Insulin Improves Survival in a Canine Model of Acute β-Blocker Toxicity

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Received for publication October 18, 1996. Revision received February 3, 1997. Accepted for publication March 6, 1997.

Presented at the ACEP Research Forum, Cincinnati, March 1996.

Financed in part by a postdoctoral research grant from the American Academy of Clinical Toxicology and Texaco.

Study objective: To compare the efficacy of a novel antidote, insulin, with standard treatments, glucagon and epinephrine, in a canine model of acute β-blocker toxicity.

Methods: Anesthetized dogs were fitted with instruments by means of thoracotomy and vascular cutdown for multiple cardiodynamic, hemodynamic, metabolic, and electrical measures. After basal measurements were taken, animals received intravenous propranolol (.25 mg/kg/minute) continuously for the remainder of the experiment. Toxicity was defined as a 25% decrease in the product of heart rate times mean blood pressure. Thirty minutes after the development of toxicity, toxic measures were taken (treatment 0 minutes), and then the animals (n=6 each group) received either sham (saline solution), insulin (4 IU/minute with glucose clamped), glucagon (50 µg/kg bolus, then 150 µg/kg/hour infusion), or epinephrine (1 µg/kg/minute). Animals were monitored until death or for 240 minutes.

Results: Propranolol decreased contractility, left ventricular pressure, and systemic blood pressure, and resulted in death of all sham-treated animals by 150 minutes. Six of six insulin-treated, four of six glucagon-treated, and one of six epinephrine-treated animals survived. Survival was greater for insulin-treated animals, compared with either glucagon-treated ($P<.05$) or epinephrine-treated animals ($P<.02$) by the log-rank test. Insulin-treated animals were characterized by improved cardiodynamics and hemodynamics, increased myocardial glucose uptake, and decreased serum potassium.

Conclusion: Insulin is a superior antidote compared with glucagon or epinephrine in an anesthetized canine model of acute β-blocker toxicity.

[Kerns W, Schroeder D, Williams C, Tomaszewski C, Raymond W: Insulin improves survival in a canine model of acute β-blocker toxicity. *Ann Emerg Med* June 1997;29:748-757.

INTRODUCTION

Myocardial dysfunction with bradycardia, decreased contractility, and resulting hypotension is the hallmark of β-blocker toxicity.[1] The therapeutic goal in cases of β-blocker toxicity is to improve myocardial function, thereby restoring critical organ perfusion. Current pharmacotherapy is largely anecdotal and includes β-adrenergic agonists, glucagon, atropine, and phosphodiesterase inhibitors. These therapies have met with varied success.[1] Glucagon is accepted clinically as first-line therapy for β-blocker poisoning. In one series glucagon improved heart rate and blood pressure in 86% of patients.[1] However, in only two cases has glucagon been the sole pharmacotherapy,[2,3] and glucagon failed in several reports.[4-6] The reported efficacy of epinephrine and other catecholamines is less, even at high doses.[1] No prospective human study evaluating optimal therapy has been reported.

A few animal studies appear in the literature. In one model, anesthetized dogs received an intravenous bolus of propranolol followed by immediate experimental treatment with glucagon or a phosphodiesterase inhibitor (amrinone or milrinone). Glucagon was superior to both agents in restoring heart rate, and all treatments improved cardiodynamics.[7,8] Combined treatment with glucagon and phosphodiesterase inhibitor yielded no additional benefit.[9,10] In another study, prenalterol, a selective β_1-adrenergic agonist, improved myocardial function in dogs poisoned with increasing concentrations of intravenous metoprolol.[11] In no reported study has glucagon been compared with epinephrine, a nonspecific adrenergic agonist more frequently used in β-blocker toxicity. The authors of these studies did not compare treatments with regard to survival.

Insulin may be of value in reversing myocardial dysfunction caused by β-blocker toxicity through positive inotropic effects on the myocardium.[12,13] In addition, it antagonizes the negative inotropic effects of β-blockade. In one study, insulin overcame a propranolol-induced decrease in isometric tension in canine papillary preparations.[14] In another study involving intact piglets, high-dose insulin increased left ventricular pressure development despite β-blockade with practolol.[15] High-dose insulin increased myocardial contractility in intact neonatal lambs given practolol.[13] These findings have not been applied in a model of β-blocker toxicity.

The purpose of our study was to compare the efficacy of insulin, a novel antidote, with that of standard treatments, glucagon and epinephrine, in reversing severe β-blocker poisoning induced by propranolol in anesthetized dogs.

