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EXTREME BRADYCARDIA IN BRASH SYNDROME UNMASKED BY SEVERE AMIODARONE-INDUCED HYPOTHYROIDISM

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ABSTRACT

Introduction: BRASH syndrome – bradycardia, renal failure, AV nodal blockade, shock and hyperkalaemia – is a self-amplifying pathophysiological loop. Its association with severe amiodarone-induced hypothyroidism is rarely described in detail.

Case description: A 79-year-old woman with permanent atrial fibrillation on long-term amiodarone and bisoprolol presented after prolonged unwitnessed floor immobilisation with extreme bradycardia (24–30 bpm), haemodynamic instability, KDIGO stage 3 acute kidney injury, hyperkalaemia (5.5 mmol/l), metabolic acidosis, rhabdomyolysis and profound hypothyroidism (TSH 68.5 mUI/l; free T4 4.62 pmol/l) against a normal thyroid baseline 13 months prior. The Popoveniuc myxoedema coma score was 45 (high-risk zone). High-sensitivity troponin T showed flat kinetics consistent with type 2 myocardial injury. Isoproterenol was required for bradycardia refractory to initial metabolic correction, achieving a ventricular rate of 62–68 bpm with QTc shortening from 0.62 s to 0.38 s. The patient was discharged on day 8 with renal recovery and improving thyroid function. Thyroid antibody negativity at 30-day follow-up was consistent with an amiodarone-induced rather than autoimmune aetiology.

Conclusion: This case illustrates BRASH syndrome presenting with only mild hyperkalaemia in the context of severe amiodarone-induced hypothyroidism, which may have potentiated the pathophysiological loop. Systematic thyroid monitoring during long-term amiodarone therapy and multi-target metabolic correction, including isoproterenol as a pharmacological bridge, may avert invasive pacing.

KEYWORDS

BRASH syndrome, hypothyroidism, amiodarone, bradycardia, isoproterenol

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LEARNING POINTS

- BRASH syndrome may occur with only mild hyperkalaemia when severe hypothyroidism potentiates AV nodal blockade – disproportionate bradycardia relative to potassium level is the key diagnostic signal.
- In any patient on long-term amiodarone presenting with otherwise unexplained bradycardia, profound hypothyroidism should be actively excluded before attributing the presentation to drug toxicity alone; thyroid function testing every 3–6 months is guideline-recommended during such therapy.
- Isoproterenol may serve as an effective pharmacological chronotropic bridge in BRASH syndrome refractory to initial metabolic correction, potentially avoiding invasive temporary pacing.

INTRODUCTION

BRASH syndrome, defined by Farkas et al. in 2020, is a self-amplifying clinical loop arising from the interaction of atrioventricular (AV) nodal blocking drugs with hyperkalaemia in the setting of renal failure[1]. Impaired renal elimination of AV nodal blocking agents drives drug accumulation, deepening bradycardia, reducing cardiac output, worsening renal perfusion and promoting further potassium retention *(Fig. 1)*. The cardinal diagnostic feature is bradycardia disproportionate to the degree of hyperkalaemia[1,2].

Hypothyroidism independently depresses cardiac chronotropy and potentiates pharmacological AV nodal blockade through myocardial beta-adrenergic receptor downregulation[3,4]. Whether severe hypothyroidism may amplify the BRASH loop by contributing to several of its components simultaneously has not been formally reported. Recognising this potential interaction matters clinically, as standard BRASH management focuses solely on hyperkalaemia, and drug withdrawal may be insufficient if underlying thyroid failure is not corrected. This report describes BRASH syndrome occurring in a patient with severe amiodarone-associated hypothyroidism, in whom extreme bradycardia developed at a potassium concentration of only 5.5 mmol/l, and in whom isoproterenol served as an effective pharmacological bridge to avoid invasive pacing.

CASE DESCRIPTION

A 79-year-old woman with permanent atrial fibrillation on amiodarone 200 mg/day, bisoprolol 5 mg twice daily, apixaban, furosemide, empagliflozin and mirtazapine was brought to the emergency department after being found on the floor of her home, with estimated immobilisation exceeding 24 hours. Thyroid function 13 months earlier had been normal (TSH 1.92 mUI/l); no monitoring had been repeated despite ongoing amiodarone therapy.

On arrival, blood pressure was undetectable, stabilising at 97/67 mmHg (MAP 74 mmHg) after 500 ml of crystalloid; heart rate was 24–30 bpm. Glasgow Coma Scale was 15/15; temperature was 36.7°C. The admission electrocardiogram *(Fig. 2)* showed atrial fibrillation with extremely slow ventricular response and markedly prolonged QTc (≈0.62 s), without ischaemic changes.

