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Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine

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Abstract

Objective: Myocardial depression from verapamil toxicity may result from alterations in carbohydrate metabolism as well as calcium-channel antagonism. We hypothesized that pharmacologic doses of insulin may be effective in reversing both of these deficits.

Design: Randomized, controlled, prospective study.

Setting: Laboratory of an urban hospital.

Subjects: Thirty mongrel dogs.

Interventions: Thirty mongrel canines were anesthetized with alpha-chloralose. Toxicity was induced by the administration of 0.1 mg/kg/min iv of verapamil, until there was a 50% reduction in mean arterial pressure, for 30 mins (titration), followed by a continuous verapamil infusion of 1 mg/kg/hr. Animals (n = 6 per group) were randomized to the control group (saline only) or to one of four treatment protocols: a) calcium chloride (20 mg/kg), then 0.6 mg/kg/hr; b) hyperinsulinemia-euglycemia (4.0 U/min of recombinant insulin, with arterial glucose concentration clamped to +/-10 mg/dL [+/-0.5 mmol/L] of the basal value); c) epinephrine, with a starting rate of 1.0 micro gram/kg/min, titrated to maintain left ventricular pressure at basal values; or d) glucagon, a 0.2-mg/kg bolus, followed by a 150-micro gram/kg/hr infusion. Animals were monitored until death or 240 mins; infusate volumes were held constant for all groups.

Measurements and Main Results: During verapamil titration, the myocardial respiratory quotient increased from 0.84 +/- 0.05 to 1.07 +/- 0.11 ($p < .05$, paired t-test) and myocardial glucose uptake doubled, despite a reduction in cardiac work ($p < .05$, paired t-test). Net myocardial lactate uptake also increased significantly, excluding myocardial ischemia. In controls, this trend continued, indicating preferential carbohydrate metabolism during untreated verapamil toxicity. Despite hyperglycemia, the plasma insulin concentration was not significantly different in controls (basal value 11 +/- 2 vs. 39 +/- 21 mu U/mL at 30 mins). Hyperinsulinemia-euglycemia increased both myocardial glucose and lactate uptake five-fold, and significantly increased the ratio of myocardial oxygen delivery/work, along with superior improvements in maximal left ventricular elastance at end systole compared with other treatments ($p < .05$ vs. other treatments, contrast analysis).

Conclusions: Verapamil toxicity renders the heart dependent on carbohydrate metabolism. Inasmuch as the positive inotropic effects of all treatments were coincident with increased indices of myocardial carbohydrate uptake, adequate treatment of verapamil toxicity appeared to require maximal myocardial carbohydrate utilization. Hyperinsulinemia-euglycemia allows larger increases in myocardial carbohydrate

metabolism and myocardial contractility than calcium chloride, epinephrine, or glucagon, resulting in improved survival rates during severe verapamil toxicity.

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KEY WORDS: calcium-channel blocker; insulin; glucagon; myocardial metabolism; verapamil; epinephrine; calcium chloride; drug toxicity; critical illness; glucose; lactate

We [1] previously reported beneficial survival, hemodynamic, and cardiodynamic effects of insulin during severe verapamil toxicity in anesthetized canines. Verapamil toxicity appears to alter myocardial metabolism and pancreatic function such that insulin becomes important in reversing verapamil toxicity. Verapamil decreases myocardial uptake of free fatty acids in canines [2,3], and in the nonischemic human heart [4], rendering the heart relatively dependent on glucose uptake for energy. In intact canines and in man, verapamil inhibits insulin release from pancreatic islet cells, producing hyperglycemia in overdose [5-11]. Thus, the interaction of verapamil's calcium-channel antagonism, decreased free fatty acid uptake, together with decreased insulin secretion, may lead to cardiac failure that requires exogenous insulin for recovery of myocardial function. Several human cases of verapamil toxicity have required insulin infusion to treat hyperglycemia [10,12]. Insulin also increases cardiac contractility during drug and ischemic-induced cardiac failure [13-15]. Although the mechanism of this positive inotropic effect is unclear, indirect evidence suggests that increased calcium entry may be responsible [16]. In the absence of calcium-channel antagonism, this inotropic effect occurs independently of increases in myocardial glucose uptake [15,17-19]. However, during verapamil toxicity, myocardial glucose uptake may be a key determinant of myocardial contractility.

In this study, insulin's metabolic effects and its efficacy as an antidote for verapamil toxicity were compared with three other positive inotropic agents commonly recommended to treat verapamil poisoning: epinephrine; calcium chloride; and glucagon [20]. Glucagon has gained recent attention as an effective agent in reversing the hemodynamic effects of verapamil intoxication in animals [21-23] and in humans [24-26]. It is intriguing that two hormones, conventionally considered to be counter-regulatory in most tissues, could both stimulate cardiac function during calcium-channel antagonism. The rationale for the use of glucagon in treating verapamil toxicity is largely based on animal studies that have not evaluated glucagon's myocardial metabolic effects, or compared glucagon's survival benefits with other positive inotropic agents. The purpose of this study was to determine the myocardial metabolic effects of verapamil toxicity alone, and to compare the myocardial metabolic and mechanical effects of insulin with other positive inotropic agents during a treatment phase. We were specifically interested in elucidating the metabolic effects of insulin and their temporal relationship to changes in myocardial performance.

MATERIALS AND METHODS

All methods were approved by our institution's Animal Care and Use Committee in accordance with Guide for the Care and Use of Laboratory Animals (National Institutes for Health publication No 85-23, revised 1985).

Surgical Procedure.

Thirty fasted mongrel dogs of either sex, weighing between 19.8 and 27.5 kg, were anesthetized with sodium thiamylal (15 mg/kg iv) followed by alpha-chloralose (30 mg/hr/kg). Animals were intubated and mechanically ventilated using a respirator (Harvard Apparatus, South Natick, MA) with 5 to 7 cm H_2O of positive end-expiratory pressure. Catheters were placed in a femoral artery for measuring mean arterial pressure and for collecting blood samples for chemical analyses. Femoral veins were cannulated and used for infusion of alpha-chloralose and experimental drugs. Via a left subcostal incision, a 2.4-mm pulse Doppler-ultrasound flow probe (Triton Technology, San Diego, CA) was positioned around the left renal artery near the aorta to measure renal blood flow. The subcostal incision was closed with towel clamps.

A left thoracotomy was made in the fifth intercostal space and the pericardium was incised longitudinally to expose the heart. Cardiac output was measured with an electromagnetic blood flow probe (In Vivo Metric, Healdsburg, CA), positioned around the ascending aorta. To collect cardiac venous effluent for metabolic and blood gas measurements, a Silastic catheter was inserted, via the right atrial appendage, into the coronary sinus. Instantaneous left ventricular pressure and heart rate (HR) were measured with a micromanometer transducer (Konigsberg Inst Corporation, Pasadena, CA) inserted via an apical stab incision, and secured with a purse-string suture. Left ventricular pressure was differentiated with a differentiator amplifier (Gould, Cleveland, OH) and used to measure change in pressure over time. A Doppler flow probe (Triton Technology) was positioned around the left circum-flex coronary artery and used to measure circum-flex artery blood flow.

The left ventricular anterior-posterior internal minor axis diameter was measured using the ultrasonic transit time method [27,28]. Piezoelectric crystals (20 MHz, Triton Technology) were placed through stab incisions in the left ventricular anterior and posterior walls. Internal left ventricular dimensions were measured using a Triton Technology sonomicrometer.

Hemodynamic Measurements.

