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ORIGINAL ARTICLE

Cardiovascular and Adverse Effects of Glucagon for the Management of Suspected Beta Blocker Toxicity: a Case Series

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Abstract

Background Although glucagon use in beta blocker toxicity has been recommended for many years, evidence for its safety and efficacy in humans is limited. This study aims to determine the magnitude of effect of glucagon on heart rate (HR) and systolic blood pressure (SBP) in patients with suspected beta blocker toxicity and describe potential adverse effects of the medication.

Methods We conducted a retrospective, multi-center case series of patients greater than 12 years of age who received glucagon for suspected beta blocker toxicity. The primary outcome was the mean difference in HR from immediately pre- to 20-minutes post-glucagon administration. Secondary outcomes included the median difference in SBP, and occurrence of nausea, vomiting, and hyperglycemia.

Results A total of 107 patients met inclusion criteria accounting for 144 glucagon orders. The mean difference in HR from pre- to post-glucagon administration was 4 bpm ± 10.6 (95% CI [2.25–5.76], $p < 0.001$). The median difference (IQR) in SBP was 4.5 (−6 to 16) mmHg ($p = 0.004$). Similar increases were observed when patients receiving concomitant vasopressors were excluded. A total of nine glucagon administrations (6.3%) were associated with nausea and 14 (9.7%) with vomiting; however, 52 doses (36.1%) were administered concomitantly with antiemetic medications. Fifteen administrations (10.4%) were associated with hyperglycemia.

Conclusion Glucagon administration was associated with a statistically significant increase in HR, but a small absolute difference of uncertain clinical significance. A similar observation was noted for SBP. Few patients experienced adverse events.

Keywords Glucagon · Toxicity · Beta blocker · Antidote

Introduction

Glucagon is a hormone produced in pancreatic cells that stimulates glycogen breakdown to increase the body's circulating glucose serum drug concentrations when under stress. While glucagon's traditional use is for correction of hypoglycemia, the drug is also known for its cardiovascular effects. Under normal physiologic circumstances, binding of catecholamines to cardiac beta receptors activates G_s excitatory proteins that increase heart rate (HR) and contractility. In the setting of beta blocker toxicity, beta receptors are antagonized. Administration of glucagon, which also has cardiac receptors coupled to G_s proteins, can restore HR and contractility through an alternative pathway. Although its use in beta blocker toxicity has been recommended for many years, evidence supporting glucagon's efficacy has been limited to animal trials and case reports [1, 2].

A systematic literature review in 2003 evaluated the existing evidence on glucagon use in beta blocker and calcium channel blocker overdose. Only five controlled studies of beta blocker overdose in animal subjects were identified, each including between 5 and 10 subjects. No controlled studies were found in humans through the comprehensive literature search. Overall, animal models of propranolol

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overdose showed a consistent increase in HR with no effect on mean arterial pressure after glucagon administration. Its impact on survival is unclear; however, a single study did find an increase in survival rate of 83% in dogs who received a glucagon bolus and infusion [3].

Several case reports exist in humans suggesting that glucagon increases heart rate and blood pressure following beta blocker overdose [4–12]. The largest case series, by Love et al., evaluated nine cases of drug-induced symptomatic bradycardia in which patients received IV glucagon after atropine failure. Patients received between 1 and 10 mg of intravenous glucagon as a bolus dose, which was followed by an infusion of 3–6 mg/h in six of the nine patients. Several cases involved overdose with multiple concomitant medications; however, glucagon's impacts were positive overall. HR improved in all but one case, and by greater than 11 beats per minute (bpm) in six cases. Systolic blood pressure (SBP) increased by 19 to 83 mmHg in eight of the nine patients. Nausea, vomiting, and hyperglycemia are all potential side effects of glucagon administration in this setting; however, none were reported in the case series [12].

Based on the above evidence, bolus doses ranging between 3 and 15 mg followed by continuous infusion of 1–15 mg/h titrated to hemodynamic response have been suggested for the treatment of beta blocker overdose in various primary and tertiary references [1, 2, 13, 14]. This study aims to determine the magnitude of effect of glucagon on HR and SBP in patients with suspected beta blocker toxicity, as well as describe potential adverse effects of the medication.