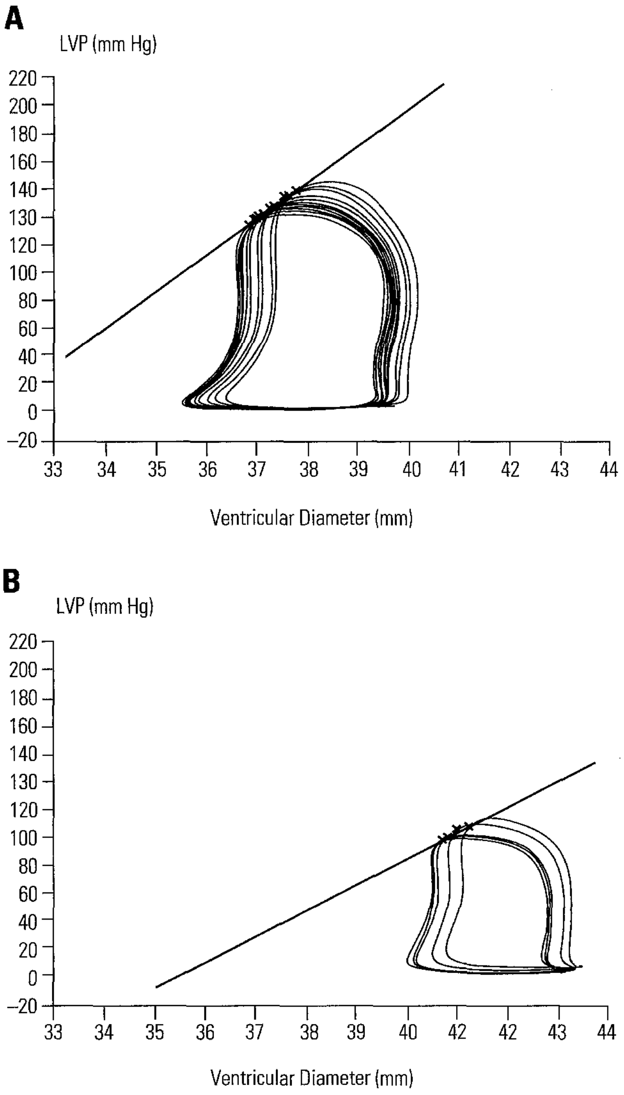
MATERIALS AND METHODS

The study, approved by the Institutional Animal Use and Care Committee, involved 27 mongrel dogs of both sexes, weighing between 16.3 and 28.4 kg. Anesthesia was induced with intravenous sodium pentothal (25 mg/kg) and maintained with a continuous infusion of α-chloralose (30 mg/kg/hour). After the induction of anesthesia, each animal was intubated and mechanically ventilated with 5 cm positive end-expiratory pressure to maintain arterial PO_2 at 90 to 100 mm Hg and PCO_2 at 35 to 40 mm Hg.

Catheters were placed in the left and right femoral veins and the left external jugular vein for fluid and experimental drug infusion. The right femoral artery was catheterized for arterial blood sampling and systolic, diastolic, and mean arterial blood pressure. A left thoracotomy was performed in the fifth intercostal space and the pericardium incised to expose the heart. A pneumatic vascular occluder was positioned around the ascending aorta. A catheter was placed into the coronary sinus, by means of an incision in the right atrial appendage, for the collection of coronary venous blood samples. A micromanometer transducer was secured in the left ventricle by means of an apical stab incision to permit continuous measurement of left ventricular peak pressure and heart rate. Ultrasonic crystals were placed in the anterior and posterior left ventricular walls by means of stab incisions to permit measurement of internal ventricular dimension. A Doppler ultrasound flow probe was secured around the circumflex artery to measure coronary artery blood flow. After surgery, the animals were stabilized for 1 hour before the experimental protocol was started.

After stabilization, basal cardiodynamic, hemodynamic, metabolic, and electrical measures were made. After basal data collection, D,L-propranolol was dissolved in .9 % saline solution and infused at .25 mg/kg/minute to induce toxicity. This infusion rate was determined in preliminary trials (n=16) designed to find a dose of propranolol that would cause reproducible, severe toxicity. Toxicity was defined as a decrease greater than 25% in the product of heart rate× mean arterial blood pressure. Thirty minutes after toxicity was achieved, data were recorded (treatment 0 minutes). The propranolol infusion was continued throughout the experiment. After data collection at treatment 0 minutes, the animals were randomly assigned to receive one of the following five experimental treatments. (1) Control (n=3): Each animal was given a .9 % saline solution in lieu of toxin or treatment. These animals served as time controls. (2) Sham treatment (n=6): Animals were given a .9 % saline solution infusion and served as toxic controls. (3) Insulin (n=6): Recombinant insulin was dissolved in .9 % saline solution and infused at 4 IU/minute, beginning at treatment 0 minutes. In previous work, this infusion rate maximally increased myocardial glucose uptake and improved blood pressure in canine endotoxic shock[16] and resuscitated dogs from verapamil-induced cardiogenic shock.[17] Arterial glucose was clamped at ±10% of the baseline values by means of an infusion of 50% dextrose through a separate catheter. (4) Glucagon (n=6): Glucagon was dissolved in .9 % saline solution and given as a 50 µg/kg intravenous bolus (2 mL), followed by a continuous infusion of 150 µg/kg/hour. This dosage is equivalent to current human therapy for β-blocker overdose[18] and is equal to or greater than the dosages reported in previous dog studies.[7,8,19,20] (5) Epinephrine (n=6): Epinephrine was diluted with .9% saline solution and initially infused at 1.0 µg/kg/minute and titrated to restore the product of heart rate×mean arterial blood pressure to baseline values.