All cardio--and hemodynamic measurements were recorded on a direct writing polygraph recorder (Astro-med Registered Trademark, which was equipped with amplifiers (Gould). Data were acquired on-line through a digitizing data acquisition system (2.0, Po-Ne-Mah Registered Trademark, Storrs, CT). The slope of the end-systolic left ventricular pressure-dimension relationship was used as our index of contractility, as previously described [27,28]. The respirator was shut off at end-expiration, and the aorta was incrementally occluded to generate seven to ten cardiac cycles for post hoc computer analysis (2.0, Po-Ne-Mah) of each loop for the point of maximum pressure/dimension ratio.

Chemical and Metabolic Measurements.

During each measurement period (outlined in ``Experimental Protocol''), 2.0 mL of arterial and 2.0 mL of coronary sinus blood were collected and analyzed for the following characteristics: a) glucose and lactate concentrations (2300 Stat Analyzer, Yellow Springs Instrument Laboratory, Yellow Springs, OH); and b) pH, PCO sub 2, PO_2, total oxygen concentration, total CO_2 (mM), and hemoglobin content by a blood gas analyzer (Acid Base Laboratory 2000, Radiometer, Copenhagen, Denmark). Arterial electrolyte concentrations (sodium, potassium, and ionized calcium) were determined with an analyzer (NOVA 6, Nova Biomedical, Waltham, MA). Myocardial oxygen, glucose, and lactate uptakes were determined as the product of the circumflex artery flow and the appropriate arterial-coronary sinus concentration difference. In separate experiments, myocardial blood flow in the region of the circumflex artery was shown to be directly proportional to total myocardial blood flow (data not shown).

Calculation of Respiratory Quotient.

For the purposes of this study, the myocardial respiratory quotient is defined as the molar ratio of CO_2 produced/oxygen consumed by the heart. Myocardial oxygen consumption (VO_2) and CO_2 production were assumed to occur under equal temperature and pressure in all hearts, and total myocardial blood flow was assumed to be proportional to circumflex artery blood flow. Blood oxygen concentration (mL of oxygen/L of blood) was converted to millimolar by dividing by 22.4 mL/mM. Oxygen uptake was calculated as the product of the arterio-coronary sinus difference and circumflex artery flow. CO_2 production, in millimolar, was calculated as the product of coronary sinusarterial difference and circumflex artery flow.

Verapamil and Insulin Measurements.

During each measurement period, 10.0 mL of heparinized arterial blood was centrifuged and analyzed for verapamil concentrations [29]. Alkalinized plasma was mixed with heptane to extract verapamil. After centrifugation and collection of the aqueous phase, verapamil concentration determinations were made by excitation fluorometry. Insulin concentrations were determined using ^{125} I radioimmunoassay (International Chemical Nuclear, Costa Mesa, CA).

Experimental Protocol.

After surgical instrumentation, all animals received approximate 20 mL/kg of 0.9% sodium chloride as a bolus over 10 to 15 mins. This bolus was followed by approximately a 60-min stabilization period, with 1 mL/min of 0.9% sodium chloride infusion. Two basal control measurements were then performed within 20 mins to generate average basal control data for cardio-and hemodynamic, electrolyte, blood gas, glucose and lactate measurements. After the second basal measurement, (+/-) verapamil hydrochloride (1.0 mg/mL in 0.9% sodium chloride; Sigma Chemical, St. Louis, MO) was infused (0.1 mg/min/kg) via a femoral venous catheter until at least one of two hemodynamic set-points were achieved: a) a 50% reduction in average basal mean arterial pressure; or b) complete atrioven-tricular dissociation. Once one of these parameters was achieved, the verapamil infusion was switched to a titration phase to maintain the product of the mean arterial pressure and the HR (rate pressure product) constant for 30 mins before treatment. At 30 mins during verapamil titration, data were collected. After this 30-min titration period, the verapamil infusion was changed to a constant infusion of 1 mg/kg/hr for the duration of the experiment. The animals were then randomly assigned to one of four experimental treatment groups.

In the control group (n = 6), 0.9% of sodium chloride was administered at 2.0 mL/min. In the epinephrine experimental treatment group (n = 6; Abbott Laboratories, Chicago, IL), epinephrine was begun at 1.0 micro gram/kg/min iv and was titrated to maintain left ventricular pressure at basal levels. The concentration of epinephrine was adjusted for each animal's weight, such that 1.0 micro gram/kg/min of drug required a 2.0 mL/min infusion rate. In the glucagon experimental treatment group (n = 6; Eli Lilly, Indianapolis, IN), a loading dose of glucagon (0.2 to 0.25 mg/kg iv) was injected, followed by a maintenance infusion of 150 micro gram/kg/hr in 0.9% of sodium chloride; the concentration was adjusted to maintain a 2.0 mL/min infusion rate. In the hyperinsulinemia-euglycemia experimental treatment group (n = 6), calcium-free recombinant insulin (NOVOLIN, Bagsvaerd, Denmark) was infused at 4.0 U/min. Via a separate catheter, 20% dextrose was simultaneously infused at 0.7 to 1.0 mL/min to maintain the arterial glucose concentration within +/-10 mg/dL (+/-0.5 mmol/L) of the basal concentration. Potassium chloride (0.2 mEq/mL) was infused at approximate 10 to 20 mL/hr to maintain serum potassium within 1.0 mEq/L of the average basal concentration. Arterial glucose and [potassium] were analyzed every 10 mins during the first hour of treatment. To maintain a total infusion rate at 2.0 mL/min, 0.9% sodium chloride was simultaneously infused. In the calcium chloride experimental treatment group (n = 6), 10% aqueous calcium chloride (Venue Laboratories, Bedford, OH) was infused as a bolus dose of 20 mg/kg, followed by a continuous infusion of 0.6 mg/kg/min of calcium chloride in 0.9% sodium chloride. The concentration was adjusted to maintain an infusion rate of 2.0 mL/min.

All animals were monitored until either death or 4 hrs of treatment. During treatment, measurements were taken at 15, 30, 60, 120, 180, and 240 mins. All animals that survived to 240 mins of treatment received a rapid, 3.0-mg/kg iv verapamil bolus, followed by hemodynamic and cardiodynamic measurements 15 mins later (after bolus), if the animal survived the bolus. The purpose of this additional bolus was to further evaluate the antidotal potential of each treatment. Any animal surviving to this point was killed with saturated potassium chloride injection.

Statistical Analysis.

All hemodynamic data were initially recorded by the data acquisition system (Po-Ne-Mah) and subsequently were transferred to a computer (Quadra 950, Macintosh, Cupertino, CA) for statistical analysis, using a statistical program (version 1.2, SuperAnova). All data were tested for homogeneity of variance using Bartlett's test. Nonhomogeneous data were transformed by appropriate techniques. Basal and verapamil titration data were tested for differences among the four groups, using one-way analysis of variance. Overall significance between treatments (control, hyperinsulinemia-euglycemia, and glucagon) for continuous data (e.g., maximal left ventricular elastance at end systole) was determined using a multivariate analysis of variance, with time as a repeated measure. Significance in changes in continuous data over time during treatment within a single treatment group was determined using the repeated-measures time statement. Significant differences at specific times during treatment--even if overall differences between treatments for a variable were not significant--were determined using contrast analysis. A p <or=to .05 was considered significant for all tests. The type III sums of squares was used in the general linear model to calculate F values, which allows for reduction in the number of animals over the experiment. Data are presented as mean +/- SEM. Differences in survival rates were compared using the log-rank statistic, with p <or=to .05 considered significant.

RESULTS

Baseline and Titration.