Laboratory findings *(Table 1)* revealed TSH 68.5 mUI/l with free T4 4.62 pmol/l, confirming profound hypothyroidism; creatinine rising to 228 µmol/l within 24 hours (KDIGO stage 3 acute kidney injury); severe hyponatraemia (124 mmol/l); potassium 5.5 mmol/l; ionised hypocalcaemia (0.98 mmol/l); metabolic acidosis (HCO_3^-12.3 mmol/l;

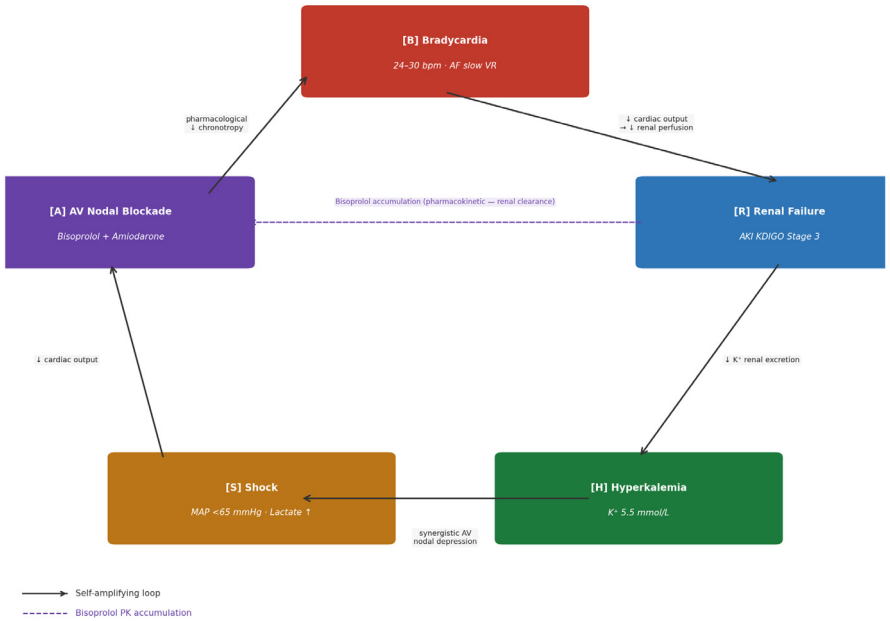


Figure 1. *Schematic of the BRASH syndrome self-amplifying loop. Bisoprolol accumulates through reduced renal clearance; amiodarone contributes through direct AV nodal depression. Severe hypothyroidism is hypothesised to potentiate this loop at several nodes; a hypothesis-generating observation rather than a demonstrated mechanism.*



Figure 2. Admission electrocardiogram showing atrial fibrillation with extremely slow ventricular response (~27 bpm) and markedly prolonged QTc (≈0.62 s), without ischaemic changes.

Parameter	Reference range	H0 (admission)	H24
TSH (mUI/l)	0.27–4.2	68.5	–
Free T4 (pmol/l)	12–22	4.62	–
Creatinine (µmol/l)	45–84	134	228
eGFR (ml/min/1.73m^2)	≥90	32	17
Sodium (mmol/l)	136–145	124	123
Potassium (mmol/l)	3.4–4.5	5.1	5.5
Ionised calcium (mmol/l)	1.13–1.27	not measured	0.98
HCO_3^- (mmol/l)	21–28	–	12.3
Lactate (mmol/l)	<1.3	–	2.6
hs-Troponin T (ng/l)	<24	51 (H0) / 54 (H4) / 48 (H8)	–
Creatine phosphokinase (IU/l)	20–180	1 291	–
C-reactive protein (mg/l)	<5	17.1	35.2

Table 1. Key laboratory findings at admission and at 24 hours.