Figure 1.
E_{max} determination. An example of the pressure-volume relationship ***A,*** *before and* ***B,*** *during propranolol infusion (treatment 0 minutes) in one study animal.*

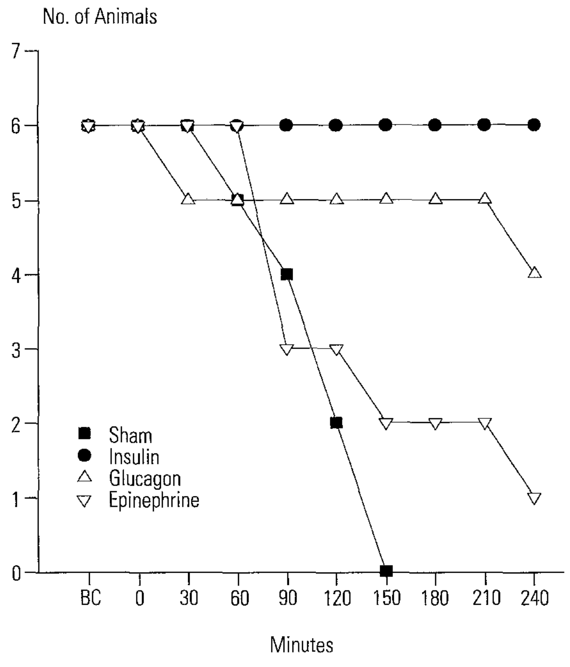


A, E_{max}=25.5 mm Hg/mm; r=1.00. **B,** E_{max}=17.6 mm Hg/mm; r=.97.
Software was used to determine the point of maximum left ventricular pressure at end systole for individual cardiac cycles with varying afterload. Linear-regression analysis was used to determine the slope (E_{max}) of the points of maximum pressure at end systole for each group of cardiac cycles. After exposure to propranolol, left ventricular pressure decreased, ventricular diameter increased, and E_{max} decreased.

All dogs received 20 mL/kg of .9% saline solution during surgery. During the experimental protocol, intravenous solutions were maximally concentrated so that each dog received a total volume of 80 mL/hour of .9% saline solution.

Cardiodynamic (left ventricular pressure and heart rate), hemodynamic (systolic, diastolic, and mean arterial blood pressures; coronary artery blood flow), and ECG measurements were continuously recorded on a multichannel polygraph. Data were also digitized and stored with the use of on-line data-acquisition software. The slope of the left ventricular pressure dimension relationship (maximal elastance

Figure 2.
Kaplan-Meier survival curve.



All sham-treated animals died within 150 minutes. Six insulin-treated animals, four glucagon-treated animals, and one epinephrine-treated animal survived the entire 240-minute treatment period. Survival was significantly greater with insulin therapy than with glucagon ($P<.05$) or epinephrine treatment ($P<.02$), by the log-rank test.

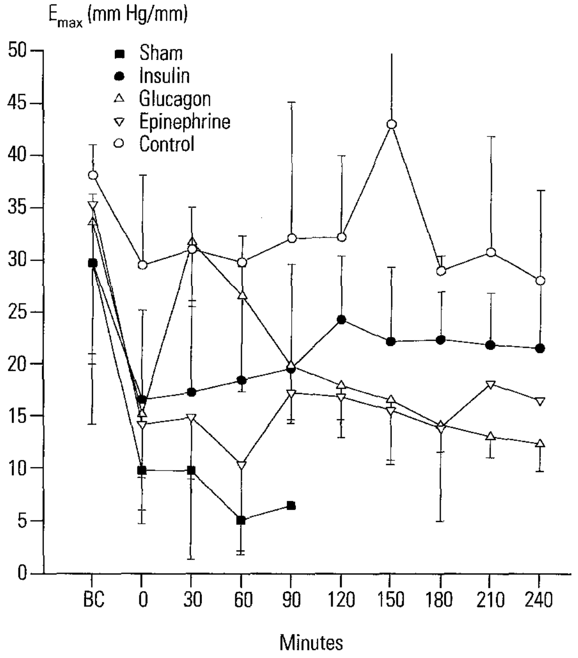
at end systole; E_{max}) served as our index of contractility.[17,21] Previous work showed E_{max} to be independent of factors that influence contractility such as heart rate or preload.[22] E_{max} was determined at timed intervals during the experiment as follows: The ventilator was turned off to eliminate the variability of myocardial function resulting from respiration. The aorta was then gradually occluded to vary afterload for 15 seconds. Software was used to determine the point of maximum pressure at end systole for each individual cardiac cycle during aortic occlusion. We used linear-regression analysis to determine the slope (E_{max}) of the points of maximum pressure at end systole for each group of cardiac cycles (Figure 1).