Methods

Study Design

We conducted a retrospective, multi-center case series of patients within our health system, which consists of five hospitals, four suburban community hospitals ranging from 318 to 182 beds and one suburban, independent academic medical center with 923 beds, located across Northern VA and contains a total of 1936 licensed beds. The study was approved by the Western Institutional Review Board with waiver of informed consent due to its retrospective design.

Study Protocol

This study included patients greater than 12 years of age who received glucagon for beta blocker toxicity between January 1, 2013 and December 31, 2020. Patients with inadequate documentation of vital signs, inaccessible charts, and those who received atropine concomitantly or in the 5 minutes prior to glucagon administration were excluded. A Web Intelligence (WebI®) report was used to identify patients who received glucagon, and further narrowed using ICD-10 codes related to beta blocker toxicity or expected cardiovascular effects (e.g., bradycardia). Provider notes were then reviewed in the electronic health record (Epic©) to verify that glucagon was used for suspected beta blocker toxicity. One investigator (AMS) was responsible for this process, and the first 20 charts were reviewed by a second investigator (LAL) for integrity. If at any time the investigator responsible for this process (AMS) was uncertain whether a case was appropriate for inclusion, a second review was performed by the second investigator (LAL) who made the final determination. Data collected from the electronic health record included (1) demographic information such as age, gender, and weight; (2) information regarding the toxicologic emergency, including number and type of substances involved, other medications used for treatment of beta blocker toxicity (e.g., high-dose insulin, atropine, vasopressors, fluid boluses, lipid emulsion), whether toxicity was suspected or confirmed, and if the overdose was intentional; (3) information on glucagon dosage including timing, dose, and/or administration rate; (4) vital signs including HR and SBP pre- and 20-minutes post-glucagon administration; and (5) information related to glucagon side effects such as blood glucose at 20-minutes post-glucagon administration and documentation of nausea, vomiting, or antiemetic use. Given glucagon's onset of approximately 20 minutes, bolus doses given within 20 minutes of each other were evaluated as a single dose [15]. All data points were determined a priori and collected using a standardized form.

Outcomes

The primary outcome was the mean difference in HR from immediately pre- to 20-minutes post-glucagon administration. Secondary outcomes included median difference in SBP from immediately pre- to 20-minutes post-glucagon administration, occurrence of nausea and vomiting, and occurrence of hyperglycemia. Nausea and vomiting were defined as documentation of nausea and vomiting in the medical record or administration of an antiemetic following glucagon. Hyperglycemia was defined as an increase in blood glucose to greater than or equal to 180 mg/dL while receiving glucagon in patients not receiving concomitant insulin and/or dextrose. The percentage of patients whose bradycardia and SBP improved post-glucagon administration were also examined as secondary outcomes. Based on existing case reports, improvement in bradycardia was defined as an increase in heart rate by greater than or equal to 10 bpm, and improvement in SBP was defined as an increase by greater than or equal to 20 mmHg.

Statistical Analysis

Means and standard deviations were reported for normally distributed continuous variables; medians and interquartile ranges (IQRs) otherwise. Kolmogorov–Smirnov and Shapiro–Wilk tests were performed to test for normality, which showed normal distribution for HR and non-normal distribution for SBP. Therefore, a two-sided paired *t*-test was used to evaluate the mean difference in heart rate for the primary endpoint, and the median difference in systolic blood pressure was evaluated as a secondary endpoint using a Wilcoxon signed-rank test. The remaining secondary outcomes are reported only as descriptive statistics. A pre-specified sensitivity analysis was conducted for outcomes related to heart rate and blood pressure to assess for confounding secondary to administration of vasopressors. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY, USA).

Upon examination of our result data, multiple unanticipated confounding factors were noted. Approximately 52% of patients received suboptimal doses of glucagon; therefore, a post-hoc subgroup analysis was completed to compare the primary outcome for patients who received a glucagon bolus of 1–2 mg and those who received the recommended dose of 3–5 mg. Doses greater than 5 mg were not analyzed as a subgroup due to a low number of administrations ($n = 4$). We also conducted a subgroup analysis to determine if there were any differences in results for administrations associated with suspected toxicity compared to confirmed toxicity, as we suspected that glucagon may have more meaningful effects in patients with excess beta blockade. Patients who receive a loading dose followed by a glucagon infusion are also more likely to reach peak drug serum drug concentrations faster than those who receive only a bolus. Due to these differences in pharmacokinetics, an additional sensitivity analysis was completed to determine if results differed when patients receiving glucagon infusions were excluded.

