Coronary Vascular Effects of Glucagon in the Isolated Dog Heart

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ABSTRACT

Glucagon decreases peripheral vascular resistance by direct action on the arterioles. The present experiments were performed to study the effect of glucagon on the coronary resistance vessels. In isolated hearts from eight dogs the coronary arteries were perfused at a constant rate and the change in coronary pressure was used as an index of change in resistance after the intracoronary injections of glucagon (50 μg/kg). In the beating heart, glucagon caused a 22% decrease in the average coronary pressure (from 102 to 80 mm Hg); however, with this decrease in coronary resistance, myocardial contractility rose an average of 45% (from 11 to 16 units), the average heart rate increased 38% (from 156 to 213 beats/min), and the average coronary venous oxygen saturation decreased from 79.7% to 63.7%. However, when similar intracoronary injections of glucagon were made after cardiac arrest by potassium there was no change in coronary venous oxygen saturation and no significant decrease in coronary pressure. We conclude that the decrease in coronary resistance in the beating heart after glucagon injection is secondary to the metabolic effects of the increased myocardial contractility and heart rate, and that there is no significant direct vasodilating effect on the coronary resistance vessels.

ADDITIONAL KEY WORDS

potassium cardiac arrest
positive inotropism and chronotropism
non-beta-receptor sites

Glucagon, the hyperglycemia-provoking polypeptide, produces positive inotropic and chronotropic effects on cardiac muscle in both isolated papillary muscle preparations and intact animals (1-4). Recent clinical experience with this hormone suggests that these myocardial effects may be of value in the treatment of myocardial depression particularly when it is refractory to catecholamines and digitalis glycosides (5, 6). Although a decrease in coronary vascular resistance would be expected in consequence of the metabolic effects of the increase in heart rate and myocardial contractility after glucagon, the direct effect of the hormone on the coronary resistance vessels is unknown; glucagon has been shown to cause moderate peripheral vasodilatation (3). The present report is a study of the effects of glucagon on the coronary resistance vessels in both beating and potassium-arrested canine hearts.

Methods

Eight mongrel dogs weighing 10 to 20 kg were anesthetized with morphine (1 mg/kg sc) and sodium thiopentone (20 mg/kg iv). Positive pressure breathing was established through an occlusive intratracheal tube, and a bilateral cervical vagotomy was done. An isolated heart preparation perfused via a bag oxygenator was then prepared as follows. The left chest was opened and ligatures were placed around both cavae, the azygos vein, the right brachiocephalic and left subclavian arteries, the pulmonary artery, and the aorta just distal to the origin of the left subclavian artery. Drainage catheters were placed in the right ventricle through a stab wound, and in the left ventricle through the left atrial appendage; these catheters drained the total coronary venous return into the bag oxygenator where the blood was oxygenated by a mixture of 95% O₂, 5% CO₂ and then pumped back into the systemic circulation by a constant-flow occlusive


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pump through a constant-temperature water bath heated sufficiently to maintain the perfusate at 37°C. The right brachiocephalic artery was cannulated for recording aortic pressure with a rigid cannula, around which the vessel was ligated; the left subclavian artery was also cannulated and served as the arterial perfusion channel from the constant-rate pump. When the cavae, the azygos vein, and pulmonary artery were ligated, both right and left ventricles were by-passed and beating empty. The aorta was then ligated just below the left subclavian artery, which confined the arterial perfusion to the coronary circulation; thus, the pressure recorded from the right brachiocephalic cannula represented the coronary vascular resistance exclusively. This isolated heart preparation has been previously described.

A Walton-Brodie strain gauge was sewn on the anterior free wall of the left ventricle for estimating changes in myocardial contractility; changes in contractile force were estimated as increases in millimeters of deflection from the control.