(Table 1 and Table 2) No data were statistically different during basal control between groups. Likewise, no data were different between groups during verapamil titration (titration at 30 mins). All hemodynamic data were significantly different at titration at 30 mins compared with basal control, except for circumflex artery blood flow (which increased initially). Changes in pH, PCO_2, PO_2, and electrolytes were not significant at titration at 30 mins compared with basal control. Arterial and coronary sinus lactate and glucose concentrations increased significantly for all groups. Myocardial oxygen uptake decreased significantly during titration and myocardial glucose uptake increased significantly. The respiratory quotient increased significantly from basal control to titration at 30 mins for all groups Table 3. The amount of verapamil required and the plasma concentrations achieved during titration were not significantly different between groups (1.44 +/- 0.2 mg/kg and 634 +/- 30 ng/mL, respectively). All animals eventually demonstrated complete atrioventricular dissociation (in most cases with bradycardic junctional rhythms in absence of any sinus electrical activity) before starting any treatment protocol. No animals died during the titration period in this study.

Time	E_{max} (mm Hg/mm)	LVP (mm Hg)	+dP/dt (mm Hg/sec)	CABF (mL/min)
BC	26 ± 2	109 ± 3	1390 ± 56	41 ± 3
$TITR_{30}$	11 ± 1	65 ± 2[a]	731 ± 65[a]	49 ± 4[a]

E_{max}, maximal left ventricular elastance at end systole; LVP, peak positive left ventricular pressure; +dP/dt, peak positive first derivative of LVP; CABF, circumflex artery blood flow.
[a] $p < .05$ vs. BC.

Table 1. Hemodynamic and cardiodynamic data at basal control (BC) and 30-min verapamil toxicity ($TITR_{30}$) for all animals (mean +/- SEM)

	Basal Control			30-Min Verapamil Toxicity		
	Arterial	Coronary Sinus	Myocardial Uptake[a]	Arterial	Coronary Sinus	Myocardial Uptake[a]
Glucose (mg/dL)	72 ± 3	65 ± 2	1.15 ± 0.30 mg/min	86 ± 7	80 ± 5	2.1 ± 0.58 mg/min
Lactate (mmol/L)	0.94 ± 0.04	0.52 ± 0.03	20 ± 3 mmol/min	1.66 ± 0.12[c]	1.21 ± 0.10[c]	81 ± 7 mmol/min
t_cO_2%	16.2 ± 0.5	5.5 ± 0.3	4.5 ± 0.3 mL O_2/min	17.8 ± 0.5	10.3 ± 0.6[c]	6.2 ± 0.3 mL O_2/min

t_cO_2%, total oxygen concentration (mL O_2/dL blood).
[a]Calculated as arteriocoronary sinus difference times circumflex artery flow; [b]to convert glucose from mg/dL to mmol/L, multiply the value by 0.05551; [c]$p < .05$ vs. basal control.

Table 2. Metabolic data at basal control and 30-min verapamil toxicity for all animals (mean +/- SEM)

	Time					
Group	BC	$TITR_{30}$	30 Mins	60 Mins	120 Mins	240 Mins
Calcium	0.85 ± 0.07	1.24 ± 0.17[a]	0.78 ± 0.13	0.57 ± 0.12	0.80 ± 0.05	0.69 ± 0.16
Control	0.77 ± 0.10	1.07 ± 0.07[a]	1.06 ± 0.05	1.00 ± 0.18	—	—
Epinephrine	0.79 ± 0.06	0.99 ± 0.07[a]	0.75 ± 0.06	0.80 ± 0.14	0.85 ± 0.17	0.89 ± 0.1
Glucagon	0.87 ± 0.04	1.10 ± 0.12[a]	0.94 ± 0.12	0.84 ± 0.07	0.80 ± 0.12	0.79 ± 0.11
Insulin[b]	0.87 ± 0.08	1.10 ± 0.09[a]	1.00 ± 0.04	0.96 ± 0.09	1.08 ± 0.10	0.97 ± 0.04

BC, basal control; $TITR_{30}$, 30-min verapamil toxicity.
[a]$p < .05$ vs. BC; [b]$p < .05$ vs. all other treatments (repeated measures).

Table 3. Myocardial respiratory quotient during treatment (mean +/- SEM)

Metabolic Effects: Arterial Glucose and Lactate Concentrations.

(Figure 1) Control animals demonstrated significant increases in both glucose and lactate concentrations compared with basal measurements. Glucagon induced a biphasic glucose response: initial hyperglycemia, followed by hypoglycemia ($p < .05$, repeated-measures time statement). Coincident with hypoglycemia, glucagon treatment demonstrated decreasing lactate concentrations. Lactate concentration, with hyperinsulinemia-euglycemia treatment, was increased compared with basal control. Epinephrine increased both glucose and lactate concentrations significantly compared with all other treatments. Both glucose and lactate concentrations remained unchanged from basal control throughout treatment with calcium chloride.