Arterial and coronary sinus blood was collected before the induction of toxicity (baseline), after toxicity was achieved (0 minutes), and then at 30-minute intervals during treatment. The blood was analyzed for (1) pH, PO_2, and PCO_2; (2) glucose and lactate; and (3) sodium, potassium, and calcium. The maximal total amount of blood obtained from an animal surviving to 240 minutes was approximately 50 mL. To minimize the effects of cumulative blood loss, we replaced blood volume for volume with .9% saline solution at the time of sampling. For insulin-treated animals, additional glucose determinations (.5 mL arterial blood) were performed every 15 minutes during the first hour of treatment to permit adjustment of supplemental glucose infusion.

All animals were monitored for 240 minutes of treatment or until death (defined as heart rate×mean arterial blood pressure=0). Myocardial glucose uptake was calculated as the product of coronary artery blood flow and the difference of arterial minus coronary sinus glucose concentration.

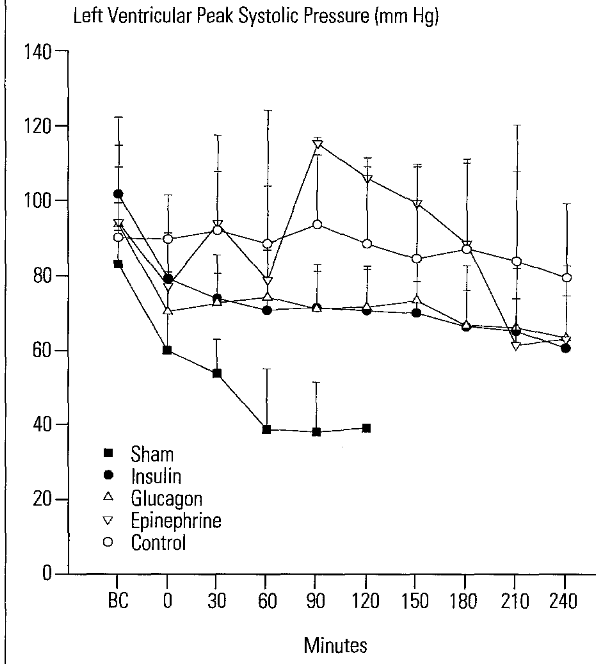
We compared differences in survival using the log-rank test.[23] Cardiodynamic, hemodynamic, electrical, and metabolic data of surviving animals are expressed as mean±SD and were compared with the use of SAS Statistical Software 6.08 (SAS Institute). The analysis software accounted for uneven cell size after the death of some animals. Overall significance among treatment groups was determined with the use of repeated-measures ANOVA. When between-group

Figure 3.
Contractility (E_{max}).



After exposure to propranolol, animals in all groups demonstrated decreased E_{max} (P=.024 versus control) before experimental treatment was started at 0 minutes. Insulin produced a consistent increase in E_{max} (no difference versus control group at 120 minutes). Glucagon transiently increased E_{max} during the first 30 minutes (P=.0007 versus insulin and epinephrine groups). Although two sham-treated animals remained alive at 120 minutes, cardiac function was so depressed that E_{max} could not be determined.

Figure 4.
Left ventricular peak systolic pressure.



Left ventricular peak systolic pressure decreased progressively in the sham-treated group (P=.011 versus control group by 0 minutes). Insulin and glucagon prevented the decline in left ventricular pressure (P=.0002 versus sham-treatment group by 90 minutes). Peak left ventricular pressure during epinephrine treatment occurred at 90 minutes (P=.0002 versus all other groups).

differences were found, ANOVA was performed at individual time points, followed with the post hoc Student-Newman-Keuls test. We considered P values less than .05 significant.

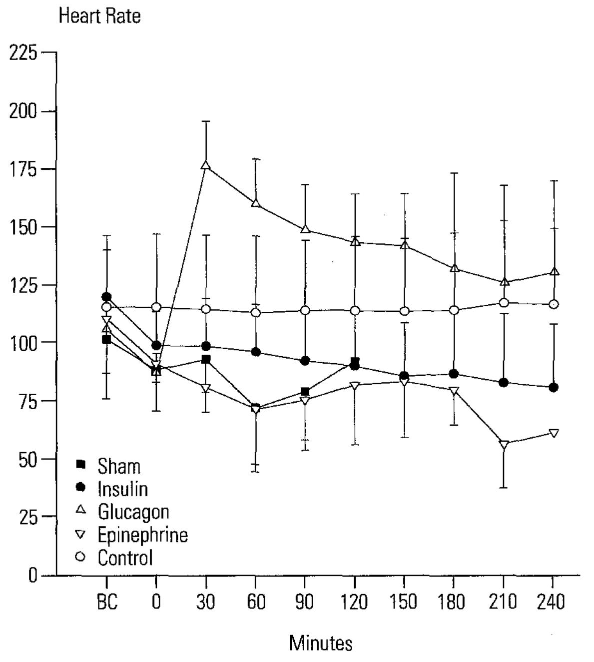
RESULTS

All animals given the sham treatment died within 150 minutes. All six propranolol-intoxicated animals treated with insulin survived for 240 minutes. Four of the six animals given glucagon survived to the end of the experiment. One epinephrine-treated animal survived to the end of the experiment. However, in this animal the cardiodynamic and hemodynamic indexes were consistent with agonal shock. As determined with the log-rank test, survival was significantly higher with insulin treatment than with glucagon (P<.05) or epinephrine treatment (P<.02) (Figure 2). All control animals survived to time 240 minutes (not shown in Figure 2).