Results

Baseline Characteristics

A total of 181 glucagon administrations met inclusion criteria, 37 of which were excluded, leaving 144 administrations in 107 patients in the final analysis (Fig. 1). The independent academic medical center within our health-system accounted for approximately half of all glucagon administrations (51.4%), while the four community hospitals each accounted for between 6.3% and 16.6% of administrations. Baseline characteristics are summarized in Table 1. Due to the possibility that each patient could have received more than one glucagon administration, population data is reported using the number of patients ($n = 107$), and treatment data is reported using the number of glucagon administrations ($n = 144$). Overall, the patients included in this case series had beta-blocker toxicity that was suspected by the treating provider, but unconfirmed by the patient or a witness. Most patients were classified as experiencing an unintentional or accidental overdose, which is generally associated with milder symptoms compared to patients who intentionally overdosed. The treatment characteristics of the patients included in this case series support this, as a low percentage received vasopressors, high insulin euglycemic therapy, and/or intravenous fat emulsion; therapies typically utilized for more severe symptoms.

Pre-specified Outcomes

Results for all pre-specified outcomes are summarized in Table 2. Data were analyzed using the number of glucagon administrations ($n = 144$) rather than the number of patients, as each patient could have received glucagon more than once. HR increased by ≥ 10 bpm in 34 patients (23.6%), and SBP increased by ≥ 20 m mHg in 29 patients (20.1%). With respect to adverse events, nine glucagon administrations (6.3%) were associated with nausea and 14 (9.7%) with

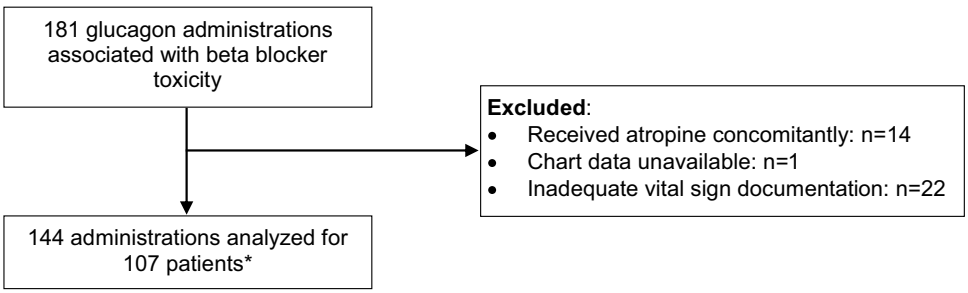

Fig. 1 Subject enrollment.

Table 1 Baseline characteristics*.

Patient characteristics	**Population ($n=107$)**
Age (years)	
12–18	4 (3.7)
19–39	5 (4.7)
40–59	20 (18.7)
60–79	41 (38.3)
≥ 80	37 (34.5)
Male	51 (47.6)
Weight (kg)	82.1 ± 23.6
Confirmed overdose	27 (25.2)
Intentional overdose	18 (66.6)
Polysubstance overdose	22 (81.5)
Unconfirmed overdose	80 (74.7)
Intentional overdose	1 (1.25)
Polysubstance overdose	20 (80)
Treatment characteristics	**Administrations ($n=144$)**
Fluid bolus	36 (25)
Calcium gluconate	26 (18)
Vasopressors	21 (14.6)
High dose insulin euglycemic therapy	2 (1.38)
IV fat emulsion	2 (1.38)
Glucagon formulation	**Administrations ($n=144$)**
Glucagon bolus	117 (81.2)
Glucagon bolus + infusion	6 (4.2)
Glucagon infusion	21 (14.4)
Dosing information	**Bolus administrations ($n=117$)**
Average glucagon bolus dose (mg)	2.66 ± 1.76
	Infusion administrations ($n=27$)
Average glucagon infusion start rate (mg/h)	4.04 ± 2.08

*Data reported as n(%) and mean ± standard deviation unless denoted otherwise

Table 2 Pre-specified outcomes and sensitivity analyses.