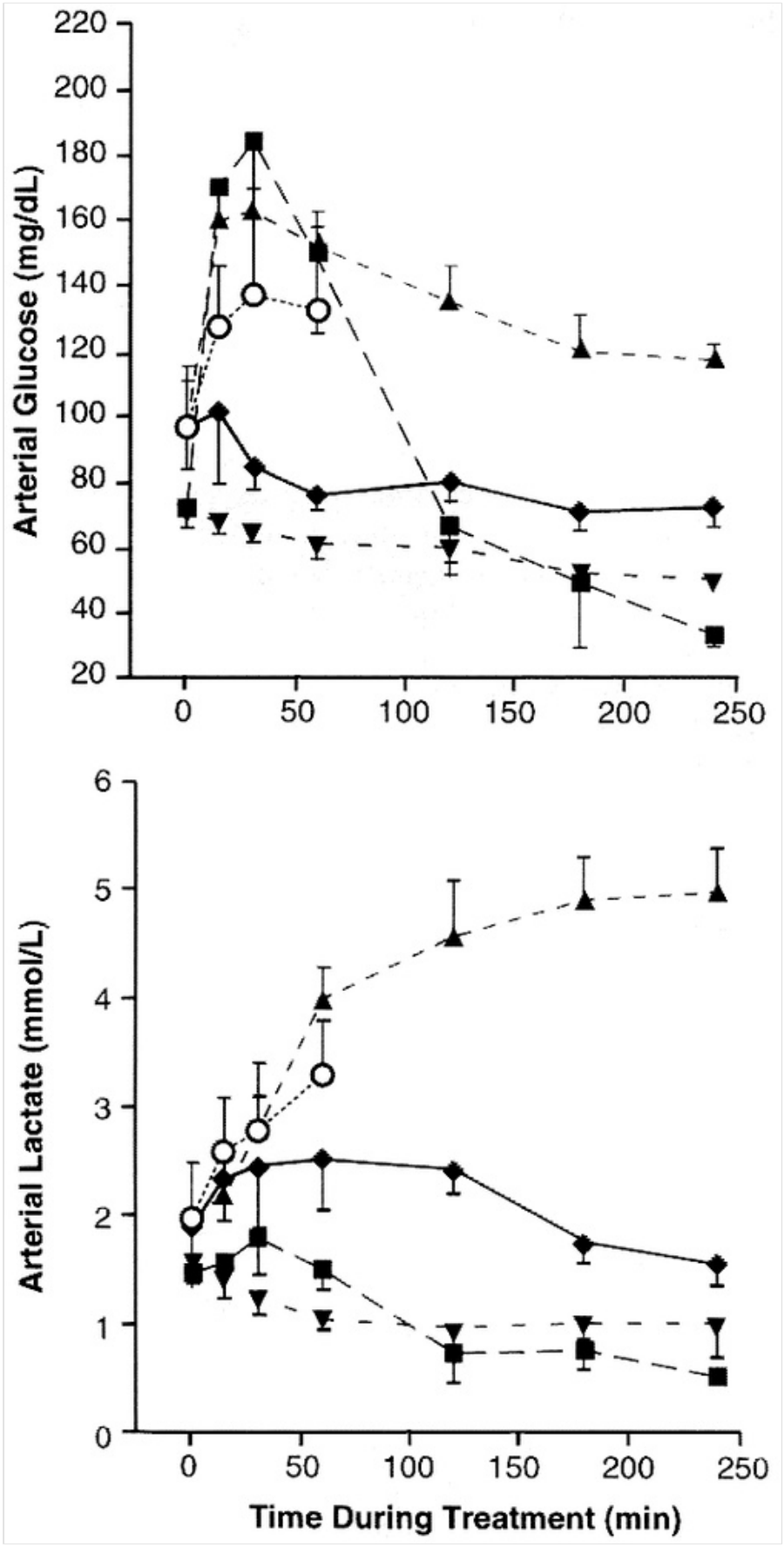

Figure 1. Arterial glucose (top) and lactate (bottom) concentrations during treatment. Epinephrine increased the lactate concentration significantly ($p < .05$, repeated measures) vs. all other treatments. Glucagon initially increased glucose concentration, followed by relative hypoglycemia late in treatment ($p < .05$, repeated measures time statement). For insulin, glucose was experimentally clamped. Open circles, control; inverted triangles, calcium chloride; triangles; epinephrine; squares, glucagon; diamonds, hyperinsulinemia-euglycemia. Mean +/- SEM values.

Metabolic Effects: Myocardial Glucose and Lactate Uptake.

(Figure 2) Hyperinsulinemia-euglycemia increased myocardial uptake of glucose and lactate compared with control and all treatments. Glucagon initially increased glucose and lactate uptake (vs. control), followed by a decrease late in the treatment protocol that was coincident with reduced arterial glucose. With epinephrine, myocardial glucose uptake did not appear to increase significantly, but myocardial lactate uptake increased steadily over time ($p < .05$, repeated-measures time statement). Calcium produced no significant change in either myocardial glucose uptake or myocardial lactate uptake vs. basal control.

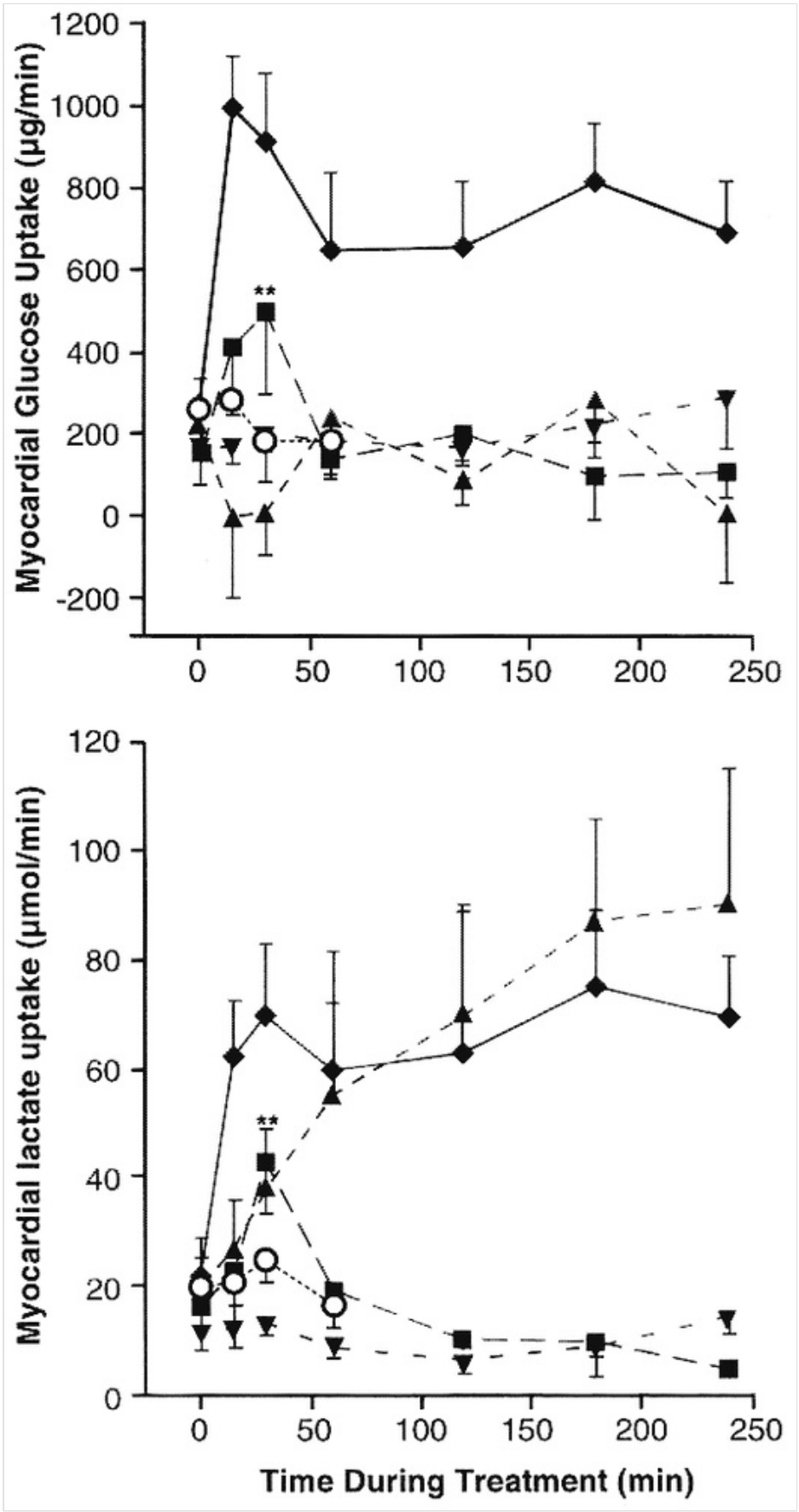

Figure 2. Myocardial glucose (top) and lactate (bottom) uptake. Insulin significantly increased myocardial glucose and lactate uptake ($p < .05$, repeated measures). At 30 mins, glucagon increased both myocardial glucose and lactate uptake (**$p < .05$ vs. control, contrast analysis), but this increase was not sustained. With epinephrine, myocardial lactate uptake paralleled [lactate]. Open circles, control; inverted triangles, calcium chloride; triangles, epinephrine; squares, glucagon; diamonds, hyper-insulinemia-euglycemia. Mean +/- SEM values.

Metabolic Effects: Myocardial Respiratory Quotient.

(Table 3) Verapamil titration produced a significant increase in myocardial respiratory quotient (mean values from all groups 0.84 +/- 0.05 to 1.07 +/- 0.11). This increase was sustained in controls and in hyperinsulinemia-euglycemia-treated animals. Myocardial respiratory quotients were significantly lower in epinephrine--and calcium chloride-treated animals compared with hyperinsulinemia-euglycemia-treated animals and controls. Myocardial respiratory quotients in glucagon-treated animals were not significantly lower than myocardial respiratory quotients in hyperinsulinemia-euglycemia-treated animals or controls. However, changes in myocardial respiratory quotients in glucagon-treated animals appeared to parallel changes in myocardial glucose uptake (initially increased, then decreasing later as myocardial glucose uptake diminished [$p < .05$, repeated-measures time statement]). With epinephrine treatment, myocardial respiratory quotients initially returned to near-normal values. However, late in treatment, as myocardial lactate uptake increased, so did the myocardial respiratory quotient.

Metabolic Effects: Ratio of Myocardial Oxygen Delivery to Cardiac Work.

