d., digoxin, spironolactone, fosinopril	6.8	2.7	HR 48 beats/min, MAP 73 mm Hg	Not described	Vuckovic 2004 (19)
54	Atenolol 100 mg, diltiazem 300 mg, irbesartan	6.4	1.8	HR 22 beats/min, MAP 40 mm Hg	External pacer, fluid, calcium, insulin	Bonvini 2006 (3)
63	Verapamil	6.8	Not provided, on dialysis	Not provided	Not specified	Letavernier 2006 (2)
57	Verapamil	6.4	Not provided, on dialysis	Not provided	Atropine, withheld verapamil	Letavernier 2006 (2)
58	Verapamil	6.7	Not provided, on dialysis	Not provided	Emergent dialysis, withheld verapamil	Letavernier 2006 (2)
70	Metoprolol XL 100 mg, enalapril, spironolactone	6.5	3.3	HR 44 beats/min, MAP 71 mm Hg	Calcium, albuterol, kayexalate, transvenous pacing, dialysis	Isabel 2006 (18)
78	BB, ACE inhibitor, CCB	7.9	2.1	HR 33 beats/min	Calcium, insulin/glucose, furosemide, fluid	Unterman 2008 (17)
77	Diltiazem, propranolol	6.7	2.7	HR 30 beats/min, MAP 53 mm Hg	Dopamine, calcium, insulin/glucose	Mirandi 2008 (16)
79	Metoprolol	6.4	4.4	HR 28 beats/min, MAP 79 mm Hg	Calcium, bicarbonate, volume resuscitation, insulin/glucose, sodium polystyrene sulfonate	Argulian 2009 (15)
76	Carvedilol, spironolactone, ramipril	9.2	1.3	HR 28 beats/min, MAP 79 mm Hg	Transvenous pacing, insulin/glucose, bicarbonate	Erden 2010 (14)
70	Carvedilol, valsartan, spironolactone	6.1	2.1	HR 38 beats/min, MAP 62 mm Hg	Calcium, insulin/glucose	Aziz 2011 (13)
97	Amlodipine	6.3	1.6	HR 56 beats/min, MAP 75 mm Hg	Calcium, insulin/glucose	Aziz 2011 (13)
65	Verapamil, valsartan	5.6	3.0	HR 48 beats/min, MAP 85 mm Hg	Calcium, insulin/glucose	Hegazi 2012 (1)
57	Verapamil	5.1	1.7	HR 44 beats/min, MAP 67 mm Hg	Calcium, albuterol	Hegazi 2012 (1)
85	Sotalol	10.1	2.5	HR 33 beats/min, MAP 61 mm Hg	Calcium, bicarbonate, albuterol, insulin/glucose, dialysis	Juvet (22)
81	Bisoprolol, amlodipine	5.8	2.8	HR 33 beats/min, MAP 104 mm Hg	Atropine, isoproterenol	Ahmad (23)
24	Metoprolol	7.4	On dialysis	HR 40 beats/min	Atropine, calcium, fluids, bicarbonate, epinephrine, transvenous pacemaker	Simmons (6)
51	Carvedilol, eplerenone, trimethoprim-sulfamethoxazole	8.6	3.3	HR 20 beats/min, MAP 40 mm Hg	Atropine, calcium, bicarbonate, albuterol, insulin/glucose, hydrocortisone[22]	Diribe 2019 (12)

BRASH = Bradycardia, Renal failure, AV blockade, Shock, and Hyperkalemia; Cr = creatinine; q.i.d. = four times per day; HR = heart rate; BP = blood pressure; t.i.d. = three times per day; SR = sustained release; MAP = mean arterial pressure; b.i.d. = twice per day; BB = beta-blocker; ACE = angiotensin-converting enzyme; CCB = calcium channel-blocker.

problems. Usually, deploying numerous noninvasive therapies will allow avoidance of more invasive treatments (e.g., transvenous pacing, hemodialysis) (7).

