Hemodynamic Effects of Glucagon: A Literature Review

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Context: Glucagon's effects on hemodynamic parameters, most notably heart rate and cardiac contractility, are often overlooked. The glucagon receptor is a central target in novel and anticipated type 2 diabetes therapies, and hemodynamic consequences of glucagon signaling have therefore become increasingly important. In this review, we summarize and evaluate published studies on glucagon pharmacology with a focus on clinical hemodynamic effects in humans.

Evidence Acquisition: PubMed, Embase, and the Cochrane Library were searched for clinical studies concerning hemodynamic effects of glucagon (no year restriction). Papers reporting effects of a defined glucagon dose on any hemodynamic parameter were included. Reference searches were conducted in retrieved articles.

Evidence Synthesis: Hemodynamic effects of glucagon have been investigated mainly in cohort studies of patients suffering from heart failure receiving large glucagon bolus injections. The identified studies had shortcomings related to restricted patient groups, lack of a control group, randomization, or blinding. We identified no properly conducted randomized clinical trials. The majority of human studies report stimulating effects of pharmacological glucagon doses on heart rate, cardiac contractility, and blood pressure. The effects were characterized by short duration, interindividual variation, and rapid desensitization. Some studies reported no measurable effects of glucagon.

Conclusions: The level of evidence regarding hemodynamic effects of glucagon is low, and observations in published studies are inconsistent. Actual effects, interindividual variation, dose-response relationships, and possible long-term effects of supraphysiological glucagon levels warrant further investigation. **(*J Clin Endocrinol Metab* 103: 1804–1812, 2018)**

Glucagon is secreted from the pancreatic alpha cells and possibly from enteroendocrine cells in the intestine (1, 2). Glucagon increases glucose production in the liver and is the counterregulatory hormone to insulin; together, they maintain normoglycemia in the fasting state. However, the actions of glucagon go beyond glucose homeostasis and involve direct effects on the cardiovascular system (3–7), and, based on animal experiments and clinical case studies (8–15), high-dose glucagon is recommended for reversal of cardiogenic shock induced by poisonings with cardioinhibitory drugs (7). Recently, a renewed focus on glucagon signaling has emerged because the glucagon receptor is a key element in new and emerging treatments for obesity and type 2 diabetes (16): glucagon-like peptide 1 (GLP-1)/glucagon co-agonists are under investigation as potential therapy

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Abbreviations: AC, adenylyl cyclase; bpm, beats per minute; cAMP, cyclic adenosine monophosphate; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter 2.

for obesity and type 2 diabetes (17, 18), and diabetes therapy based on closed-loop artificial pancreas systems is emerging (19). Furthermore, some current diabetes therapies [*e.g.*, inhibitors of the sodium-glucose cotransporter 2 (SGLT-2)], which have been found to improve cardiovascular outcomes in type 2 diabetes, increase endogenous glucagon secretion (20–22). Thus, glucagon receptor activation may have a bearing on the hemodynamic effects and cardiovascular safety of these therapies. Increased glucagon levels may be harmful due to possible chronic tachycardia (23, 24), which in and of itself is a risk factor for cardiovascular morbidity (25). Cardiovascular effects of pharmacological treatments of obesity and type 2 diabetes are important; the unexpected increase in cardiovascular risk with rosiglitazone was a clear example thereof (26). Altogether, understanding the consequences of increased glucagon levels on the cardiovascular system has become increasingly important. We therefore reviewed and evaluated the literature regarding the pharmacology of glucagon with a focus on clinical hemodynamic effects.