(Figure 3) Hyperinsulinemia-euglycemia produced a significantly greater increase in ratio of oxygen delivery/cardiac work compared with all other treatments. Glucagon initially increased the ratio vs. control, followed by a sharp decrease later in treatment. Neither epinephrine nor calcium chloride significantly improved this ratio compared with basal control at any time.

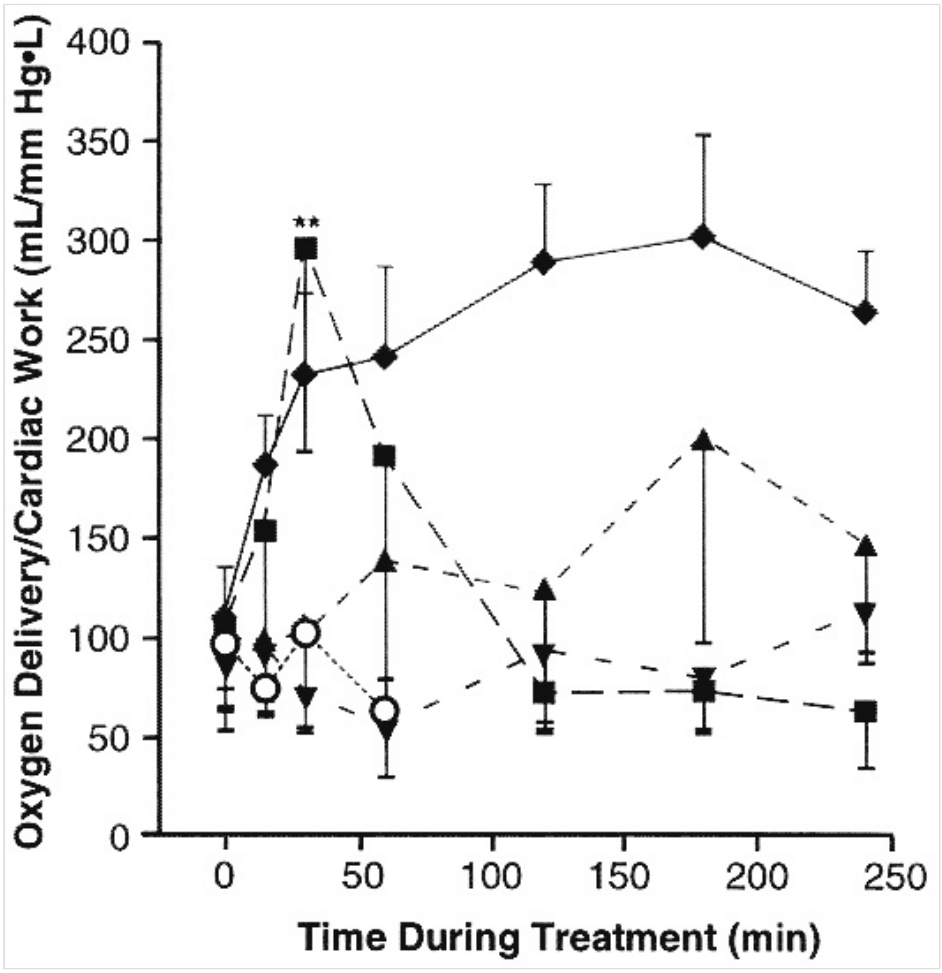

Figure 3. Ratio of myocardial oxygen delivery/cardiac work (calculated as the product of cardiac output and mean arterial pressure). Insulin increased this ratio vs. all other treatments ($p < .05$, repeated measures). At 30 mins, glucagon increased this ratio compared with control (**$p < .05$, contrast analysis). Open squares, control; inverted triangles, calcium chloride; triangles, epinephrine; squares, glucagon; diamonds, hyperinsulinemia-euglycemia. Mean +/- SEM values.

Hemodynamics and Cardiodynamics.

(Table 4) Control animals (saline infusion with 1 mg/kg/hr of verapamil) underwent progressive reductions in maximal left ventricular elastance at end systole, left ventricular pressure, change in pressure over time, and circumflex artery blood flow until death. Hyperinsulinemia-euglycemia significantly improved maximal left ventricular elastance at end systole and circumflex artery blood flow. Left ventricular pressure and change in pressure over time were not different between hyperinsulinemia-euglycemia and epinephrine groups. In all epinephrine-treated animals, to maintain left ventricular pressure at basal control level, the initial epinephrine infusion rate (1.0 micro gram/kg/min) required continual increases (the mean epinephrine infusion rate in four survivors was 1.47 +/- 0.176 micro gram/kg/min at treatment time of 240 mins), followed by a greater increase after the 3.0-mg/kg verapamil bolus. Neither epinephrine nor hyperinsulinemia-euglycemia restored sinus rhythm in any animal. However, epinephrine produced more frequent episodes of ventricular and junctional tachycardia than hyperinsulinemia-euglycemia treatment ($p < .05$, analysis of variance for total duration of ventricular tachycardia between groups).

Group	Time (min)	E_{max} (mm Hg/mm)	LVP (mm Hg)	+dP/dt (mm Hg/sec)	CABF (mL/min)
Calcium	30	16 ± 3	85 ± 8	875 ± 156	42 ± 5
	60	13 ± 2	81 ± 7	795 ± 112	30 ± 6
	120	15 ± 3	95 ± 6	878 ± 143	31 ± 8
	240	16 ± 3	91 ± 6	788 ± 153	32 ± 5
Control	30	10 ± 6	65 ± 8	475 ± 156	42 ± 5
	60	4 ± 3[a]	51 ± 5	216 ± 155	30 ± 6
	120	—	—	—	—
	240	—	—	—	—
Epinephrine	30	24 ± 4	132 ± 11	1830 ± 272	82 ± 8
	60	22 ± 7	125 ± 14	1535 ± 149	83 ± 9
	120	25 ± 3	124 ± 12	1625 ± 102	69 ± 7
	240	18 ± 1	112 ± 6	1403 ± 211	71 ± 6
Insulin[b]	30	38 ± 4	101 ± 9	1530 ± 272	87 ± 4
	60	36 ± 3	109 ± 7	1535 ± 149	88 ± 10
	120	34 ± 6	106 ± 7	1437 ± 144	95 ± 6
	240	35 ± 5	103 ± 9	1407 ± 127	92 ± 7
Glucagon	30	20 ± 3	75 ± 16	1208 ± 144	74 ± 14
	60	15 ± 5	79 ± 15	850 ± 136	76 ± 14
	120	12 ± 4	77 ± 4	664 ± 73	54 ± 9
	240	6 ± 1	62 ± 5	325 ± 125	29 ± 6

E_{max}, maximal left ventricular elastance at end systole; LVP, peak positive left ventricular pressure; +dP/dt, peak positive first derivative of LVP; CABF, circumflex artery blood flow.
[a] $p < .05$ (contrast analysis) vs. all other treatments; [b] $p < .05$ (repeated measures) for E_{max} and CABF vs. all treatments.

Table 4. Hemodynamic data during treatment (mean +/- SEM)

Glucagon increased HR significantly compared with other groups, and was the only treatment that restored sinus rhythm at any time (HR 74 +/- 6 beats/min at 30 mins titration, 95 +/- 11 beats/min at treatment time of 30 mins). This effect occurred in four of six animals, and was transient in each case. In two of these four animals, sinus rhythm degenerated to sustained ventricular tachycardia; in the other two of these four animals, atrioventricular dissociation recurred. In these four animals, as HR decreased, circumflex artery blood flow decreased sharply with glucagon Table 4. Glucagon produced significantly smaller increases in left ventricular pressure, change in pressure over time, and maximal left ventricular elastance at end systole compared with epinephrine or hyperinsulinemia-euglycemia.

Verapamil Concentrations.

