Efficacy of Isoproterenol-Glucagon Infusion in Patients with Heart Disease

By RALPH A. POLUMBO, M.D., RICHARD F. LEIGHTON, M.D., and ARNOLD M. WEISSLER, M.D.

SUMMARY
Isoproterenol and glucagon were administered separately and in combination by constant rate of intravenous infusion to 13 patients with organic heart disease. Glucagon produced modest increases in cardiac output, heart rate, and arterial pulse pressure. Isoproterenol produced increases in cardiac output and heart rate greater than that achieved with glucagon alone and also increased arterial pulse pressure, stroke volume, and mean rate of left ventricular ejection and decreased systemic vascular resistance.

The same doses of isoproterenol and glucagon in combination produced a greater effect on cardiac output than that achieved with either drug alone and had a greater effect on heart rate and arterial pulse pressure than did glucagon alone. There was no increase in the side effects of either drug associated with their administration in combination.

The present study suggests that the clinical usefulness of glucagon may be enhanced by administering glucagon in combination with isoproterenol in order to obtain the additive hemodynamic benefit of these drugs while minimizing their undesirable side effects.

Additional Indexing Words:
Cardiac output Hemodynamics

IN 1960 Farah and Tuttle\(^1\) first demonstrated that glucagon produced positive inotropic and chronotropic effects in isolated animal hearts and in heart-lung preparations. Subsequent studies during the past decade have confirmed these findings in isolated cardiac tissue,\(^2,\)\(^3\) intact animals,\(^2-5\) and in man\(^6-12\) and have demonstrated that the effects of glucagon persist in the presence of digitalis glycosides,\(^2,\)\(^6,\)\(^9,\)\(^11,\)\(^12\) catecholamine depletion,\(^2\) and beta-adrenergic blockade.\(^2,\)\(^3\) Studies in man indicate that the positive inotropic effects and low arrhythmogenic potential of glucagon may be beneficial in the treatment of certain patients with heart disease.\(^6-12\) Its practical usefulness as a therapeutic measure, however, has been limited because of troublesome gastrointestinal side effects, but these may be minimized at low doses.\(^6,\)\(^7,\)\(^9,\)\(^11\)

Isoproterenol, a beta-adrenergic stimulating agent, has been shown to exert potent cardiostimulatory activity in normal individuals and patients with a wide variety of cardiac disorders.\(^13,\)\(^14\) While the positive inotropic effects of this agent are enhanced by increasing the dose, the dose range is limited by such side effects as arrhythmias, angina, and hypotension.

In view of these considerations, it was hypothesized that isoproterenol and glucagon in combination might produce an additive hemodynamic effect and that improvement in cardiac performance might be obtained with

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From the Department of Medicine (Division of Cardiology), The Ohio State University College of Medicine, Columbus, Ohio.
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low doses of each drug, thereby minimizing undesirable side effects. Accordingly, the present study of the effects of glucagon and isoproterenol given separately and in combination to a group of patients with organic heart disease was undertaken.

**Methods**

Thirteen hospitalized patients with organic heart disease, 11 men and two women, 26 to 71 years of age, were studied. Three patients had arteriosclerotic heart disease, four, nonobstructive primary myocardial infarction, two, calcific aortic stenosis and insufficiency, one, rheumatic heart disease with mitral insufficiency, and three, arteriosclerotic heart disease combined with rheumatic heart disease and mitral insufficiency. Ten patients had prior clinical evidence of heart failure and were on maintenance digitalis therapy.

Right heart catheterization was performed under minimal or no sedation in the postabsorptive state. Pressure recordings were obtained through fluid-filled catheters using Statham P23Db transducers and an Electronics for Medicine DR-8 recorder. Cardiac output was determined in duplicate by an indicator-dilution method employing injections of indocyanine green dye in the pulmonary artery with sampling of brachial or femoral arterial blood at constant rate. Blood was reinjected through the catheter in the pulmonary artery following each determination. Isoproterenol and glucagon solutions were infused into a convenient peripheral vein at constant rate with a Harvard infusion pump.