Outcome	Pre-glucagon	Post-glucagon	Mean difference [95% CI]	P value
Mean HR (bpm)*	53.4 ± 13.2	57.4 ± 14.7	4 ± 10.6 [2.3–5.7]	< 0.001
Median SBP (mmHg)†	101.5 [85.2–130]	109.5 [93–133]	4.5 [− 6 to 16]	0.004
Sensitivity analysis excluding vasopressor use ($n=123$)				
Mean HR (bpm)*	53.3 ± 3.4	56.8 ± 14.9	3.5 ± 10.4 [1.6–5.3]	< 0.001
Median SBP (mmHg)†	102 [85–134]	110 [93–139]	5 [− 5.5 to 13.5]	0.009
Sensitivity analysis excluding glucagon infusions ($n=117$)				
Mean HR (bpm)*	52.5 ± 13.1	56.2 ± 14.7	3.7 ± 11.4 [1.6–5.8]	< 0.001
Median SBP (mmHg)†	105 [87–134]	113 [94–135]	2 [− 7 to 16]	0.47

*Data reported as mean ± SD and analyzed using two-sided paired t test

†Data reported as median [IQR] and analyzed using Wilcoxon signed-rank test

vomiting; however, 36% of doses were administered with antiemetic medications. Fifteen administrations (10.4%) were associated with hyperglycemia.

Post-hoc Analyses

Two post-hoc subgroup analyses were conducted; outcomes are summarized in Table 3. In the subgroup analysis examining the impact of dosing on the primary outcome, a statistically significant rise in HR was only observed in the group receiving higher doses (i.e., 3–5 mg). In the second subgroup analysis examining the impact of an overdose being suspected versus confirmed or witnessed on the primary outcome, a statistically significant increase in heart rate was observed in both groups; however, the mean difference in heart rate was larger in the confirmed overdose subgroup. Lastly, a sensitivity analysis was conducted for the primary outcome excluding patients on glucagon infusions to determine if pharmacokinetic differences would impact our findings. The mean difference in HR when excluding glucagon infusions deviated marginally from the overall analysis (Table 2).

Discussion

Despite statistical significance, absolute differences in HR and SBP observed in our case series were small and of a magnitude that may be explained by normal physiologic fluctuation leading to uncertain clinical relevance. Compared to our study, the largest human case series by Love et al. showed greater differences in HR and SBP; however, the series had a small sample size [12]. It should also be noted that the glucagon formulation utilized in the Love et al. series was extracted from pancreatic cells and contained varying amounts of insulin; whereas, the currently available glucagon formulation is recombinant and completely without insulin [16]. As such, the increases in HR and SBP reported in Love et al. may have been caused by insulin rather than glucagon itself. Since the initiation of our study, a more recent randomized crossover trial by Petersen et al. evaluated the hemodynamic impacts on HR and SBP of esmolol, glucagon, and placebo combinations in 10 men. Glucagon, at a dose of 50 mcg/kg, was found to increase mean HR by 13 beats per minute, SBP by 15 mmHg, diastolic blood pressure by 9 mmHg, and cardiac output by 18%. Like the case series, Petersen et al. observed larger differences in HR and blood pressure compared to our study; however, a possible explanation for this may relate to the higher average glucagon bolus dose used in this study (3.6 mg versus 2.7 mg) [17]. The results of our subgroup analysis support this explanation, as a statistically significant increase in HR was observed only in the 3–5 mg subgroup. This suggests that a larger absolute difference may have been detected in the primary analysis if more patients received recommended doses of glucagon. Differences in time point at which HR was documented may also explain the larger differences in HR found by Petersen et al., whose study evaluated vital signs at 5 minutes, compared to our 20-minutes mark. It is possible that the peak effect was missed in our study despite pharmacokinetic data suggesting an onset of approximately 20 minutes [15]. It should also be noted that similar increases in HR and SBP were observed by Petersen et al. regardless of whether patients received beta blockade with esmolol, suggesting that glucagon may have an impact on hemodynamics even if beta blockade is not present [17]. The results of our study contrast this slightly, as patients with confirmed beta blocker overdose experienced a greater increase in HR compared to those with unconfirmed overdose in our subgroup analysis; however, a statistically significant increase in HR was still present in both groups. With regard to safety, the most common adverse event in the study by Petersen et al. was nausea, which occurred in 80% of patients despite pretreatment with ondansetron [17]. We observed a lower occurrence of nausea and vomiting, which may be related to the lower doses administered or missing data due to the retrospective nature of the case series. The occurrence of hyperglycemia was also low in our study and has not been reported in previous case series or studies evaluating glucagon for beta blocker toxicity. It should be noted that nausea, vomiting, and hyperglycemia are not specific to the administration of glucagon and their occurrence may also have been impacted by other factors such as underlying disease or co-ingestants.