Methods

Different search strategies were applied to identify studies on the hemodynamic effects of glucagon: in September 2017, we searched the PubMed database for full-text articles reporting human clinical studies investigating glucagon with the search string (((((((((glucagon) OR "Glucagon"[Mesh]) OR glucagon (title)) OR "Glucagon"[nm]))) NOT ((glucagon like peptide 1) OR Glucagon-Like Peptide 1 [Mesh]))) AND ((((((“Cardiac Output/drug effects"[MeSH Terms]) OR "Blood Pressure/drug effects"[MeSH Terms]) OR "Hemodynamics/drug effects" [MeSH Terms]) OR "Heart Ventricles/drug effects"[MeSH Terms]) OR "Cardiovascular System/drug effects"[MAJR]) OR "Heart Rate/drug effects"[MeSH Terms])) AND (((((((“Humans"[Mesh]) OR "Clinical Study"[Publication Type])) OR human) OR man) OR trial)). An article was included if it reported effects of a defined glucagon dose on a hemodynamic parameter measured at specified time points (no year restrictions). Reference searches were conducted in retrieved articles. Twenty-four human studies reporting hemodynamic effects of glucagon were identified and included (Supplemental Tables 1 and 2). Embase was searched for full-text articles using the string *glucagon/ or *glucagon blood level/ AND exp hemodynamic parameters/ or exp hemodynamic stress/ or hemodynamics/ AND Human/, and the Cochrane Library database was searched using the single key word "glucagon," yielding no additional studies.

Pharmacology of glucagon

Stimuli acting on the pancreatic alpha cell regulate glucagon secretion: neural, hormonal, and local paracrine factors, possibly including glucagon itself, amylin, insulin, somatostatin, and incretin hormones (27–30). Plasma glucose is an important and well-characterized regulator (19, 31), but recent evidence suggests that plasma amino acids may play an even more important role (32). The secretion from extrapancreatic sources of glucagon remains to be fully described (2). The effects of glucose-lowering therapies on glucagon secretion are in general poorly understood—in particular, long-term effects and effects of older therapies (33). SGLT-2 inhibitors and sulfonylurea compounds may, under certain conditions, increase glucagon levels, however, within the physiological range (21, 33). In contrast, several therapies have been reported to lower glucagon levels, including GLP-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and the amylin mimetic pramlintide (16, 33). Physiological plasma concentrations of glucagon are within 3.5 to 100 pg/mL (1 to 30 pmol/L) (34). The major degradation sites and clearance of glucagon are plasma and kidney, whereas the contribution by the liver seems surprisingly small (35). Renal failure and liver cirrhosis elevate endogenous glucagon levels, possibly by altered elimination kinetics and/or secretory patterns (36–38). In healthy individuals, glucagon clearance follows first-order kinetics within physiological and slightly supraphysiological plasma levels (39). The metabolic clearance rate of glucagon in patients with type 1 diabetes is similar to that of healthy controls following intravenous administration (40, 41). However, patients with type 1 diabetes may have altered glucagon disposition, contributing to a longer elimination half-life (one study reported 12 minutes compared with 7 minutes in matched healthy controls) (41). Apparent half-life after intramuscular administration is 30 to 45 minutes because the absorption is rate limiting in this situation. The inaccuracy of many glucagon assays complicates interpretation of glucagon kinetics and suggested dose-response curves (33, 34), and studies reporting plasma glucagon concentrations and clearance rates differ substantially in methodology, including biochemical assays used (36, 40, 42). Still, many available assays perform poorly, especially within the lower end of the physiological range (34, 43). The introduction of sandwich assay technology has, however, solved some of the sensitivity and specificity problems (44). Of note, early studies (up until the 1990s) investigating hemodynamic effects of glucagon used glucagon extracted from pig or cow pancreas that may have been contaminated by other pancreatic hormones which could have some hemodynamic effects (*e.g.*, insulin) (3, 45, 46). Glucagon is now produced with recombinant DNA technology or chemical synthesis, yielding purified human glucagon.

Glucagon signal transduction in the heart

The glucagon receptor is a G protein-coupled receptor present in a variety of tissues in animals and humans, including the heart (6, 47–49). Multiple downstream pathways involved in glucagon signaling are identified. Pharmacological glucagon levels—high glucagon levels obtained with exogenous glucagon doses in the microgram and milligram range—exhibit actions that are associated with positive cardiac inotropy and chronotropy. Glucagon may also stimulate cardiomyocyte fuel metabolism, and subtypes of glucagon receptors appear to exhibit heterogeneous glucagon affinity (50). A (simplified) overview of major glucagon signaling pathways in the cardiomyocyte is presented in Fig. 1. Furthermore, some evidence for cross-reactivity between the related ligands and receptors in the glucagon family (*e.g.*, glucagon and GLP-1) is suggested from experimental data (51, 52).