Immediate treatment of hyperkalemia. Hyperkalemia should be treated, even if it appears relatively mild. Evidence of peaked T waves, QRS prolongation, junctional rhythm, significant ST/T wave changes, and bradycardia on electrocardiogram (ECG), or evidence of hemodynamic instability, should be treated with i.v. calcium (Figure 3) (24,25). Intravenous calcium stabilizes the myocardium, which may drastically improve heart rate and cardiac output. If the patient's ECG does not demonstrate normalization with the first dose of i.v. calcium, repeat doses should be administered. If central access is not present and the patient is not in cardiac arrest, calcium gluconate 3 g i.v. should be administered. Calcium chloride should otherwise be administered (25). Intravenous insulin and dextrose should be given to shift potassium intracellularly (25,26). Nebulized albuterol may be considered, with potential benefits in terms of both hyperkalemia and bradycardia (7,24–26).

Immediate treatment of bradycardia. The front-line therapy for bradycardia is i.v. calcium to counteract the effects of hyperkalemia (7,26–30). If this fails to resolve the bradycardia, a low threshold to initiate an infusion of epinephrine is recommended. Epinephrine may achieve two objectives rapidly. First, epinephrine may increase heart rate and cardiac output, thereby improving hemodynamics and renal perfusion (7). Second, epinephrine will shift potassium intracellularly, thereby improving hyperkalemia. Epinephrine may safely be infused via a peripheral i.v. line (noting that epinephrine is safe for subcutaneous injection, so epinephrine extravasation should not cause skin necrosis). Isoproterenol is an alternative chronotropic agent, which may be successful in occasional patients who fail to respond to epinephrine. Isoproterenol is preferred over alternative beta-agonists, such as dobutamine or dopamine, as it has a much more profound chronotropic effect, and is the agent of choice when hypotension is the result of bradycardia (7).

It should be noted that standard advanced cardiac life support algorithms for bradycardia will fail to optimally