An electrocardiogram and an external pressure tracing of the carotid artery were recorded at a paper speed of 100 mm/sec, and the left ventricular ejection time was measured according to the method of Weissler and associates. The mean rate of left ventricular ejection (MRLVE) was calculated from the ratio of stroke volume to ejection time and is expressed in milliliters per second of ejection.

The following procedures and drug interventions were carried out in the same sequence for each patient studied: control measurements, isoproterenol infusion, repeat control measurements after a 30-min interval provided to allow the effects of isoproterenol to dissipate, glucagon infusion, and finally the infusion of isoproterenol and glucagon in combination.

The dose of glucagon was determined on the basis of previous studies which showed that 1 to 5 mg injected intravenously as a bolus produced significant cardiotimulatory effects and from preliminary studies in our laboratory utilizing constant infusion techniques to determine whether comparable doses administered over a longer period of time could produce significant improvement in cardiac performance without the troublesome gastrointestinal side effects frequently encountered with large bolus injections. It was determined that an infusion rate of 0.125 mg/min for 15 min most consistently improved cardiac performance with minimum side effects.

The dose of isoproterenol was selected on the basis of previous studies which showed that a relatively low dose of 1 µg/min infused intravenously at constant rate produced potent cardiotimulatory effects with minimal side effects even in patients with low cardiac output due to a variety of heart diseases.

After control hemodynamic measurements were obtained, isoproterenol was infused at a rate of 1 µg/min, and hemodynamic measurements were obtained after a 15-min period of infusion. A 30-min interval was provided to allow the effects of isoproterenol to dissipate, and control hemodynamic measurements were again obtained. Repeat control measurements were not obtained in one patient because of his critical condition.

Glucagon (Eli Lilly) was then infused at a rate of 0.125 mg/min for 15 min in nine patients. Two patients received a dose of 0.25 mg/min early in the study before the lower dose of 0.125 mg/min had been selected as the standard dose. Two other patients received an additional infusion at the higher dosage of 0.25 mg/min immediately after the initial infusion of 0.125 mg/min produced no apparent cardiovascular effect as indicated by no change in heart rate, arterial pressure, or the oscillographic appearance of the cardiac output dye curves. Hemodynamic measurements were obtained after a 15-min infusion period in each patient.

Following these measurements, a solution of isoproterenol and glucagon was infused in the same dosage and rate as each patient had previously received, so that nine patients received isoproterenol, 1 µg/min, plus glucagon, 0.125 mg/min, and four patients received isoproterenol, 1 µg/min, plus glucagon, 0.25 µg/min. Hemodynamic measurements were obtained after a 15-min infusion period.

Statistical analysis of the data was performed using the t-test for paired samples according to Snedecor.

**Results**

The individual changes in cardiac output, heart rate, and arterial pulse pressure which occurred when isoproterenol and glucagon were infused separately and in combination are shown in figures 1 to 3.

Administration of glucagon alone increased the average cardiac output (+0.68 liters/min),
The effect of the glucagon alone (average, +22). The effect of the glucagon alone was significantly greater than that achieved by either drug alone.

Heart rate (+6 beats/min), and arterial pulse pressure (+6 mm Hg), P < 0.01 for each, without changing stroke volume, mean rate of left ventricular ejection, or systemic vascular resistance. The effect of the two doses of glucagon, 0.125 mg/min compared to 0.25 mg/min, was not statistically significant.

Isoproterenol alone also produced an average increase in cardiac output (+2.12 liters/min, P < 0.001), heart rate (+18 beats/min, P < 0.001), and arterial pulse pressure (+11 mm Hg, P < 0.01), and in addition increased stroke volume (+11 ml/beat, P < 0.01) and mean rate of left ventricular ejection (+68 ml/sec, P < 0.01), and diminished systemic vascular resistance (−5.5 Wood units, P < 0.001). The increases in cardiac output and heart rate induced by isoproterenol were greater than the increases induced by glucagon (+1.44 liters/min, P < 0.01, and +13 beats/min, P < 0.001).