Glucagon signaling in the normal heart

Cardiostimulatory actions of glucagon are linked with adenylyl cyclase (AC) stimulation through G_s protein-coupled

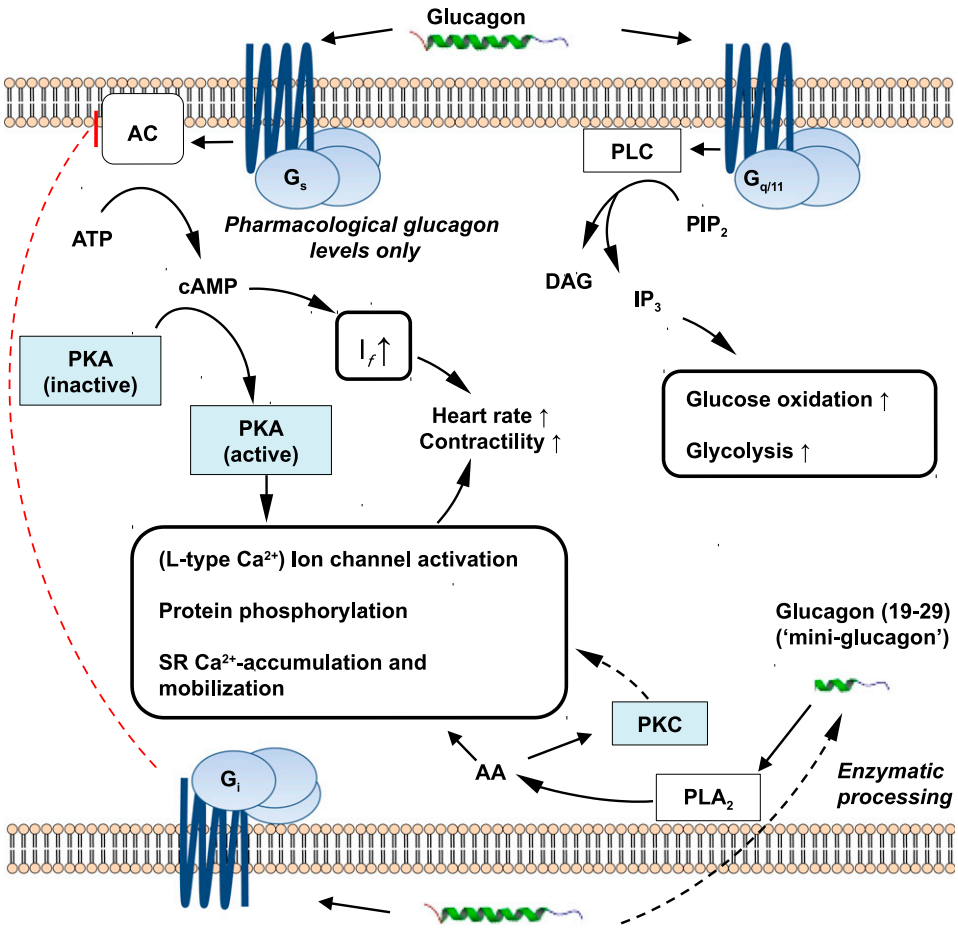

Figure 1. Simplified overview of major glucagon signaling pathways in general and proposed mechanisms of action in the cardiomyocyte, mediated through the glucagon receptor or possibly other members of the glucagon receptor family. Raised cAMP levels increase open probability of funny channels (located in the cell membrane of the sinoatrial node myocyte), consequently increasing the funny current and heart rate. Effects of physiological glucagon levels on the cardiomyocyte and cardiostimulatory effects of mini-glucagon *in vivo* are speculative. AA, arachidonic acid; ATP, adenosine triphosphate; DAG, diacylglycerol; I*f*, pacemaker "funny" current; IP_3, inositol 1,4,5-trisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLA_2, phospholipase A_2; PLC, phospholipase C; PIP_2, phosphatidylinositol 4,5-bisphosphate; SR, sarcoplasmic reticulum.