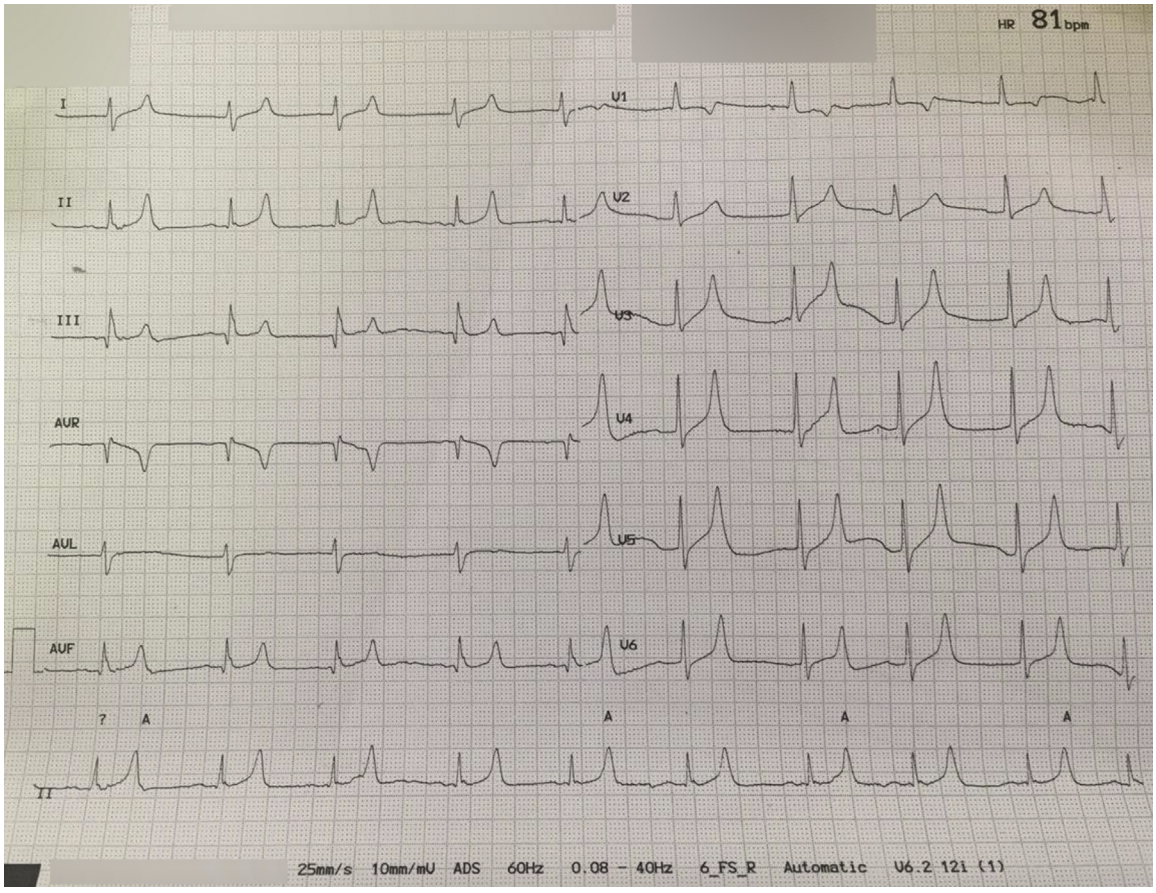

Figure 3. Electrocardiogram in hyperkalemia with peaked T waves, QRS prolongation, and bradycardia. From https://commons.wikimedia.org/wiki/File:Hyperkalemia_ECG.jpg.

treat patients with BRASH syndrome, as they do not include the use of i.v. calcium (7,28). Such algorithms may lead to unnecessary placement of a transvenous pacemaker in a patient who otherwise could have responded well to medical therapy. This is one further reason that recognition of BRASH syndrome is clinically important (7).

Some patients will present with a normal blood pressure despite severe bradycardia (Table 1). These patients are compensating for bradycardia with a pronounced vasoconstrictive response, which succeeds in defending their blood pressure. Unfortunately, despite a normal blood pressure, these patients continue to suffer from malperfusion, as cardiac output is directly proportional to heart rate. Thus, treatment of bradycardia remains important to re-establish systemic perfusion and renal function. For these patients, isoproterenol might be ideal (as a pure beta-agonist without any vasoconstrictive properties, it will increase heart rate without inducing hypertension) (7). An alternative therapy is dobutamine (with the drawback that dobutamine is selective for beta-1 adrenergic receptors over beta-2 receptors, so it will not decrease the serum potassium level) (7).

Fluid resuscitation. Fluid status varies widely among patients with BRASH syndrome. Hypovolemia is a common trigger of BRASH syndrome, so many patients are hypovolemic. However, some patients with ongoing BRASH syndrome progress to a point of oliguric renal failure and subsequently retain fluid, leading to a state of volume overload. Fluid status must be assessed individually, based on clinical history and bedside examination (7).

If present, hypovolemia should be treated promptly. Patients with uremic acidosis and hyperkalemia will often improve with isotonic bicarbonate (150 mEq/L sodium bicarbonate in 1 L D5W). Isotonic bicarbonate may improve pH (thereby avoiding the need for immediate dialysis) and also improve the hyperkalemia due to both dilution and intracellular shifting (7,29–31). For patients who are not acidotic, a balanced crystalloid may be used. Normal saline resuscitation should be avoided, as this may cause a transient increase in serum potassium (7,32).

Definitive treatment of hyperkalemia. The above measures will often be successful in treatment of mild-moderate hyperkalemia, particularly in the context of a rapid recovery in renal function. However, additional measures may be required in patients with severe hyperkalemia and renal dysfunction (7).