Isoproterenol and glucagon infused in combination resulted in increases in cardiac output (+2.64 liters/min, P < 0.001), heart rate (+22 beats/min, P < 0.001), arterial pulse pressure (+14 mm Hg, P < 0.01), and mean rate of left ventricular ejection (+89 ml/sec, P < 0.001), and a diminution in systemic vascular resistance (−7.2 Wood units, P < 0.001). There was no significant change in mean arterial pressure when isoproterenol and glucagon were infused separately or in combination. The effect of the two doses of glucagon, 0.125 mg/min compared to 0.25 mg/min, given in combination with isoproterenol, was not statistically significant.

The increase in cardiac output induced by the isoproterenol-glucagon combination was greater than the increase induced either by isoproterenol (+0.52 liters/min, P < 0.05) or by glucagon (+1.96 liters/min, P < 0.001) alone. The combination also induced greater increases in heart rate (+16 beats/min, P < 0.001) and in arterial pulse pressure (+8 mm Hg, P < 0.01). The chronotrophic response to the combination was significantly greater than that to glucagon alone but not to isoproterenol alone.
Change in cardiac output. On the vertical axis is the change in cardiac output from control to values obtained with the combination of isoproterenol and glucagon. On the horizontal axis is the change in cardiac output from control to values obtained with isoproterenol alone. A good correlation is evident. \( r = 0.78 \)

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\begin{align*}
\text{Δ C.O. CONTROL TO ISP-GWAGON} \quad &\text{Δ C.O. CONTROL TO ISOPROTERENOL} \\
\text{(L/Min)} &\text{(L/Min)} \\
1.0 &2.0 \\
2.0 &3.0 \\
3.0 &4.0 \\
4.0 &5.0 \\
\end{align*}
\]

Figure 4

mm Hg, \( P < 0.01 \)) than the increases induced by glucagon alone.

The change in cardiac output obtained with the isoproterenol-glucagon combination correlated well with the change in cardiac output obtained with isoproterenol infused separately, \( r = 0.78 \) (fig. 4), but did not correlate well with the change in cardiac output obtained with glucagon alone (\( r = 0.37 \)).

During the infusions, isoproterenol alone caused angina in one patient and no other side effects. Five patients had nausea and vomiting with glucagon infused alone and with the combination, and three of these patients had received the higher dose of glucagon, 0.25 mg/min. There were no additional side effects when the drugs were given in combination, and no arrhythmias were encountered.

Discussion

As noted in previous studies in man, \(^6-12\) infusion of glucagon results in a modest positive inotropic and chronotropic effect in most patients. Although some patients have been reported to demonstrate an increase in mean arterial pressure \(^8,8\) and a decrease in systemic vascular resistance \(^7,9\) other studies have reported no change in arterial pressure \(^7,9\) and systemic vascular resistance \(^10\) as was observed in the present study. Some patients do not respond to glucagon, and this does not seem to correlate with the presence or absence, duration, or severity of cardiac disease \(^9\).

In our patients, isoproterenol produced a greater effect on two of the parameters significantly influenced by glucagon: cardiac output and heart rate, and in addition resulted in increased stroke volume and mean rate of left ventricular ejection and decreased systemic vascular resistance. These observations are in agreement with the study of Williams’ group \(^9\) who reported that "maximally tolerated" doses of isoproterenol had greater hemodynamic effects than did glucagon given to the same patients. While it has been shown in intact canine hearts that the maximal inotropic effects of glucagon and isoproterenol are similar \(^18\), the above observations seem more relevant to the treatment of patients where the maximal dose that may be achieved with each drug is limited by its side effects.