glucagon signaling (6, 49, 50, 53–56): AC synthesize 3′,5′-cyclic adenosine monophosphate (cAMP). Raised cAMP levels increase the open probability of hyperpolarization-activated, cyclic nucleotide-gated channels (*i.e.*, "funny" channels) in cardiac conduction tissue. This results in an increased cardiac pacemaker funny current (an inward sodium/potassium current) at diastolic voltages and thus a positive chronotropic effect (57). Glucagon activates AC independently of the beta-adrenergic receptor (58). Partly because of this, glucagon became a widely accepted treatment against cardiodepression caused by beta-blocker and calcium channel-blocker overdoses (59). Activation of the AC pathway in the heart seems, however, to require pharmacological glucagon levels (Fig. 1). In comparison, glucagon levels within the physiological range may primarily stimulate fuel metabolism via the phospholipase C/phosphoinositide 3-kinase pathway (50). These actions are possibly mediated through G_q protein coupling of the glucagon receptor (6, 50, 60, 61).

Desensitization

Cardiac desensitization to glucagon occurs upon continuous exogenous administration (62, 63) due to uncoupling of the AC complex from the glucagon receptor (64) and hydrolysis of cAMP by phosphodiesterases (65). Furthermore, the number of internalized glucagon receptors increases in parallel with the duration of (pharmacological) glucagon stimulation, reducing the membrane-bound receptor population within 30 minutes (66). Repeat bolus doses of pharmacological glucagon are recommended in the treatment of cardiac-depressant drug overdoses because of rapid desensitization, which is supported by animal data (67, 68).

Phosphodiesterase inhibition

Phosphodiesterase inhibition enhances cAMP responses and has experimentally been shown to increase the inotropic response to concomitant glucagon stimulation (69). *In vitro*, pharmacological glucagon concentrations may in themselves inhibit phosphodiesterases in the cardiomyocyte, contributing to stimulatory effects (70). Others have, in contrast, found that phosphodiesterase inhibition had no effects on the cardiac responses to glucagon (in rodents) (56). These conflicting findings could possibly be due to different experimental designs or interspecies differences with respect to glucagon receptor populations and distribution and activity of phosphodiesterases (56).

Cardiac actions of metabolites

The C-terminal fragment of glucagon (19–29) (called "mini-glucagon" by some) may be produced in small amounts via enzymatic processing in cardiomyocytes, although documentation for this is scarce. Experimentally, it has been found to potentiate the effects of glucagon (in chicken embryo ventricular myocytes) by synergistically increasing intracellular Ca^{2+} and cAMP levels (71–73) (Fig. 1). Mini-glucagon signaling possibly involves a G protein signaling pathway (73). The role of mini-glucagon and arachidonic acid in glucagon signaling and cardiac action *in vivo* is unclear.

Increased catecholamines

High-dose glucagon administration can lead to increased catecholamine levels (74, 75), which may contribute to stimulatory effects on the cardiovascular system. Catecholamine depletion of dog and cat heart muscle did not, however, affect the response to pharmacological glucagon levels compared with normal controls (76). Thus, catecholamines do not seem central for the cardiostimulatory effects of pharmacological glucagon levels, and catecholamine responses observed in humans may be a secondary phenomenon.

Glucagon signaling in the failing heart

Glucagon receptors also couple to G_i protein in human atrial myocytes (49). Upregulation of G_i in the cardiomyocyte may play a role in the pathophysiology of heart failure (77, 78) due to inhibition of cAMP formation and G_s protein–coupled signal transduction (49, 78) (Fig. 1). Therefore, glucagon action in the chronically failing heart may theoretically be impaired due to dysregulated signal transduction within the cardiomyocyte.