(Table 5) Plasma verapamil concentrations decreased with both treatments compared with control. Verapamil concentrations with glucagon were significantly lower vs. verapamil concentrations in other groups. Plasma samples were not collected for verapamil concentrations after the final 3-mg/kg verapamil bolus.

	Time				
	$TITR_{30}$	30 Mins	60 Mins	120 Mins	240 Mins
Calcium	644 ± 113	660 ± 28	859 ± 90	833 ± 80	1249 ± 246
Control	688 ± 24	1156 ± 227	3296 ± 1025	—	—
Epinephrine	637 ± 70	659 ± 48	792 ± 121	777 ± 63	959 ± 82
Glucagon[a]	625 ± 82	470 ± 19	514 ± 34	646 ± 51	731 ± 59
Insulin	657 ± 74	597 ± 55	707 ± 53	711 ± 52	984 ± 135

$TITR_{30}$, 30-min verapamil toxicity.
[a] Lower verapamil concentrations vs. all other treatment groups ($p < .05$, repeated measures).

Table 5. Verapamil concentrations (ng/mL; mean +/- SEM)

Survival.

(Table 6) All control animals died within 85 mins after start of the treatment period. All six hyperinsulinemia-euglycemia animals survived to 240 mins and subsequently survived the verapamil bolus ($p < .05$, log-rank statistic). The survival rate to treatment time of 240 mins in the remaining groups was 67% (four of six animals) for the epinephrine-treated group and 50% (three of six animals) for glucagon--and calcium chloride-treated groups. Only two epinephrine-treated animals survived the 3-mg/kg bolus, despite increases in the epinephrine infusion rate to 10.0 micro gram/kg/min; no glucagon--or calcium chloride-treated animals survived this bolus.

	Time				
	30 Mins	60 Mins	120 Mins	240 Mins	After Bolus
Calcium	6	5	5	3	1
Control	6	4	0	0	0
Epinephrine	5	5	4	4	2
Glucagon	5	5	4	3	0
Insulin[a]	6	6	6	6	6

[a]Improved survival vs. all other treatments ($p < .05$, log-rank statistic).

Table 6. Number of animals surviving during treatment

Insulin Concentrations.

(Table 7) Insulin concentrations were determined in plasma samples using radioimmunoassay. Insulin concentrations during basal control were not different between groups (mean 10.9 +/- 1.5 mu U/mL). Insulin concentrations did not increase in controls compared with the basal measurement. Insulin concentrations were significantly higher for the hyperinsulinemia-euglycemia group than for all other groups. Insulin concentrations were higher for glucagon- vs. calcium chloride-treated animals, control, and epinephrine.

Calcium (n = 4)	Control (n = 4)	Epinephrine (n = 4)	Glucagon (n = 5)	HIE (n = 5)
12 ± 6	39 ± 21	19 ± 12	392 ± 26	23,512 ± 1052

HIE, hyperinsulinemia-euglycemia.
Measurements were made at 30 mins for controls and at 60 mins for all other groups.

Table 7. Plasma [insulin] by ^{125}I radioimmunoassay at maximal arterial [glucose] (mu U/mL; mean +/- SEM)

Electrolytes.

Control animals demonstrated no significant change in sodium, potassium, or calcium concentrations. The potassium concentration was significantly decreased for the epinephrine-treated animals at all times (mean 2.44 +/- 0.27 mmol/L). The calcium concentration increased slightly during treatment with hyperinsulinemia-euglycemia compared with the basal control measurement (1.33 +/- 0.02 vs. 1.14 +/- 0.03 mmol/L at 30 mins, [$p < .05$, contrast analysis]). The calcium concentration approximately tripled with calcium chloride treatment, to a maximum of 2.9 +/- 0.3 mmol/L at 240 mins of treatment. Hyperinsulinemia-euglycemia decreased potassium concentration to a mean of 2.49 +/- 0.12 mmol/L (experimentally clamped at that level). All animals that died during treatment demonstrated an increase in potassium (mean 5.5 +/-0.16 mmol/L during agonal stages, immediately before death) compared with the basal control measurement.

DISCUSSION

Effect of Verapamil on Myocardial Metabolism.

Intravenously administered verapamil toxicity produced myocardial carbohydrate dependence in alpha-chloralose-anesthetized canines. In controls, the myocardial respiratory quotient increased, together with a significant increase in myocardial glucose uptake. Although arterial plasma glucose concentration increased 100%, concomitant plasma insulin concentration did not change significantly compared with pre-verapamil basal values (12.3 mu U/mL at 30 mins for control vs. 10.9 mu U/mL at basal measurement). Verapamil appears to exert dual toxicity on the heart: in addition to calcium-channel antagonism, verapamil may produce cardiodepression by converting the heart to a primarily carbohydrate-utilizing state, while inhibiting endogenous insulin secretion. These findings support the findings of Masters et al. [2,3], who demonstrated that intracoronary verapamil infusion decreases myocardial uptake of free fatty acids, and that streptozocin-pretreated animals were more susceptible to myocardial failure than animals with normal pancreatic function [30]. The fact that verapamil inhibits insulin release has been well documented in vivo and in vitro [5,6]. However, the mechanisms by which verapamil alters myocardial fatty acid uptake is less well described [31]. It cannot be convincingly argued that myocardial free fatty acid uptake was decreased as a result of decreased myocardial perfusion or oxygen delivery, since neither myocardial perfusion nor oxygen delivery was decreased in controls compared with the basal measurement. It is doubtful that these metabolic alterations were solely a result of verapamil's calcium-channel antagonism (or decreases in work), since the alterations are not reproduced by withdrawing calcium from perfusates in isolated myocyte or beating-heart preparations [32], or by treating isolated hearts with dihydropyridines or benzothiazepines (T. N. Masters, personal communication, 1993). Verapamil treatment does not significantly decrease fasting arterial plasma free fatty acid concentrations, which could contribute to decreases in free fatty acid uptake during verapamil toxicity [4,33-35]. Perhaps verapamil alters free fatty acid binding to specific protein carriers in plasma [36], cardiomyocyte [32], or mitochondrial membranes [37]. In short, we can only speculate on cellular mechanisms by which verapamil interferes with myocardial uptake of free fatty acids, since these mechanisms were not within the scope of this study.

In controls, myocardial VO_2 initially decreased, followed by a trend toward increasing myocardial VO_2 during decreasing myocardial work (as toxicity progressed), suggesting a change in myocardial metabolism that resulted in less efficient use of oxygen. These findings can be explained by a switch in myocardial metabolism from primarily oxidizing free fatty acids to aerobic glycolysis as the heart progressed into worsened cardiodepression during the titration period. Thus, we would expect the heart to use oxygen less efficiently, requiring greater oxygen delivery to normalize cardiac contractility compared with a state of predominant free fatty acid oxidation [38,39].

Insulin Treatment.

Insulin improved survival, myocardial contractility, and provided greater increases in myocardial glucose uptake and oxygen delivery compared with standard treatments for verapamil toxicity. Improvements in myocardial mechanical function with hyperinsulinemia-euglycemia may result from the positive inotropic effect that hyperinsulinemia-euglycemia provides, with increases in myocardial carbohydrate oxidation and oxygen delivery during verapamil toxicity. With hyperinsulinemia-euglycemia treatment, myocardial oxygen uptake increased four-fold compared with titration at 30 mins. However, oxygen supply was adequate, as confirmed by increases in lactate extraction. Under these conditions, insulin appeared to augment the ability of the myocardium to utilize carbohydrate by increasing both myocardial glucose and lactate uptake, while maintaining favorable coronary artery perfusion, and providing positive inotropic effects that improved survival [1].