With each of the animals on cardiopulmonary by-pass the coronary circulation was perfused at flow rates sufficient to maintain mean coronary perfusion pressure at physiological levels. These flow rates varied from 100 to 400 ml/min but were held constant during each study. Instantaneous injections of glucagon (50 μg/kg) were then made into the coronary circulation through the subclavian arterial perfusion line in each of the eight animals while arterial perfusion pressure and myocardial contractility were continuously recorded; heart rate was measured by the strain gauge arch deflections. Arterial blood samples were obtained from the subclavian arterial perfusion line, and coronary venous samples were collected from the right ventricular drainage catheter for estimation of O₂ saturation. This was determined spectrophotometrically by a modification of the method of Roos and Rich (8). Serum electrolytes and pH were also measured on each of the arterial blood samples. After allowing a sufficient recovery period (average 10 minutes) after the glucagon injections, 2 μg isoproterenol was similarly injected into the arterial perfusion line in each animal.

In seven of the animals, repeat arterial injections of glucagon in similar doses were made after cardiac arrest had been induced by 10% potassium chloride injected directly into the arterial perfusion line. Initial doses of 4 to 8 ml of potassium chloride were given as a single rapid injection. This was then supplemented by a constant pump infusion at rates of 0.75 to 1.91 ml/min to maintain the arrest. In every case, a decrease in coronary pressure was associated with the initial injection, but coronary resistance subsequently rose as the supplemental potassium chloride was infused. The coronary flow rate was then adjusted to maintain the coronary perfusion pressure as close as possible to the control (beating) level. Complete arrest was verified by continuous absence of myocardial contractions as monitored by the strain gauge arch. In each of these animals 2 to 10 μg isoproterenol and 100 to 500 μg nitroglycerin were injected to verify reactivity of the coronary resistance bed after potassium cardiac arrest.

The bag oxygenator perfusion system used in this study maintained arterial O₂ saturation above 97%. The arterial pH in the beating hearts averaged 7.42 and serum electrolytes remained normal throughout the studies. However, with cardiac arrest induced by potassium chloride, arterial pH fell to an average of 7.22 and the average value of serum chloride responsible for the fall in pH increased from 112 mEq/liter before to 128 mEq/liter after potassium chloride arrest; serum potassium rose from an average of 3.8 mEq/liter before to 31 mEq/liter after potassium chloride injections.

Results

Figure 1 illustrates the myocardial and coronary vascular response of the beating heart to arterial injections of glucagon and isoproterenol. In both instances there is an increase in heart rate and myocardial contractility and a decrease in coronary vascular resistance as manifested by a fall in arterial perfusion pressure. However, the onset of both the chronotropic and inotropic effect of isoproterenol is characteristically more rapid than that of glucagon where both of these responses are delayed for some seconds after injection. This difference in the mode of onset of the chronotropic and inotropic response to glucagon and isoproterenol was seen in each of the eight studies of beating hearts over a wide range of constant coronary flow rates.

The decrease in coronary vascular resistance after glucagon as manifested by the change in coronary arterial perfusion pressure while coronary flow was held constant is shown for each of the eight studies of beating hearts in Figure 2; the average fall in perfusion pressure of 22% (from 102 to 80 mm Hg) is significant (F < 0.01, sign test). Coincident with this
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Figure 1

Strain gauge arch (upper tracing) and coronary perfusion pressure in mm Hg (lower tracing) responses after A, isoproterenol (ISO) and B, glucagon injections. HR = heart rate (beats/min). Flow is constant inflow rate from arterial perfusion pump (ml/min).

Decrease in coronary vascular resistance there is evidence of increased myocardial O2 consumption as shown by the average decrease of O2 saturation of coronary venous blood from 80% to 64%; this is also a significant change (P < 0.01, sign test).

Figure 3 shows the increases in heart rate and myocardial contractility responsible for the increase in myocardial O2 consumption after glucagon injection. Both the average increase in heart rate of 38% (from 156 to 213 beats/min) and contractility of 45% (from 11 to 16 deflection units) are significant (P < 0.01, sign test).

Figure 4 illustrates the coronary vascular response to arterial injections of glucagon, isoproterenol, and nitroglycerine in the potassium-arrested heart. Glucagon causes a slight increase in coronary resistance, whereas both isoproterenol and nitroglycerine produce a vasodilator response. The serum potassium level of 36 mEq/liter remained constant through this series of observations, but control coronary vascular resistance continued to increase somewhat, as indicated by the need to reduce the coronary flow rate from 105 to 95 ml/min to maintain similar levels of coronary perfusion pressure.