Animal data on hemodynamic effects

Effects on heart rate

Mice without glucagon receptors have lower intrinsic heart rates (heart rates in the absence of nervous stimulation) and altered parasympathetic heart rate control (51). This supports that endogenous glucagon could play a role in heart rate regulation and may agree with the findings that pharmacological glucagon stimulation increases the open probability of cardiac funny channels (56). Pharmacological glucagon concentrations between 4.2 and 10.1 μg/mL (1.2 to 2.9 μmol/L) increased heart rate significantly to 110 beats per minute (bpm) from 81 bpm at baseline in cat atria (a 30% increase) (76). In dogs, a 50-μg/kg glucagon bolus produced an average 22% increase in heart rate from 178 bpm at baseline to 217 bpm after glucagon (76). A placebo-controlled dog experiment used verapamil to reduce the average heart rate to 73 bpm from 132 bpm at baseline. A 200-μg/kg glucagon bolus followed by a 150-μg/kg/h infusion or placebo was administered. In the placebo arm, average heart rates were 58 bpm at 15 minutes. All dogs in the placebo arm died within 85 minutes. Fifteen minutes following start of glucagon, mean heart rate increased 28% (to 94 bpm). This effect was sustained for 120 minutes, but heart rates fell to 67 bpm at 240 minutes (79), likely due to desensitization. In contrast, no evidence for desensitization to the chronotropic action of glucagon was found with repeated bolus doses administered with intervals of 4 or 15 minutes (67, 68). In a placebo-controlled dog experiment, a 10-mg/kg propranolol infusion reduced the heart rate to 100 bpm from 155 bpm at baseline (80). A 20-μg/kg glucagon bolus increased heart rate to 179 bpm on average, 1 minute after infusion start. The heart rate remained significantly above control levels 30 minutes after glucagon (80).

Effects on cardiac inotropy

In a dog *in vivo* study, a 50-μg/kg glucagon bolus infusion increased left ventricular pressure development (mm Hg per second) 72 ± 18% from baseline, independent of heart rate (81). In cats, the cardiac output following a sequence of 2-, 4-, 8-, and 16-μg/kg glucagon infusions increased significantly in both controls and cats with chronic heart failure (increases of 51% and 38%, respectively, from baseline values of 548 and 347 mL/min). Ventricular pressure development was also significantly increased in both groups (82). In the placebo-controlled dog model of verapamil toxicity, glucagon increased cardiac output 55% (compared with saline infusion) 15 minutes after glucagon. This effect was sustained until 120 minutes after glucagon start, but cardiac output fell to 784 mL/min after 240 minutes (79). In propranolol-induced cardiac collapse in dogs, a 20-μg/kg glucagon bolus increased cardiac output 164%, from 1.4 L/min to 3.7 L/min, 1 minute after glucagon. The increased cardiac output remained significantly higher in the glucagon group compared with controls for 11 minutes (80).

Effects on blood pressure

Despite stimulatory effects on heart rate and contractility, pharmacological glucagon seems to have little or no effect on measures of blood pressure (3, 79–81).

A substantial number of the in vivo animal studies have investigated hemodynamic actions of glucagon together with other interventions or have explored various models of heart failure (79, 80, 82, 83). This complicates interpretation of the studies, and the overall level of evidence is low. A list of *in vivo* animal studies investigating hemodynamic effects of glucagon is available in Supplemental Table 1.

Human data on hemodynamic effects

Effects on heart rate

In general, the effects of pharmacological glucagon administration (>1 mg) on heart rate appear short lasting and varying; the majority of studies reported an increase in heart rate of 5% to 25% [with few exceptions (84)]. Interindividual differences exceeding 50% in the response to glucagon seem common. Stimulating effects rarely last longer than 20 minutes in the majority of studies. In 10 patients with chronic heart failure given a 50-μg/kg intravenous glucagon bolus injection, heart rates increased by 9% on average, from 83 bpm to 91 bpm, 2 minutes after glucagon administration. The effect lasted less than 5 minutes (85). A comparable dose (3 mg) was administered into the pulmonary artery to eight patients with heart failure, resulting in a 15% average increase, 2 to 3 minutes after glucagon, which was present for 15 to 25 minutes (86). Comparable effects on heart rate have been confirmed by other investigators with glucagon bolus doses between 1 and 6 mg administered over 1 to 10 minutes (62, 81, 86–92). Prolonged infusion (2 to 3 mg/min for 10 to 15 minutes) was found to produce heart rate changes similar to a 3- to 5-mg glucagon bolus (87, 93). Studies using prolonged glucagon infusions (>1 hour) of 2 to 7.5 mg/h for an average of 48 to 118 hours (94–97) resulted in no change or even decreased heart rates in

patients suffering from heart failure. Other studies otherwise comparable to the above using bolus glucagon observed no effects on heart rate (88, 98–100). Furthermore, a study on healthy volunteers receiving much lower glucagon infusion rates of 5 and 10 ng/kg/min for 60 minutes observed an average heart rate reduction by 8% and 6% from baseline (101).