Hyperinsulinemia-euglycemia increased myocardial performance (increased contractility, positive left ventricular pressure, and change in pressure over time), with a relative increase in the ratio of oxygen delivery/oxygen uptake. Additionally, with hyperinsulinemia-euglycemia, myocardial respiratory quotients also remained near unity, and myocardial glucose uptake and myocardial lactate uptake increased three-fold. During verapamil-induced cardiac failure, hyperinsulinemia-euglycemia increased indices of carbohydrate oxidation (increased myocardial glucose uptake, myocardial lactate uptake, and myocardial respiratory quotient), with coincident improvements in cardiac contractility. These improvements in cardiac contractility with hyperinsulinemia-euglycemia did not significantly decrease over 4 hrs, even with increasing verapamil concentration, apparently leading to prolonged survival rates compared with survival rates using other positive inotropic treatments. Increased coronary blood flow could have contributed to the increases in contractility and VO_2 that were produced by hyperinsulinemia-euglycemia during verapamil-induced calcium-channel antagonism. Kojima et al. [40] recently demonstrated that increased coronary blood flow leads to increased cytosolic calcium concentration and increased VO_2 in isolated, beating rat hearts. Hyperinsulinemia-euglycemia appears to improve survival rates during verapamil toxicity by providing combined inotropic support while facilitating increases in myocardial carbohydrate metabolism and improving oxygen delivery compared with calcium chloride, epinephrine, or glucagon. The metabolic and hemodynamic effects of hyperinsulinemia-euglycemia were not solely the result of glucose infusion, since arterial glucose concentrations were maintained at basal values, and infused volumes were equal for all groups.

Although insulin is not recognized as an exquisitely potent positive inotrope, during verapamil toxicity, insulin improved myocardial contractility and survival rate compared with three positive inotropic agents that previously have been considered standard treatments for verapamil poisoning [20]. This finding suggests a unique myocardial metabolic action of insulin that affords glycolytic fuel substrates (glucose and lactate), as well as improved availability of calcium for contractile proteins during verapamil toxicity. The dose of insulin used in this study was chosen to produce maximal myocardial glucose uptake, eliminating glucose uptake as a ratelimiting step in glucose utilization [27,41]. While glycolysis normally provides approximate 5% to 10% of total myocardial adenosine triphosphate used for mechanical work, under conditions of profound sarcolemmal L-type calcium-channel antagonism, the relative importance of glucose uptake and glycolysis in maintaining calcium homeostasis is likely to be increased [42,43]. Inasmuch as the normal mechanism of calcium-induced calcium release is likely to be disrupted with plasma concentrations of verapamil achieved in this study [44], increased myocardial cytosolic calcium may depend on intracellular mechanisms of calcium release. Accordingly, hydrogen ion produced during glycolysis may be exported via the sarcolemmal sodium-hydrogen ion antiporter [45,46], leading to an increase in cytosolic sodium, which, in turn, would be exchanged for sarcoplasmic reticulum calcium stores to increase contraction [47-50]. Moreover, recent work by Nakamura et al. [42] demonstrated that sarcoplasmic reticular reuptake of calcium is primarily dependent on adenosine triphosphate derived from glycolysis, which is increased by glucose and insulin treatment [50,51]. As a result, myocardial diastolic function may be improved with glucose and insulin treatment during verapamil toxicity. Additionally, insulin-stimulated myocardial glucose uptake increases intracellular potassium concentrations (increased ratio of intracellular to extracellular potassium concentration), which has long been associated with a prolonged action potential duration, and thus a longer period for calcium-entry during phase II depolarization [52-54]. With these mechanisms outlined, it is then reasonable to postulate that insulin could augment the effect of agents that increase myocardial cyclic adenine monophosphate. Normally, agents such as glucagon and epinephrine would increase cyclic adenine monophosphate-dependent phosphorylation of the L-type channel and sarcoplasmic reticulum phospholambin to stimulate calcium entry and sarcoplasmic reticulum calcium reuptake [55]. Under conditions of severe verapamil toxicity, the net effect of catecholamine ``stimulation'' would be enhanced calcium entry into the sarcoplasmic reticulum, without an increase in transsarcolemmal calcium, potentially reducing cytosolic calcium. The presence of insulin would stimulate glucose uptake and glycolysis (with subsequent increases in cytosolic calcium), while lengthening the duration of phosphorylated L-type channel opening (albeit antagonized by verapamil), resulting in enhanced myocardial contraction.

Glucagon Treatment.

Glucagon produced complex changes in myocardial metabolism and performance during verapamil toxicity that appear to reflect both direct and indirect myocardial metabolic effects. Early in treatment, glucagon increased myocardial glucose uptake, maximal left ventricular elastance at end systole, myocardial respiratory quotient, oxygen delivery, and insulin concentrations. During verapamil toxicity and glucagon-treatment, increases in contractility and change in pressure over time appeared dependent on increases in myocardial glucose uptake. As myocardial glucose uptake increased, so did cardiac work, resulting in coronary vasodilation and increased circumflex artery blood flow. Apparently, without increased myocardial glucose uptake, circumflex artery blood flow decreases late in treatment with glucagon, as cardiac work decreases. These findings agree with the findings of Abel [56], who reported that glucagon has no direct coronary vasodilatory effects, but produces coronary vasodilation as a result of increased production of metabolic vasodilators with increased HR during glucagon treatment. Glucagon was only beneficial as long as myocardial glucose uptake was increased. Near the end of the 4-hr protocol with glucagon survivors, arterial blood glucose concentration decreased significantly, myocardial respiratory quotients returned to basal values (0.8), and circumflex artery blood flow, myocardial glucose uptake, and maximal left ventricular elastance at end systole decreased sharply. One explanation for these observations is that over 4 hrs of simultaneous verapamil toxicity and glucagon treatment, hepatic glycogen stores are depleted, and gluconeogenesis is inhibited, while insulin activity (and total body glucose uptake) remain high, resulting in relative hypoglycemia and decreased myocardial glucose uptake. As myocardial glucose uptake diminished, maximal left ventricular elastance at end systole and change in pressure over time decreased. The role of insulin in altering myocardial glucose uptake and cardiac function during glucagon treatment remains uncertain. It is currently not possible to evaluate the effects of pure glucagon, since recombinant glucagon preparations are not commercially available, and standard preparations contain insulin. In separate experiments, we measured the concentrations of insulin in the plasma of canines treated with a glucagon protocol identical to the present study, except animals received an in situ pancreatectomy after instrumentation. In these animals, insulin concentrations were approximate 400 mu U/mL (data not shown).

Epinephrine Treatment.

After epinephrine infusion was begun, cardiac contractility increased initially, while the myocardial respiratory quotient decreased to basal ratios. Epinephrine did not increase plasma insulin concentrations or myocardial glucose uptake, despite marked hyperglycemia with epinephrine. These data are consistent with the findings of Porte [57], who demonstrated that epinephrine infusion decreased insulin secretion in a canine model. The combination of epinephrine and verapamil produced rapid increases in arterial glucose early in treatment, resulting in non-steady-state conditions of myocardial glucose delivery, making interpretation of myocardial glucose uptake early in treatment difficult. However, later in treatment (120 to 240 mins), arterial glucose concentration remained constant (repeated-measures time effect, p = NS). During this time, myocardial glucose uptake remained significantly depressed compared with the basal measurement, and since maximal left ven tricular elastance at end systole was increased compared with the control value, the heart was likely oxidizing other fuels. With epinephrine treatment, myocardial lactate extraction paralleled changes in arterial lactate concentrations, and the myocardial respiratory quotient increased late in treatment as myocardial lactate uptake began to plateau maximally. Perhaps, with epinephrine, hearts initially oxidized free fatty acids as a primary fuel, but later, as lactate concentrations increased, the myocardium preferentially extracted lactate uptake as a primary oxidizable carbon source. Previous studies [58] have shown that the canine heart oxidizes lactate for 80% to 90% of its energy needs when in vivo lactate concentrations reach 4.5 mmol/L.