As shown in Figure 5 in the seven animals with potassium-induced cardiac arrest there is no consistent change in coronary vascular resistance after glucagon. Although in three animals there is an increase in coronary pressure, the average increase of 8% (from 103 to 109 mm Hg) is not significant (P > 0.10, t-test). However, isoproterenol caused an average decrease of 8% in coronary pressure (from 103 to 95 mm Hg), and nitroglycerine decreased coronary pressure by an average of 19% (from 104 to 84 mm Hg); both of these changes are significant (P < 0.01, t-test).

Associated with the failure of coronary vasodilatation after glucagon in the potassium-arrested heart was the absence of signs of an increase in myocardial O2 consumption as indicated by the lack of significant change in coronary venous O2 saturation; this is illustrated in Figure 6.
Discussion

As anticipated, the increase in heart rate and myocardial contractility after glucagon was associated with a decrease in coronary vascular resistance in the beating heart preparation. However, this coronary vasodilatation was caused by an increased myocardial O2 consumption as manifested by the decline in coronary venous O2 saturation after injection of the hormone. In this respect, then, glucagon is a 'malignant' coronary vasodilator (9) and as an inotropic agent has no advantage over catecholamines that stimulate beta receptors. Indeed, the cardiac arrest studies failed to show a direct vasodilating effect of glucagon on the coronary resistance vessels, and in this regard glucagon may be at a disadvantage as compared to catecholamines, since Klocke et al. have shown an intrinsic adrenergic vasodilator mechanism in the coronary resistance vessels of the potassium-arrested heart (7).

Nonetheless, the metabolic conditions of our cardiac arrest studies make it difficult to rule out the possibility of a direct vasodilating effect of glucagon in the normal beating heart. Although the low arterial pH of our preparations would be expected to decrease coronary vascular resistance (10), the high serum potassium levels that were necessary to maintain cardiac arrest caused increased coronary resistance (11). In spite of this, the coronary vascular bed remained responsive to the vasodilating effect of isoproterenol and nitroglycerine and showed no consistent response to glucagon. However, since the peripheral vasodilating effect of glucagon has been shown not to be due to stimulation of beta receptors (3), the lack of coronary vasodilatation in the face of responsiveness of the preparation to isoproterenol does not rule out a vasodilator mechanism for the hormone which has been blocked by the metabolic conditions associated with the cardiac arrest. Such a mechanism would also be different from that causing
the vasodilatation of nitroglycerine in the potassium-arrested heart.

Although no attempt was made to quantify the "cost" in myocardial $O_2$ consumption for the increased inotropism and chronotropism of glucagon as compared to isoproterenol, the former would seem to have no distinct advantage over the latter in this regard. The use of glucagon in situations of myocardial depression associated with a relatively fixed coronary inflow, e.g., coronary occlusion with cardiogenic shock, would therefore seem to be open to the same perils as other inotropic agents which increase myocardial metabolism (9). It is not yet clear from the preliminary reports of its use in experimental canine myocardial infarction and shock (12) in what way the hormone might be of more benefit than catecholamines except in the presence of beta-receptor blockade.

The difference in time of onset of the inotropic and chronotropic effects of isoproterenol and glucagon as illustrated in Figure 1 supports the hypothesis that activation of adenyl cyclase with the consequent stimulation of cyclic 3',5'-AMP as the cause of the cardiac effects of the hormone is produced through a non-beta-receptor site (13). While this view has been previously deduced from studies of beta-receptor blockade (3, 13), the characteristic difference in response to isoproterenol and glucagon in the hearts without beta-receptor blockade in our study is further evidence for this hypothesis.
Cardiac arrest. Changes in coronary resistance as manifested by coronary perfusion pressure in mm Hg after glucagon (GLU), isoproterenol (ISO) and nitroglycerine (NTG) injections in the potassium arrested hearts. Mean values are shown by (+).

References


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