Table 3 Subgroup analyses.

Outcome	Pre-glucagon	Post-glucagon	Mean difference [95% CI]	*P* value
1–2 mg subgroup ($n=75$)				
Mean HR (bpm)*	51.85 ± 13.2	54.21 ± 14.5	2.4 ± 11.4 [− 0.252 to 4.97]	0.076
3–5 mg subgroup ($n=44$)				
Mean HR (bpm)*	56.7 ± 7.8	60.7 ± 9.5	4.1 ± 9.2 [0.97–7.1]	0.011
Confirmed overdose subgroup ($n=46$)				
Mean HR (bpm)*	55.6 ± 10.1	60.5 ± 10.5	4.8 ± 9.4 [2–7.6]	0.001
Suspected overdose subgroup ($n=98$)				
Mean HR (bpm)*	52.4 ± 14.4	56 ± 16.3	3.6 ± 11.2 [1.4–5.9]	0.002

*Data reported as mean ± SD and analyzed using two-sided paired *t* test

Limitations

Accuracy of the data was dependent upon proper chart documentation and diagnosis coding given the study's retrospective design and the use of ICD-10 codes and provider notes to identify patients with beta blocker overdose. Along these lines, in the absence of verifying the presence of toxic beta blocker concentrations by serum or other biologic testing, we cannot be certain that all patients included in this case series were exposed to supratherapeutic doses of beta blockers. However, as these tests are not available in routine practice, a study of this nature may be difficult or impractical. Due to the low probability that any patient did not receive glucagon for beta blocker toxicity, as it is the current standard of care, there was no control group in this study. The lack of a control group prevented us from determining if the improvements in hemodynamics observed were due to glucagon or if they were naturally occurring. Considering glucagon's onset of approximately 20 minutes, all glucagon bolus administrations given within 20 minutes of each other were evaluated as a single dose. This would have masked any effects that may have been observed with a single dose. However, doses were combined for only two patients in our study, which is unlikely to have a significant impact on our results. Finally, the study was not adjusted for multiple comparisons; therefore, all secondary outcomes and analyses should be interpreted as hypothesis generating only.

We expected that the concomitant use of vasopressors would confound our primary and secondary outcomes, as they would influence HR and SBP. However, in our prespecified sensitivity analysis, minimal differences in HR or SBP were observed when excluding patients with vasopressors, suggesting that concomitant use had little clinical impact on our study outcomes. We also hypothesized that a sensitivity analysis excluding glucagon infusions would reduce the effect size of the bolus group, as patients receiving a bolus and an infusion would reach peak glucagon serum drug concentrations at a faster rate. No such differences were observed, as the results of our sensitivity analysis excluding glucagon infusions varied minimally from the primary analysis.

There are several patient populations to whom our results may not apply. As previously mentioned, the doses utilized in our study were frequently lower than those recommended in the literature and used in other published studies. As such, the lack of effect observed in our cases series may not be reflective of glucagon's effects at higher doses. Also, the majority of patients included in this cases series appeared to be experiencing mild to moderate symptoms of beta-blocker toxicity based on baseline demographic information collected; therefore, extrapolation to patients presenting with more severe toxicity may not be appropriate. Our study did not evaluate outcomes beyond 20 minutes; therefore, future studies are needed to evaluate the cardiovascular effects of glucagon infusions independently. Similarly, a low number of pediatric patients were included in our study, limiting its generalizability beyond the adult population; thus, further study may be beneficial to identify any effect differences that may be present in the pediatric population.

Conclusion

Glucagon administered in the setting of beta-blocker toxicity was associated with a statistically significant increase in HR, although the absolute difference was small and of uncertain clinical significance.