Diagnosis	Likelihood	Supporting features	Limiting factors
Severe hypothyroidism (primary mechanism)	High	TSH markedly elevated; FT4 (free thyroxine) critically low; hyponatraemia; extreme bradycardia; haemodynamic compromise; Popoveniuc score 45	No thyroid antibodies at admission; normothermia; GCS 15
BRASH syndrome (co-primary mechanism)	Moderate–high	All five BRASH criteria met; bradycardia disproportionate to potassium level; progressive acute kidney injury; dual AV nodal blockade	Potassium only 5.5 mmol/l – below typical isolated BRASH threshold
Type 2 myocardial injury	Moderate–high	hs-TnT flat kinetics (51→54→48 ng/L/8h); extreme bradycardia; low-flow state	No coronary angiography performed
Adrenal insufficiency (relative)	Low	Hyponatraemia + hyperkalaemia pattern; formally not excluded	Cortisol not measured; clinical context favours thyroid aetiology

Table 2. Differential diagnosis.

lactate 2.6 mmol/l); and rhabdomyolysis (CPK 1 291 IU/l). High-sensitivity troponin T (hs-TnT) showed flat kinetics (51→54→48 ng/l over 8 hours), compatible with type 2 myocardial injury rather than type 1 infarction. Coronary angiography was deferred given haemodynamic instability, the absence of ischaemic ECG changes and a clinical presentation more consistent with type 2 myocardial injury secondary to extreme bradycardia and systemic hypoperfusion. The Popoveniuc myxoedema coma score was 45 (high-risk zone). All five BRASH criteria were fulfilled *(Table 2)*.

Amiodarone, bisoprolol, empagliflozin, furosemide and oxazepam (prescribed without indication) were discontinued. Intravenous calcium gluconate and insulin-glucose were administered. Oral levothyroxine was initiated after endocrinological consultation; intravenous



Figure 3. Electrocardiogram after isoproterenol initiation showing ventricular rate ~65 bpm and QTc shortened to ≈0.38 s, without ischaemic changes.

administration was considered, given haemodynamic compromise, but ultimately deferred owing to arrhythmic risk. At H8, bradycardia (24–30 bpm) persisted despite drug discontinuation and metabolic correction. Isoproterenol 0.02 µg/kg/min was initiated, improving the ventricular rate to 62–68 bpm with QTc shortening to 0.38 s *(Fig. 3)*, without proarrhythmic events. Temporary pacing was not required, and renal replacement therapy was held in reserve.

The patient was discharged on day 8 with renal recovery (creatinine 88 µmol/l), improving thyroid function and hs-Troponin T normalised to 18 ng/l. At 30-day follow-up she was ambulatory, in sinus rhythm (68 bpm), with TSH 4.2 mUI/l and free T4 15.1 pmol/l on adjusted levothyroxine. Thyroid antibodies were negative, supporting an amiodarone-induced aetiology. Echocardiography showed a left ventricular ejection fraction of 52% with no pericardial effusion.

DISCUSSION

What is already known: BRASH syndrome typically arises from the synergy between AV nodal blocking drugs and hyperkalaemia in renal failure, producing bradycardia disproportionate to the potassium level[1,2]. Hypothyroidism is independently recognised to depress cardiac chronotropy through downregulation of ion channel gene expression and to potentiate the chronotropic effects of beta-blockers through myocardial beta-adrenergic receptor downregulation[3,4].

What is new: In this case, profound bradycardia (24–30 bpm) occurred at a potassium concentration of only 5.5 mmol/l – well below the threshold typically required for isolated hyperkalaemic bradycardia. This dissociation is explicable by BRASH synergistic toxicity, by direct hypothyroid chronotropic depression in a patient under dual AV nodal blockade, or by both mechanisms acting concurrently. We cannot determine the dominant mechanism from a single case, and we explicitly avoid proposing a new syndrome; rather, this observation generates the hypothesis that severe hypothyroidism may potentiate several components of the BRASH loop simultaneously, a hypothesis that requires validation in future case series.

Why it is significant: Isoproterenol provided effective chronotropic support when bradycardia persisted despite drug discontinuation and metabolic correction, avoiding invasive temporary pacing – a clinically relevant alternative in resource-limited settings where pacing may not be immediately available[5]. Dedicated evidence comparing isoproterenol with temporary pacing specifically in BRASH syndrome remains limited to anecdotal reports; this therapeutic choice was guided by pharmacological reasoning rather than controlled comparative data. The 13-month gap in thyroid monitoring during amiodarone therapy illustrates a preventable contributing factor; current guidelines recommend thyroid function testing every 3–6 months in this population[6].

Have the results explained the conclusion? The differential diagnosis *(Table 2)* could not fully discriminate between severe hypothyroidism as the sufficient primary mechanism and BRASH syndrome as a co-primary mechanism. This uncertainty does not weaken the clinical message: simultaneous correction of metabolic, endocrine and haemodynamic abnormalities – including early thyroid hormone replacement and pharmacological chronotropic support – achieved full recovery without invasive intervention, supporting a multi-target therapeutic approach in this clinical scenario.

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