After exposure to propranolol and before treatment, E_{max} (Figures 1 and 3), our measure of contractility, was depressed in all experimental groups (P=.024 versus control at 0 minutes) (Figures 1 and 3). With insulin treatment, E_{max} was gradually restored to the control value by 120 minutes. Transient improvement of contractility occurred in the glucagon and epinephrine groups. During the first 30 minutes of glucagon treatment, E_{max} increased (P=.0007 versus insulin and epinephrine) but then steadily declined so that by 120 minutes, E_{max} was significantly lower than that in the control group (P=.020). With epinephrine treatment, E_{max} had transiently increased to the control value at 90 minutes. Thereafter contractility decreased and, by 120 minutes, it was significantly lower than that in the control group (P=.020).

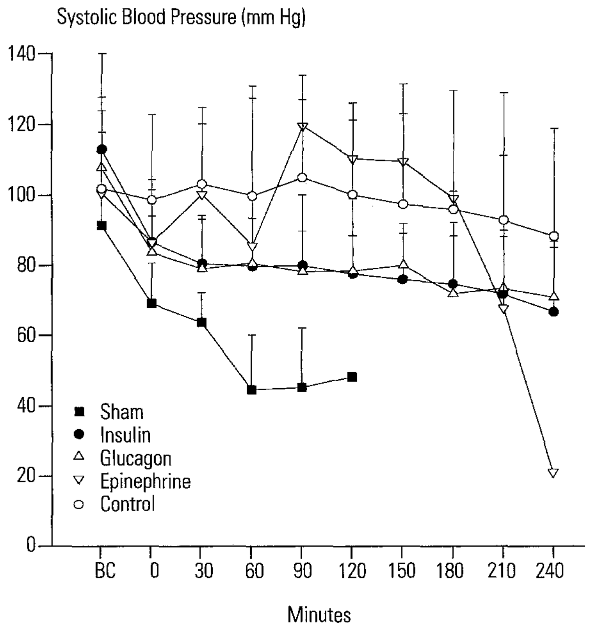
Left ventricular pressure (Figure 4) decreased with exposure to propranolol (P=.011 versus control at 0 minutes) and continued to decline in the sham-treatment group compared with the other treatments. Insulin and glucagon prevented the decline in left ventricular pressure observed with sham treatment (P=.0002 versus sham at 90 minutes). With epinephrine, left ventricular pressure fluctuated over the course of the experiment, with peaks at 30 and 90 minutes. At 30 minutes, left ventricular pressure in the epinephrine group was higher than that in the sham-treatment group

Figure 5.
Heart rate.



Propranolol toxicity did not significantly alter heart rate. During early glucagon treatment, heart rate was markedly increased compared with that in all other groups (P=.0001 at 30 minutes).

Figure 6.
Systolic blood pressure.



By 30 minutes, systolic blood pressure had decreased in the sham-treatment group (P=.011 versus control group). Treatment with insulin or glucagon prevented further decreases in systolic blood pressure. Systolic blood pressure fluctuated during epinephrine treatment.

(*P*=.0057), and at 90 minutes it was higher than that in all experimental groups (*P*=.0002). Thereafter, left ventricular pressure declined to values similar to those of the other remaining experimental groups.

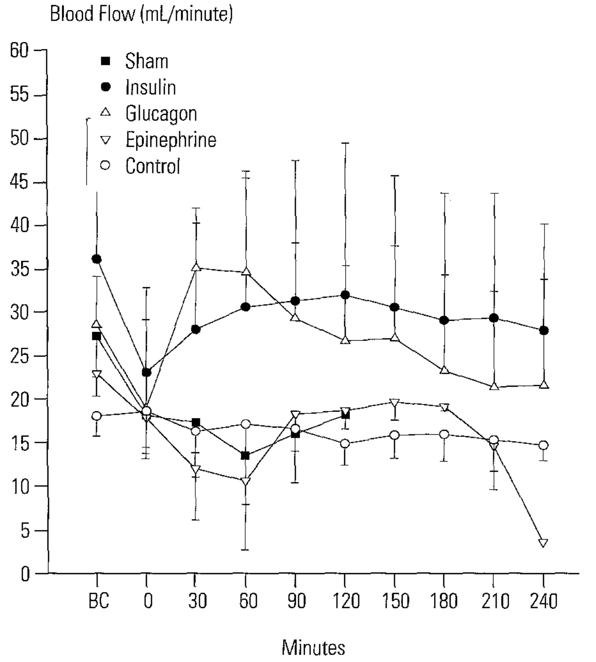
Although the mean heart rate (Figure 5) appeared to decline overall after propranolol infusion and before treatment, these values were not statistically different from those of the controls. Glucagon elicited the greatest chronotropic effect of all treatments. Heart rate increased rapidly (*P*=.0001 versus all other groups by 30 minutes), then steadily decreased to control values. Neither insulin nor epinephrine treatment altered heart rate.