The combination of isoproterenol and glucagon produced a greater increase in cardiac output than that achieved with each drug given separately. The effects of these drugs in combination are additive in terms of increasing cardiac output, but no conclusions can be made concerning their specific effects on myocardial contractility. For the group, the change in cardiac output obtained with the isoproterenol-glucagon combination correlated with the change in cardiac output obtained with isoproterenol alone, but not with glucagon. Thus, it might be anticipated that if a patient is improved by an infusion of isoproterenol, he will respond well to isoproterenol and glucagon infused in combination. Four patients did not show further improvement in cardiac output with the combination of drugs. These four could not be separated from the rest of the group either by type of heart disease or by hemodynamic findings.

The mechanism of action of glucagon on the myocardium is at present unknown. Glucagon and the catecholamines activate the
adenyl cyclase system yielding cyclic AMP (adenosine-3',5'-monophosphate).19,20 Beta-adrenergic blockade prevents the inotropic and chronotropic effects of catecholamines and also inhibits their ability to increase myocardial cyclic AMP19 but does not affect the inotropic effects of glucagon;2,21 in addition, glucagon is capable of increasing cyclic AMP in cat and human heart homogenates after beta-adrenergic blockade,20 which has led to the suggestion that the myocardium may have a single adenyl cyclase system with two different receptors, one responsive to catecholamines and one responsive to glucagon.20 Although glucagon does affect cyclic AMP, it has not been shown that the myocardial effects of glucagon are caused by the effects on the cyclic AMP system, and the mechanism of action remains to be elucidated.

Glucagon has several promising features as a therapeutic agent in treating patients with cardiac failure. Although the cardiovascular effects of single injections are of brief duration, continuous administration for periods as long as 12 to 13 days has been reported to be safe and has produced clinical improvement in patients with refractory heart failure11 and cardiogenic shock.12 It can enhance cardiac performance in fully digitalized patients;6,9,12,22 it does not cause extreme fluctuations in systemic vascular resistance or mean arterial pressure;6-12 clinically important side effects are few and consist mainly of gastrointestinal symptoms, which may be minimized at low doses;6,7,9,11 it is not associated with arrhythmias;6-12 even in fully digitalized patients;2,6,9,11,12 and since it is effective in the presence of beta-adrenergic blockade, it may be useful in treating patients with heart failure who are receiving propranolol.11

Studies of the effects of glucagon on the coronary circulation in man show that myocardial oxygen consumption and coronary blood flow increase without an increase in myocardial oxygen extraction, suggesting that the augmented coronary flow sufficiently meets the increased oxygen requirements of the heart produced by glucagon.22,23 In this regard, glucagon has effects similar to those of isoproterenol, which causes an increase in myocardial oxygen consumption, but myocardial oxygen extraction remains unchanged as coronary blood flow increases.24 Glucagon acts as a secondary coronary vasodilator, since the increase in coronary blood flow appears to be secondary to the increased myocardial oxygen requirements,23 whereas augmented coronary flow after isoproterenol is thought to be the result of both the secondary and primary coronary vasodilating effects of this drug.24 Although the increased myocardial oxygen requirements following glucagon and isoproterenol must be considered, the use of these inotropic agents which are capable of augmenting coronary blood flow without increasing myocardial oxygen extraction may be physiologically beneficial in the treatment of certain patients with heart disease, and studies to determine the combined effects of glucagon and isoproterenol on the coronary circulation and myocardial oxygen consumption are needed.

If the findings of the present study may be extended to the treatment of patients with heart failure, glucagon would seem to be much less potent than isoproterenol when given in modest doses. The major role of glucagon in the treatment of heart failure, however, may be in its concomitant use with isoproterenol, resulting in an additive hemodynamic effect while minimizing undesirable side effects of both drugs. The present study indicates that at least on a short-term basis, isoproterenol and glucagon in combination may represent a useful and important adjunctive therapeutic measure in the management of certain patients with heart failure. Additional studies are needed to characterize the combined effects of glucagon and isoproterenol on the coronary circulation and myocardial oxygen consumption and to determine the efficacy of administering these drugs in combination over a prolonged period of time.

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ISOPROTERENOL-GLUCAGON INFUSION

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