Calcium Chloride Treatment.

High-dose calcium chloride produced little change in myocardial glucose uptake, and no increase in plasma insulin radioimmunoassay, with only transient improvements in maximal left ventricular elastance at end systole. Arterial glucose concentration remained near the basal value, significantly lower than control value. calcium-channel antagonism has been associated with decreases in insulin secretion [7]. Our data reiterate this finding and also suggest that neither this effect nor the depressed myocardial contraction are reversed by high plasma [Ca sup ++] in vivo. Curiously, high [Ca sup ++] prevented the hyperglycemic response. Overall, the heart appears to respond to treatment with calcium independently of insulin. Myocardial respiratory quotient and maximal left ventricular elastance at end systole data also suggest that with calcium chloride, the myocardium primarily oxidizes fatty acids, but this oxidation allows only subnormal myocardial contractile force.

Verapamil Concentrations.

Verapamil concentrations were decreased in all treatments compared with control, indicating that treatment improved either elimination or distribution of the drug to tissues other than blood. Verapamil concentrations were significantly lower with glucagon compared with other treatments. Inasmuch as all animals received the same dosage of verapamil during titration and treatment, and glucagon produced no increase in cardiac output or renal blood flow compared with other treatments, it appears that glucagon increased hepatic elimination of verapamil.

Potential Clinical Relevance.

Insulin is an inexpensive, widely available drug that most clinicians have used frequently in clinical practice. When hypoglycemia is prevented using insulin, there are virtually no short-term side effects. The optimal dose of insulin is unknown, but based on our experience in separate studies, it appears that much lower doses are equally effective for severe verapamil toxicity. Insulin appears to have a ``prophylactic'' effect; if insulin is administered early to canines, it is difficult to induce verapamil toxicity. Moreover, insulin may be useful clinically in treating verapamilinduced cardiac failure in patients with coronary artery disease. With hyperinsulinemia-euglycemia, myocardial oxygen delivery and myocardial lactate uptake were increased compared with other treatments, indicating that hyperinsulinemia-euglycemia increased contractility without producing ischemia, a paradigm with advantages for a patient with coronary artery disease. These data also provide a rationale for the use of hyperinsulinemia-euglycemia as a treatment for insulin-deficient diabetics who may be particularly susceptible to verapamil-induced cardiac failure. Consequently, further studies are required to determine if diabetic animals with verapamil-induced cardiac dysfunction would benefit from pharmacologic doses of insulin.

Summary.

Our data show that cardiac failure induced by verapamil is accompanied by a relative increase in carbohydrate metabolism. Under these conditions, insulin increases myocardial contractility coincident with increases in myocardial glucose uptake, prolonging survival compared with glucagon, calcium chloride, or epinephrine. With epinephrine treatment, hearts initially used noncarbohydrate fuel sources until late in treatment, when lactate metabolism supervened. With glucagon treatment, changes in maximal left ventricular elastance at end systole paralleled changes in myocardial glucose uptake. Plasma insulin concentrations increased significantly with glucagon treatment at maximal hyperglycemia, coincident with maximal increases in maximal left ventricular elastance at end systole. During treatment for verapamil-induced cardiac failure, myocardial oxygen delivery appears to be maximized during periods of maximal myocardial glucose uptake.

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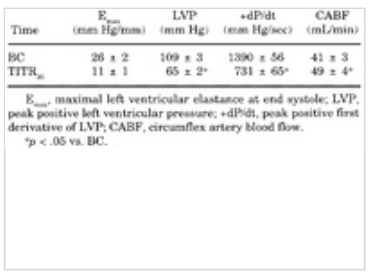
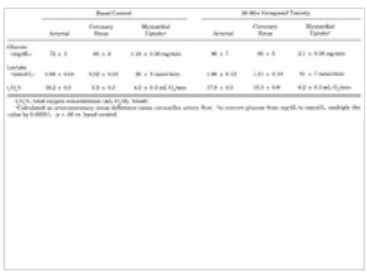


Time	E_{max} (mm Hg/mm)	LVP (mm Hg)	+dP/dt (mm Hg/sec)	CABF (mL/min)
BC	26 ± 2	109 ± 3	1390 ± 56	41 ± 3
$TITR_{50}$	11 ± 1	65 ± 2*	731 ± 65*	49 ± 4*

E_{max}, maximal left ventricular elastance at end systole; LVP, peak positive left ventricular pressure; +dP/dt, peak positive first derivative of LVP; CABF, circumflex artery blood flow.
*$p < .05$ vs. BC.



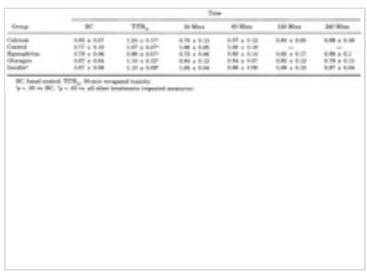


Table 1

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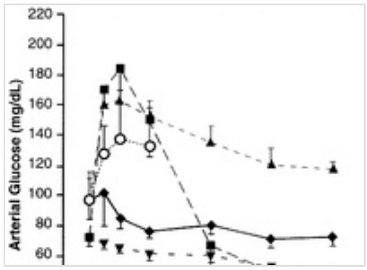


Figure 1

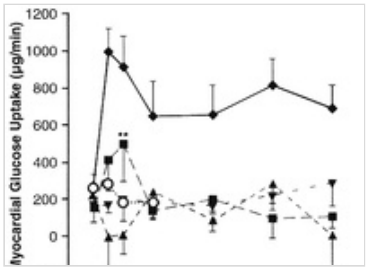


Figure 2

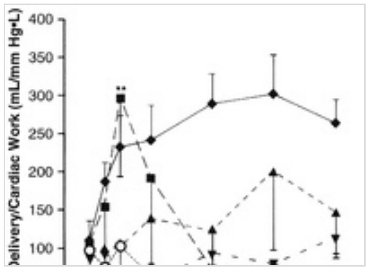
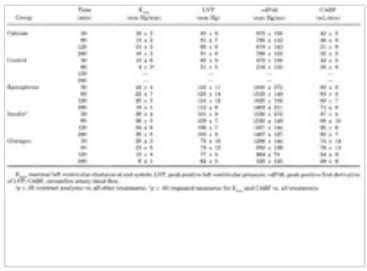


Figure 3



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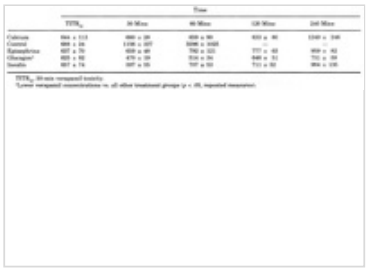

Table 5

	Time				
	30 Mins	60 Mins	120 Mins	240 Mins	After Bolus
Calcium	6	5	5	3	1
Control	6	4	0	0	0
Epinephrine	5	5	4	4	2
Glucagon	5	5	4	3	0
Insulin*	6	6	6	6	6

*Improved survival vs. all other treatments ($p < .05$, log-rank statistic).

Table 6

Calcium (n = 4)	Control (n = 4)	Epinephrine (n = 4)	Glucagon (n = 5)	HIE (n = 5)
12 ± 6	39 ± 21	19 ± 12	392 ± 26	23,512 ± 1052

HIE, hyperinsulinemia-euglycemia.
Measurements were made at 30 mins for controls and at 60 mins for all other groups.

Table 7

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