Systolic blood pressure (Figure 6) progressively decreased after exposure to propranolol (*P*=.011 sham versus control by 30 minutes). Insulin and glucagon prevented the decrease in systolic blood pressure seen with sham treatment. With epinephrine, systolic blood pressure had transiently improved, compared with sham treatment, by 90 minutes (*P*=.0068) but then declined.

Coronary artery blood flow (Figure 7) for the sham, insulin, and epinephrine treatment groups was similar to that of the control animals. During early treatment, glucagon was associated with increased coronary artery blood flow (*P*=.0012 versus sham, epinephrine, and control groups at 30 minutes). Thereafter blood flow decreased to control values.

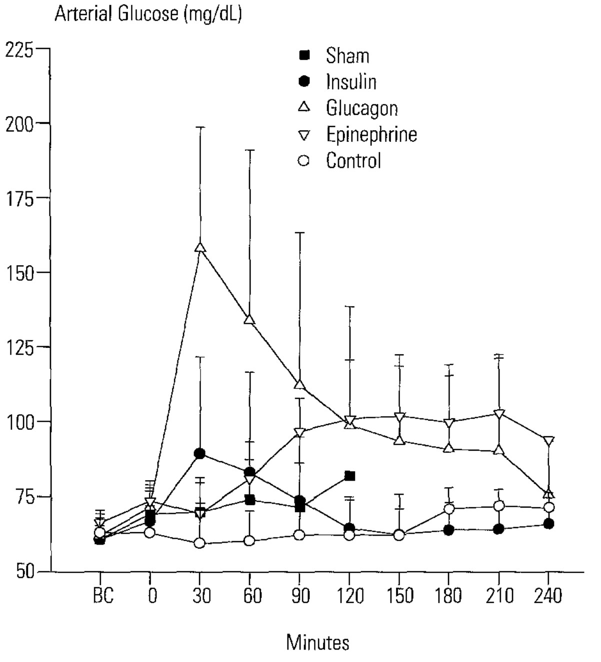
Conduction abnormalities were unusual. In 20 of 24 animals exposed to propranolol, sinus rhythm was maintained during the experiment. In two sham-treated animals, atrioventricular blocks developed: one with third-degree block and one with first-degree block. In two animals given glucagon, dysrhythmia or conduction abnormality developed. In one animal, ventricular tachycardia developed immediately after administration of the glucagon bolus, and this dog died. In the other dog, which also died, third-degree atrioventricular block developed at 180 minutes. No animal in the insulin or epinephrine treatment group demonstrated conduction abnormality or dysrhythmia. The QRS-interval duration during toxicity (0 minutes) for each group was (mean±SD): control, 70±10 milliseconds; sham, 68±16 milliseconds; insulin, 65±11 milliseconds; glucagon, 67±8 milliseconds; and epinephrine, 73±15 milliseconds.

Figure 7.
Coronary artery blood flow.



Experimental treatment with glucagon transiently increased coronary artery blood flow compared with that in the sham, control, and epinephrine groups early in the experiment (*P*=.0012 at 30 minutes). Coronary artery blood flow in the sham, insulin, and epinephrine groups was not different than that for the control group.

Figure 8.
Arterial glucose concentration.



After glucagon treatment, arterial glucose concentration increased from baseline and peaked at 30 minutes (*P*=.0001 versus all other groups). Thereafter, glucose concentration returned to control values. The sham, insulin, and epinephrine groups did not differ from the control group during the study.

We detected no differences among groups with regard to QRS-interval duration.

In the sham-treatment group, propranolol did not alter basal concentrations of arterial calcium (1.22±.11 mEq/L), arterial glucose (60.7±6.1 mg/dL), or arterial lactate (.80±.36 mEq/L) or myocardial glucose uptake (1.31±.62 mg/minute). The arterial potassium concentration had increased from the baseline reading of 3.30±.39 mEq/L to 4.15 mEq/L at 120 minutes. This concentration was different from that of all other groups at 120 minutes (*P*=.0001).