Effects on cardiac inotropy

In general, glucagon administration appears to lead to a prompt and robust increase in various measures of cardiac inotropy; however, levels are rarely above 25% to 30% from baseline. More than 50% interindividual variation is often reported, and stimulating effects rarely last more than 20 minutes. In 10 patients suffering from heart failure, 50-μg/kg glucagon bolus injections resulted in a considerable, 26% average increase in cardiac output to 5.4 L/min from 4.3 L/min at baseline. Maximum responses occurred after 10 minutes, and a notable effect lasted 20 minutes (85). Likewise, cardiac output increases of 25% to 42% and 25% to 41% from baseline were observed in studies using bolus injections of 2 to 5 mg (directly in the pulmonary artery) (62) and 50 μg/kg intravenously (98), respectively. Slightly lower glucagon doses (10 to 20 μg/kg) (85) and lower infusion rates between 5 and 10 ng/kg/min for 60 minutes (101) had no effects on cardiac output, suggesting a threshold or dose dependency (85). Increase in the cardiac index (liters per minute per meter squared) occurred 2 to 5 minutes after a 5-mg administration in 10 participants with normal coronary arteries (16% increase from baseline) and in 18 patients with substantial (>50%) coronary artery narrowing (21% increase from baseline). The stimulatory effects lasted less than 15 minutes (92). Glucagon infusion (2 to 3 mg/min) for 10 to 15 minutes increased the average cardiac index by 30%, similar to the effects observed after 3 to 5 mg intravenous bolus (87). Prolonged infusions (20 mg glucagon/d) were investigated in three patients with acute myocardial infarction with no effects on measures of cardiac contractility in two patients and diminished contractility in the third within 48 hours after infusion start (62).

Effects on blood pressure

Of 18 studies reporting blood pressure changes related to a glucagon bolus, 11 observed increased mean arterial pressure between 5% and 18%. Effects of glucagon on blood pressure measures were immediate and short lasting. In eight patients with heart conditions, a 3-mg glucagon bolus into the pulmonary artery led to a noteworthy average 12% increase in systolic blood pressure to 153 mm Hg from 137 mm Hg at baseline. The mean arterial pressure increased from 96 to 104 mm Hg on average. No changes in diastolic blood pressures occurred. Effects on blood pressure reached maximum after 2 to 5 minutes and lasted less than 25 minutes (86). Comparable increases in blood pressure parameters due to glucagon have been found in patients with heart conditions classified as New York Heart Association class I and II (87), in patients with acute myocardial infarction (62), and in patients with both normal and compromised coronary artery flow (92). Likewise, a 10% average increase in mean arterial pressure (from 92 to 101 mm Hg) was observed after a 15-minute infusion of 4.5 mg (300 μg glucagon/min over 15 minutes) (89). In contrast, the diastolic blood pressure decreased significantly (from 72 mm Hg to 63 mm Hg) 5 minutes after a 50-μg/kg glucagon bolus. The authors suggested this to be due to diminished sympathetic tone secondary to a significantly improved cardiac output (85). Other studies observed no effects on measures of blood pressure after glucagon bolus (84, 85, 88, 90, 98, 100, 102) or during 24-hour infusion of 20 mg (62).

Clinical outcomes of glucagon therapy

A few studies have evaluated whether glucagon therapy resulted in symptomatic improvement in patients experiencing heart failure (96, 103–105). In 18 patients with congestive heart failure, prolonged glucagon therapy, 1 or 4 mg/h as constant infusion or 5-mg bolus injection every 4 hours (for 76 hours on average), did not improve symptoms of heart failure in 11 patients. In the seven patients who received glucagon and improved clinically (*e.g.*, increased urine output and weight loss), the majority (four) did so due to other interventions after glucagon was stopped (103). In another study including six patients who experienced heart failure, continuous glucagon infusions (3 mg/h for an average of 93 hours) improved blood pressure and urine output and reduced body weight. Despite these changes, three patients died shortly after treatment start (96).

