Focused Echocardiography During Glucagon Administration to Diagnose Beta-Blocker-Induced Cardiomyopathy

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Beta-adrenergic blocker toxicity is most often diagnosed in the emergency department in the patient presenting with severe, refractory hypotension and bradycardia following ingestion of an excessive quantity of this class of medication.[1–3] Because the signs of beta-adrenergic blocker toxicity are nonspecific, establishing this diagnosis sometimes can be challenging, especially in patients who do not have a classic presentation.

Herein, the authors report a case of acute cardiovascular collapse in a critically ill patient with a type-B aortic dissection and multisystem organ dysfunction in which real-time transthoracic echocardiography (TTE) was used during glucagon administration to diagnose beta-adrenergic blocker overdose and guide therapy. Written consent from the patient was obtained to publish this report.

Although numerous publications discuss the immediate management and subsequent treatment of beta-adrenergic blocker toxicity, this is the first report describing the use of real-time TTE to diagnose this condition and assess treatment response to glucagon.

CASE REPORT

A previously healthy 30-year-old African American man was admitted to the intensive care unit (ICU) for medical management of a type-B aortic dissection. His initial vital signs were notable for a heart rate (HR) of 99 beats/min (bpm) and blood pressure (BP) of 209/85 mmHg. To prevent further propagation of the dissection, the primary goal on admission was to quickly control HR and BP using rapidly titratable intravenous agents,[4] and then gradually transition to an oral regimen once HR and BP control were achieved on intravenous (IV) agents. To this end, IV esmolol was started and escalated to a dose of 300 μg/kg/min; however, it quickly became apparent that additional agents would be necessary. Attaining a systolic HR target of 60 bpm and BP target of less than 120 mmHg ultimately necessitated a combination of IV diltiazem, labetalol, nitroprusside, and bolus doses of metoprolol. Oral labetalol was begun within 1 hour of admission and oral metoprolol then was added the following day. In addition, oral clonidine was started on ICU day 4. Despite all of these measures the patient's average HR remained 90 to 100 bpm and average systolic BP remained 120 to 130 mmHg during the first 4 ICU days.

A total of 2.2 grams of labetalol and 1.3 grams of metoprolol were administered enterally during the first 4 hospital days. On the morning of ICU day 6, the patient developed worsening oliguric acute kidney failure; his urine output was less than 0.3 mL/kg/hr and his creatinine was 3.75 mg/dL, up from 2.78 mg/dL the day before and 0.75 mg/dL on admission. On the same day, the patient became acutely hypotensive with a BP of 89/55 mmHg that was unresponsive to fluid challenges. Abdominal distention and an elevated lactate (5.9 mmol/L) denoting possible bowel ischemia also were noted. Antihypertensive agents were discontinued abruptly and norepinephrine and vasopressin infusions were initiated, along with broad-spectrum antibiotics because of concern for severe sepsis and septic shock. However, the patient was afebrile with a normal white blood cell count that morning. During emergent exploratory laparotomy later that day, 60 cm of ischemic small bowel were resected. Intraoperative transesophageal echocardiography revealed severely reduced left ventricular (LV) function and epinephrine was started by the anesthesiologist. Upon return to the ICU, dobutamine was added for presumed septic cardiomyopathy with the goal to wean epinephrine. Additionally, the patient required a 10% dextrose infusion for hypoglycemia of uncertain etiology. The patient's liver function tests including international normalized ratio only were elevated mildly, ruling out acute liver failure as an etiology for the acute hypoglycemia.

Given the patient's persistent hemodynamic instability, ongoing vasopressor requirement, profound hypoglycemia (nadir 43 mg/dL), and that there was no evidence of infection, ultimately a beta-adrenergic blocker-induced cardiomyopathy was considered because of acute enteral absorption of these medications following decompression of his abdominal compartment syndrome. Three hours after returning from the operating room IV glucagon was given (5 mg; 0.05 mg/kg). Within 1 hour of this intervention the mean arterial pressure increased from 62 to 69 mmHg, allowing weaning of epinephrine from 0.1 to 0.08 μg/kg/min (Table 1) and then to 0.04 μg/kg/min within 6 hours. Because of an inability to further wean the hemodynamic support, 12 hours later a second dose of 5 mg of glucagon was given. An hour following this intervention, the mean arterial pressure improved from 64 to 75 mmHg. This time concurrent TTE was utilized to examine cardiac function before and after glucagon administration. Within minutes of glucagon administration the ejection fraction normalized using both Simpson's biplane measurements and visual estimation of cardiac function with the subjective eyeball method (Video clips 1-4). Furthermore, a more detailed analysis was performed using 2-D speckle tracking software, which demonstrated that LV longitudinal strain improved by 72%, though global cardiac function was still abnormal (Fig 1). Epinephrine was weaned successfully within 6 hours of the second glucagon dose, and dobutamine was discontinued 24 hours later. The patient ultimately underwent endovascular aortic repair.