Dosing appeared to impact the efficacy of glucagon, as a significant increase in heart rate was not observed when < 3 mg was given. Similar to the effects of glucagon on HR observed in this case series, changes in SBP were statistically significant, but of a magnitude unlikely to be clinically meaningful. Few patients experienced adverse events due to glucagon use.

Author Contribution LAL conceived the study. AMS and LAL designed the study. AMS performed data collection. AMS and LAL analyzed the data. AMS drafted the manuscript; and AMS and LAL contributed substantially to its revision. AMS and LAL take responsibility for the paper as a whole.

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Declarations

Conflict of Interest None.

References

1. Brubacher JR, et al. Beta-adrenergic antagonists. In: Nelson LS, et al., editors. Goldfrank's toxicologic emergencies. 11th ed. New York: McGraw-Hill; 2019. p. 856–69.
2. Howland M, et al. Antidotes in depth: glucagon. In: Nelson LS, et al., editors. Goldfrank's toxicologic emergencies. 11th ed. New York: McGraw-Hill; 2019. p. 870–3.
3. Benoit B. Glucagon in beta blocker and calcium channel blocker overdoses: a systematic review. J Toxicol Clin Toxicol. 2003;41:595–602. https://doi.org/10.1081/clt-120023761.
4. Kosinski EJ, Malindzak GS. Glucagon and isoproterenol in reversing propranolol toxicity. Arch Intern Med. 1973;132:840–3. https://doi.org/10.1001/archinte.1973.03650120048009.
5. Ehgartner GR, Zelinka MA. Hemodynamic instability following intentional nadalol overdose. Arch Intern Med. 1988;148:801–2. https://doi.org/10.1001/archinte.1988.00380040041008.
6. Lewis M, Kallenbach Germond C, Zaltzman N, Muller F, Steyn J, et al. Survival following massive overdose of adrenergic blocking

agents (acebutolol and labetalol). Eur Heart J. 1983;4:328–32. https://doi.org/10.1093/oxfordjournals.eurheartj.a061469.
7. O'Mahony D, O'Leary P, Molloy MG. Severe oxprenolol poisoning: the importance of glucagon infusion. Hum Exp Toxicol. 1990;9:101–3. https://doi.org/10.1177/096032719000900020.
8. Smith RC, Wilkinson J, Jull RL. Glucagon for propranolol overdose. J Am Med Assoc. 1995;254:2412. https://doi.org/10.1001/jama.1985.03360170052022.
9. Fernandes CMB, Daya MR. Sotalol-induced bradycardia reversed by glucagon. Can Fam Physician. 1995;41:659–65.
10. Salzberg M, Gallagher EJ. Propranolol overdose. Ann Emerg Med. 1989;9:26–7. https://doi.org/10.1016/S0196-0644(85)81081-7.
11. Peterson C, Leeder S, Sterner S. Glucagon therapy for beta blocker overdose. Drug Intell Clin Pharm. 1984;18:394–8. https://doi.org/10.1177/106002808401800507.
12. Love JN, Sachdeva DK, Bessmen ES, Curtis LA, Howell JM. A potential role for glucagon in the treatment of drug-induced symptomatic bradycardia. Chest. 1998;114:323–6. https://doi.org/10.1378/chest.114.1.323.
13. Graudins A, Lee HM, Dino D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunctive therapies. Br J Clin Pharmacol. 2016;81:452–531. https://doi.org/10.1111/bcp.12763.
14. Beta blocking agents. IN: POISONDEX System [database on the internet]. Greenwood Village (CO): IBM Corporation; 2022 [cited 2022 Sep 29] Available from www.micromedexcolutions.com. Subscription required to view.
15. Glucagon [package insert]. Warrendale: Fresenius Kabi USA, LLC; 1960.
16. Kline JA, Leonova E, Raymond RM. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized caninie. Crit Care Med. 1995;23:1251–63.
17. Petersen KM, Bøgevig S, Riis T, Andersen NW, Dalhoff KP, Holst JJ, et al. High-dose glucagon has hemodynamic effects regardless of cardiac beta-adenoreceptor blockade: a randomized clinical trial. J Am Heart Assoc. 2020;9:e016828. https://doi.org/10.1161/CIR.0000000000000628.