It is important to note that most studies exploring hemodynamic effects of glucagon in humans generally included small groups of various patients with heart failure and were nonrandomized without a proper control group, yielding a low level of evidence. A list summarizing human studies investigating hemodynamic effects of glucagon is available in Supplemental Table 2.

Discussion and Critical Appraisal of Data

The majority of preclinical experiments report positive inotropic and chronotropic effects on the heart by glucagon (56, 67, 76, 80, 81). The available human data, in contrast, draw an inconsistent picture. Hemodynamic effects of glucagon have been investigated using large intravenous boluses in the milligram range. The majority of studies report stimulatory effects on hemodynamic measures, characterized by rapid onset and a ceiling effect of approximately 30% to 40% increase on the short-term (minutes) in measures of cardiac inotropy and heart rate. Effects rarely exceeded 20 minutes. However, most studies were in patients with chronic heart disease and with bolus injections of glucagon, in whom much (*i.e.*, ~85%) of the administered dose may have been eliminated from the circulation after 20 minutes. No available evidence demonstrates sustained effects of continuous infusion of glucagon or repeated bolus administrations, but potential prolonged effectiveness could only be evaluated from a few studies, which all had limitations such as lack of control groups or blinding (94–97, 106). To cloud the picture even further, some authors observed no stimulatory actions of glucagon (62, 98, 99, 101).

The large interindividual variation (62, 81, 85–89, 91, 94, 98, 99) appears to depend on patients' cardiac reserves. Patients with severe heart failure had relatively small or no effect of glucagon on cardiac contractility

(90, 98), compared with patients classified as New York Heart Association class I and II (87) and in healthy volunteers (84, 107).

Overall, exogenous glucagon does not seem to improve clinical outcomes in patients who have experienced heart failure, regardless of magnitude of initial hemodynamic effects (96, 97, 103–105). This appears in line with the lack of documented effect of glucagon on cardiac outcome and survival when used in poisonings with cardioinhibitory drugs (11, 108). Further, glucagon decreased survival rates in a mouse model of myocardial infarction and blockade of glucagon signaling may have cardioprotective properties after myocardial infarction (109). These observations suggest a potential harmful effect of an increased glucagon tone on the failing myocardium.

From the available evidence, the dose-response relationship between glucagon levels and hemodynamic effects in humans is unclear. However, clinical observations suggest some dose dependency—in particular, that a large glucagon dose is required. This indicates that a certain supraphysiological threshold has to be reached for hemodynamic effects to occur. This is further supported by the observation that short-term average glucagon levels of 381 ± 179 pg/mL (110 ± 51 pmol/L) (approximately 10 times normal basal levels) had no measurable effects on cardiac inotropy in healthy volunteers (101). In contrast, consequences of chronically elevated glucagon levels in the higher supraphysiological range may have implications for cardiovascular safety: levels of 1,200 pg/mL (360 pmol/L), high supraphysiological concentrations but still much lower than those reached with glucagon therapy in the milligram dose range, have been reported to lead to severe heart disease due to chronic resting tachycardia (23).

Stimulatory effects on fasting and postprandial glucagon secretion are reported for SGLT-2 inhibitors and some sulfonylurea compounds during certain experimental conditions (and compared with dipeptidyl peptidase-4 inhibitors) (33). These effects are marginal compared with the supraphysiological glucagon concentrations necessary for direct cardiac effects. However, chronic consequences on the heart of raised glucagon levels within the physiological and slight supraphysiological range are not apparent from the present evidence. This, together with the fact that the glucagon receptor is central for some diabetes therapies under development (16, 18, 19), underlines the importance of characterizing glucagon's cardiac dose-response curve and possible off-target effects of pharmacological concentrations of glucagon on the heart, such as interactions between glucagon and homologous receptors.

Conclusion

The limited evidence from animal and human studies investigating hemodynamic effects of glucagon (bolus and continuous intravenous infusion) suggests that glucagon in pharmacological doses may have positive chronotropic and inotropic effects and to a lesser degree may elevate blood pressure parameters in humans. However, the published clinical trials all have shortcomings, particularly involving restricted patient groups and lack of a control group, randomization, and/or blinding. Areas that warrant further exploration are the large interindividual variation and rapid desensitization, the threshold dose-response that may be reached in the low dose-range, as well as long-term effects of increased glucagon levels.

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