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Table 1. Hemodynamic Data

First 5 mg Glucagon Dose	t-1h	t0	t+1h	t+6h
Parameter				
HR	107	107	106	109
sBP	95	88	91	96
dBP	49	42	45	48
MAP	70	62	69	62
CVP	8	5	8	10
Infusions				
Dobutamine μg/kg/min	8	8	8	8
Epinephrine μg/kg/min	0.1	0.1	0.08	0.04
Norepinephrine μg/kg/min	0.2	0.2	0.2	0.12
Vasopressin U/hr	5	4	4	4
Second 5 mg Glucagon Dose (given 14 hours after initial 5-mg dose)				
Parameter	t-1h	t0	t+1h	t+6h
HR	110	112	115	119
sBP	95	99	110	121
dBP	56	50	62	61
MAP	69	64	75	77
CVP	9	7	8	7
Infusions				
Dobutamine μg/kg/min	8	8	8	8
Epinephrine μg/kg/min	0.04	0.04	0.04	0.02
Norepinephrine μg/kg/min	0.08	0.08	0.07	0.01
Vasopressin U/hr	4	4	4	4

NOTE. Hemodynamic data from 1 hour before, the hour of, 1 hour after, and 6 hours after 5 mg of glucagon administration. Hemodynamic support decreased within 1 hour of administration and continued to decline 6 hours later.

Abbreviations: CVP, central venous pressure; dBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; sBP, systolic blood pressure.

DISCUSSION

This case provides a new example of the value of real-time TTE to aid the diagnosis and management of a complex ICU patient with acute shock of unclear etiology with multiple potential contributing factors. Although the benefits of focused bedside TTE in the ICU have been recognized widely,[5] this is the first report describing the use of TTE during the administration of glucagon to guide diagnosis and treatment of acute beta-adrenergic blocker toxicity.

Glucagon has positive chronotropic and inotropic effects through direct myocardial action that occur within minutes after administration.[6] Glucagon reverses beta-adrenergic blocker toxicity by providing the cyclic adenosine monophosphate necessary for improved cardiac performance, stimulated via an alternative G-coupled receptor[7] that is distinctly separate from catecholamine receptors. Its utility as an antidote for beta-adrenergic blocker toxicity has been controversial in the literature. The efficacy of glucagon is supported by several case reports,[8] though it has failed in other instances in which the dose of beta-adrenergic blocker ingestion was extremely high[2] or when other medications were coingested.[9] The first report of glucagon's use for beta-adrenergic blocker toxicity emerged in 1973; the patient developed bradycardia, hypotension, and coma following ingestion of 800 mg of oral propranolol.[10] Isoproterenol infusion initially was tried but was ineffective, then a 10-mg glucagon bolus was administered, which increased the patient's heart rate from 52 to 70 bpm and systolic blood pressure from 60 to 95 mmHg.[10] Subsequent reports describe similar positive clinical responses to glucagon after catecholamine administration failed therapeutically.[3] The commonly reported initial bolus glucagon dose is typically 0.05 mg/kg, identical to the dose the authors used in their patient.[3,10]

An emerging treatment for beta-blocker toxicity is high-dose insulin (HDI) therapy and intravenous lipid emulsion (ILE). A recent case series described 2 patients who presented to the emergency department after intentional ingestion of calcium channel blocker and beta-blocker medications.[11] These patients failed traditional therapy of glucagon, calcium, and vasopressors, so HDI (1 unit/kg/hr infusion) and ILE (1.5 mL/kg/min × 60 min) were instituted with subsequent resolution of shock.[11] In a review by Woodward et al[12] in 2014, the presumed mechanism of action for this therapy was described. At very high doses, insulin acts as a positive inotrope increasing myocardial carbohydrate uptake, aiding systemic perfusion and improving response to catecholamines. ILE is thought to work by sequestering lipophilic compounds and preventing them from reaching their site of action, although this is more important for calcium channel blocking medication overdoses.[11] In the present case, the authors had more familiarity with glucagon; thus, this approach, rather than HDI or ILE, initially was tried.

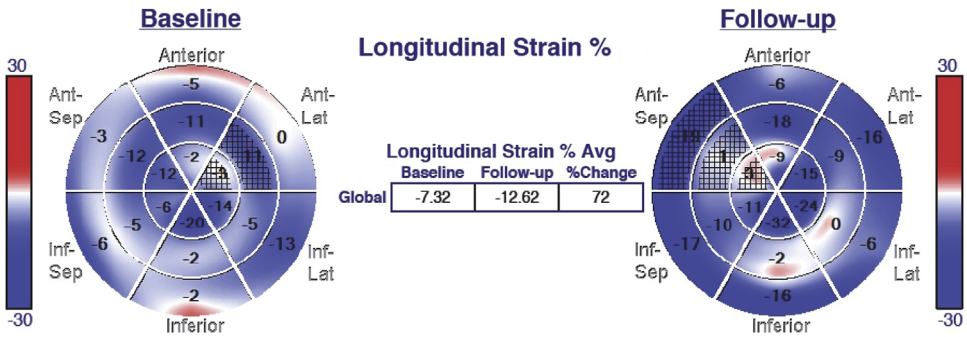

Fig 1. Serial speckle-tracking-derived segmental longitudinal strain images obtained for educational purposes demonstrating significant improvement in segmental and global strain after glucagon administration. The speckle-tracking software calculated that global strain improved from −7% to −12% globally, which is a 72% change. Approximately −18% is normal for the entire left ventricle, though the exact number depends on the specific segment. Despite the normalization of ejection fraction, the follow-up strain value of −12% remains elevated above −18%, suggesting ongoing global cardiac dysfunction.