Insulin treatment had two metabolic effects. First, arterial potassium concentration had declined from 3.40±.11 mEq/L at baseline to 2.20±.10 mEq/L at 120 minutes. The 120-minute value was lower than those in all other groups (*P*=.0001). Arterial potassium concentration remained depressed throughout the remainder of the experiment. Myocardial glucose uptake had transiently increased from the baseline reading of 1.02±.98 mg/minute to 3.90±1.80 mg/minute at 30 minutes (*P*=.0005 versus epinephrine and sham treatment groups). Arterial glucose concentration (baseline, 60.7±7.1 mg/dL) did not change in comparison with other treatment groups. Insulin-treated animals required an average of 11.8 g/hour glucose (range, 6 to 17.5 g/hour) to maintain arterial glucose at ±10% of the baseline level. The baseline concentrations of arterial calcium (1.16±.10 mEq/L) and lactate (1.03±.44 mEq/L) did not change with insulin treatment.

Glucagon induced transient changes in glucose concentration and glucose uptake. Arterial glucose concentration had increased from the baseline reading of 62±3.3 mg/dL to a peak of 158±40.5 mg/dL at 30 minutes (*P*=.0001 versus all other groups), then decreased to the control value by the end of the experiment (Figure 8). Myocardial glucose uptake also increased during the first 30 minutes of treatment, from 1.52±.88 mg/minute to 3.74±2.05 mg/minute (*P*=.0005 versus epinephrine and sham groups at 30 minutes). Glucagon therapy did not alter baseline arterial concentrations of calcium (1.13±.07 mEq/L), potassium (3.20±.10 mEq/L), or lactate (1.10±.60 mEq/L).

The epinephrine group baseline metabolic measures were similar to those of the other groups, including calcium, 1.22±.03 mEq/L; potassium, 3.31±.11 mEq/L; glucose, 66.3±4.1 mg/dL; glucose uptake, 1.07±.48 mg/minute; and lactate, .87±.38 mEq/L. No changes occurred in this group.

Cardiodynamic, hemodynamic, and electrical parameters remained stable throughout the entire experiment for the control group (Figures 3 to 8). The other experimental groups had similar basal measurements, compared with the control group, with one exception: the mean baseline coronary artery blood flow was higher for the insulin group than for the control group (*P*=.033; Figure 6). Baseline metabolic values for the control group included calcium concentration, 1.16±.27 mEq/L; potassium concentration, 3.33±.39 mEq/L; glucose concentration, 63.0±6.2 mg/dL; glucose uptake, 1.05±.39 mg/minute; and lactate, .87±.38 mEq/L. These values did not change during the experiment.

DISCUSSION

In developing our model of β-blocker toxicity, we sought to reproduce the clinical scenario of overdose as closely as possible. Propranolol, a nonselective β-blocker, was chosen because it is the β-blocker most commonly associated with human poisoning and produces typical myocardial depression.[1,24,25] Propranolol was administered by means of constant intravenous infusion to simulate continued absorption of drug from the gut after ingestion. We began experimental treatment 30 minutes after achieving toxicity to simulate a delay between overdose and hospital presentation.[26] In addition to cardiodynamic and hemodynamic measures, we monitored animals for survival. The authors of previous studies of propranolol poisoning have not evaluated the effect of experimental treatment on survival.[7-10]

In our anesthetized-dog model, propranolol depressed cardiovascular function in a manner consistent with the findings of previous animal studies.[7-10] Myocardial function was severely impaired, as measured on the basis of E_{max} and left ventricular peak systolic pressure. Hemodynamically, systolic blood pressure progressively declined. Untreated, intoxicated animals died by 150 minutes as a result of direct myocardial depression with accompanying decrease in blood pressure.

It is unlikely that factors other than the myocardial depressant effect of propranolol contributed to toxicity. At supratherapeutic blood concentrations, propranolol may antagonize fast sodium channels in a manner similar to that of quinidine, a class I antiarrhythmic.[27,28] The hallmark of sodium-channel blockade is widened QRS interval with resulting ventricular dysrhythmia. In this study, animals lacked uniform characteristic myocardial sodium-channel antagonism. Overall, QRS-interval duration did not differ between animals exposed to propranolol and the control animals. In only one animal did a ventricular dysrhythmia develop during the experiment. This occurred in temporal relationship to the glucagon bolus given during treatment and was more likely a direct effect of glucagon. Thus sodium-channel antagonism did not play a significant role in toxicity.

One might postulate that coronary vasoconstriction with resulting myocardial ischemia contributed to the cardiovascular depression we observed. Ischemia may occur as a result of unopposed α-adrenergic effect on vascular smooth muscle following β_2-blockade. However, hemodynamic conditions were not consistent with ischemia. Coronary artery blood flow was maintained during toxicity, whereas the product of heart rate×mean arterial blood pressure, an index of work, decreased. It is unlikely that demand for substrates exceeded supply, thereby providing indirect evidence that ischemia did not occur.