The front-line therapy for elimination of potassium from the body is usually an aggressive attempt at diuresis using potassium-wasting diuretics. Options include loop diuretics (e.g., i.v. furosemide or i.v. bumetanide), thiazide diuretics (e.g., i.v. chlorothiazide), and acetazolamide. High doses of multiple agents may be used in an attempt to overcome diuretic resistance due to renal dysfunction. The goal of diuresis is excretion of potassium, so if diuretics are successful at causing fluid loss, then this fluid should generally be returned to achieve isovolumic kaliuresis (e.g., by replacing urine losses with lactated ringers). For diuretics to have maximal effect, hypoperfusion and hypovolemia must be reversed (often with epinephrine and crystalloid, as discussed above) (7).

Patients with marked hyperkalemia who fail to produce urine in response to high-dose diuretics and hemodynamic stabilization will often require emergent dialysis as definitive treatment of hyperkalemia. A coordinated treatment approach to BRASH can usually avoid dialysis, but some patients have already progressed to anuric renal failure and will require short-term dialysis. Typically, dialysis can reverse hyperkalemia before temporary pacing is necessary (7).

More advanced therapies. The above therapies, when aggressively and simultaneously implemented, are usually sufficient to yield a satisfying improvement in the syndrome. For example, many patients can make dramatic recoveries from multiorgan failure within 12 h. However, rarely, patients may not respond to these interventions. Advanced therapies should be reserved for those in which the prior therapies have failed (7).

More advanced therapies to reverse beta-blocker or calcium channel blocker toxicity exist (e.g., lipid emulsion, glucagon, or high-dose insulin infusion) (33,34). These treatments could be considered in a patient taking beta-blockers, which are renally cleared and thus accumulate in the context of BRASH syndrome (33,34). Another stimulus to consider these treatments might be a patient who is on unusually large doses of multiple AV-nodal blocking agents (7). If digoxin toxicity is suspected, digoxin-specific antibody fragments should be administered (35). Adrenal insufficiency should be managed with stress dose corticosteroids, typically, hydrocortisone 100 mg i.v. (36).

Bradycardia can generally be managed by a combination of beta-agonists and i.v. calcium (along with management of the hyperkalemia). If these measures fail, transvenous pacing may be necessary, but typically is used only as a salvage maneuver when the aforementioned treatments fail (7).

CONCLUSIONS

BRASH syndrome consists of a vicious cycle involving a combination of bradycardia, renal failure, AV-nodal blocking medication, shock, and hyperkalemia. The

pathophysiology underlying BRASH syndrome has been well established for decades. Likewise, the treatments employed consist of accepted emergency medicine therapies. Nonetheless, understanding and recognizing the pathophysiology of BRASH syndrome as a distinct entity can facilitate a more comprehensive and organized management strategy for these patients. With the ever-increasing population of older patients being treated aggressively for hypertension, this syndrome will become increasingly relevant to emergency physicians.

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ARTICLE SUMMARY

1. Why is this topic important?

There is little emergency medicine and critical care literature specifically evaluating BRASH syndrome, or Bradycardia, Renal Failure, Atrioventricular blockade, Shock, and Hyperkalemia.

2. What does this review attempt to show?

This narrative review evaluates BRASH syndrome and its diagnosis and management.

3. What are the key findings?

BRASH syndrome is due to hyperkalemia and medications that block the atrioventricular node. It most commonly results from hypovolemia or medications promoting hyperkalemia or renal injury. Patients can present with a wide variety of symptoms. Treatment includes fluid resuscitation, hyperkalemia therapies (intravenous calcium, insulin and co-administered glucose, beta agonists, diuresis), management of bradycardia (which may necessitate epinephrine infusion), and more advanced therapies if needed (lipid emulsion, glucagon, or high-dose insulin infusion).

4. How is patient care impacted?

Recognition of this condition in a prompt manner may assist emergency and critical care providers in triaging the appropriate response, often in a multimodal fashion. Rapid identification and treatment can prevent downward trajectory and need for advanced therapies.