With regard to treatment of propranolol poisoning in our dog model, insulin provided superior survival benefit compared with standard and sham treatments. All insulin-treated animals survived to the end of the experiment, compared with four treated with glucagon and one treated with epinephrine. The difference in survival was significant as measured with the log-rank test. Characteristics of surviving animals included sustained improvement in myocardial function as demonstrated by an increase in E_{max} and maintenance of left ventricular peak pressure. Systolic blood pressure was maintained as well. With regard to metabolism, insulin decreased serum potassium and increased myocardial glucose uptake. It had no effect on heart rate or electrical conduction in the animals with propranolol-induced toxicity.

Potential explanations for the efficacy of insulin in β-blocker toxicity include enhanced catecholamine release, increased myocardial substrate use, and altered calcium homeostasis.

Early observations of the cardiovascular effects of insulin revealed an adrenaline-like action, which was attributed to stimulation of catecholamine release.[29] However, later work involving canine papillary muscle and catecholamine-free buffer demonstrated that the action of insulin is not likely related to catecholamines.[14] Also, if insulin works by means of catecholamine release, one would anticipate increased contractility and heart rate. We observed an increase in contractility but not an increase in heart rate during insulin treatment. This finding is not consistent with catecholamine release.

Insulin may enhance myocardial substrate use. In this study, myocardial glucose uptake was increased during insulin treatment. Increased carbohydrate uptake may be extremely important during β-blocker toxicity. In the normal myocardium, free fatty acid is the preferred energy substrate; carbohydrate contributes to a lesser extent.[30] The authors of a previous investigation involving a dog model demonstrated that propranolol alters myocardial substrate preference such that free fatty acid uptake decreases and carbohydrate uptake increases.[31] Thus exogenous insulin may support myocardial performance during β-blocker toxicity by augmenting carbohydrate use.

Last, insulin may act by altering calcium homeostasis. Insulin increases cytosolic calcium in adipose cells by enhancing calcium entry through voltage-dependent channels, as well as inhibition of calcium extrusion.[32,33] Increased cytosolic calcium enhances excitation-contraction coupling, resulting in improved contractility. However, it has not been confirmed that insulin effects similar changes in the myocardial cell, and further study is warranted.

Glucagon is the first-line treatment for human β-blocker poisoning. This practice has its origin in reports of successful treatment of congestive heart failure with glucagon.[34] Glucagon exerts positive inotropic and chronotropic effects by stimulating cyclic adenosine monophosphate through receptors thought to be distinctly different from the β_1-adrenergic receptor.[35] In our study, maximum beneficial effects were transient, occurring during the first hour of treatment, despite continuous infusion of high doses of glucagon. These data are consistent with a known brief duration of action of glucagon and the findings of previous canine studies that the maximal effects on heart rate and cardiac output occurred within 10 minutes of the administration of a single glucagon bolus.[7-9,36]

The glucagon-treated group was the only one in which a dog sustained an adverse reaction to treatment. Fatal ventricular tachycardia developed in one animal immediately after administration of the glucagon bolus. The authors of a previous study of propranolol in dogs also reported ventricular tachycardia following glucagon administration.[8]

Catecholamines exert positive inotropic and chronotropic effects on the myocardium by stimulating adrenergic receptors and increasing cyclic AMP.[37] It is reasonable to expect that, if given in sufficiently high doses, catecholamines will overcome β-receptor blockade, thereby restoring cyclic AMP levels and contractile function. In this study, epinephrine was an unsatisfactory treatment with regard to survival. Despite unlimited doses of epinephrine, with apparent improvement in contractility and blood pressure, refractory toxicity developed and animals died.

Certain limitations to interpretation of our data and extrapolation to human poisoning must be considered. First, animals were anesthetized, potentially creating a two-toxin model. To minimize anesthetic drug effect, we selected α-chloralose to maintain anesthesia because it lacks cardiovascular effects.[38] However, the interaction of α-chloralose and propranolol has not been studied extensively. In one canine study, α-chloralose did not interfere with the negative chronotropic effect of propranolol, but the investigators did not evaluate its effect on contractility.[39] Second, β-blocker toxicity in human beings most often involves both chronotropic and inotropic effects,[1,40] whereas inotropic toxicity mainly developed in our model. Because insulin treatment resulted in inotropic benefits only, insulin may not be effective in human beings. Finally, we used high-dose insulin, on the basis of findings of previous dog studies of endotoxic shock[16] and verapamil-induced cardiogenic shock.[17] No human experience exists for equivalent doses (12 U/ minute, or 720 U/hour, for a 70-kg adult).

Insulin administration improved survival in a canine model of severe β-blocker toxicity, compared with glucagon or epinephrine treatment. Surviving animals were characterized by improved contractility, stable hemodynamic parameters, increased myocardial glucose uptake, and decreased extracellular potassium concentration. Insulin is a widely available, safe, and inexpensive drug that may be of benefit in the treatment of human β-blocker–induced myocardial depression. Clinical study is warranted to evaluate the efficacy and safety of this drug in human beings. Additional studies are needed to delineate the mechanism of insulin's beneficial effect.

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Reprint no. **47/1/81696**
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