Effects of Fructose-1,6-Diphosphate, Glucose, and Saline on Cardiac Resuscitation

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Severe hypoxemia causes respiratory and cardiac arrest, in part, because severe hypoxemia decreases glycolysis and adenosine triphosphate (ATP) production by a lactic acid-induced decrease in the activity of phosphofructokinase and glyceraldehyde-3-P dehydrogenase. Fructose-1,6-diphosphate (FDP) administration increases the ATP concentration of blood. The authors hypothesized that FDP might increase the number of rabbits that could be resuscitated from hypoxemic cardiac arrest. To test this hypothesis, heart rate, arterial pressure, left ventricular end-diastolic pressure, and blood gases and pH were measured during normoxemia ($FI_{O_2} = 0.21$) and again during hypoxemia ($FI_{O_2} = 0.04$) in 28 adult, white, New Zealand rabbits anesthetized with pentobarbital. With the onset of hypoxemia, we gave either 40 mg/kg of 5% FDP (n = 10), 5% glucose (n = 11), or an equal volume (2.5 ml) of normal saline (n = 7) intravenously and began a continuous infusion of 2.0 mg·kg⁻¹·min⁻¹ of the same sugar or 0.12 ml/min of saline. FDP-treated rabbits breathed for 20.9 ± 4.9 (mean ± SEM) min after initiation of hypoxemia; glucose-treated rabbits breathed for 1.4 ± 0.2 min, and saline-treated rabbits breathed 10.3 ± 4 min. Cardiac arrest occurred 2.5 ± 0.5 min after the onset of respiratory arrest in FDP-treated rabbits, 4.1 ± 0.2 min in glucose-treated rabbits, and 2.9 ± 0.4 min in saline-treated rabbits. We could resuscitate all ten FDP-treated rabbits; two of 11 glucose-treated (FDP vs. glucose, $P < 0.001$); and one of seven saline-treated rabbits (FDP vs. saline, $P < 0.001$) from cardiac arrest. It is concluded that FDP prolongs the time to respiratory arrest and increases immediate salvage from cardiac arrest in severely hypoxemic, adult rabbits. (Key words: Hypoxemia: acute; survival time. Metabolism: fructose-1,6-diphosphate; glucose. Resuscitation: cardiopulmonary.)

GLYCOLYSIS SUPPLIES high-energy phosphates during hypoxemia and ischemia.[1] Although hypoxemia initially increases glycolysis, it soon slows because there is inadequate adenosine triphosphate (ATP) to phosphorylate fructose-6-phosphate (FDP), and because acidosis inhibits the activity of phosphofructokinase (PFK).[1–4] A further reduction in glycolysis is caused by an acidosis-induced decrease in glyceraldehyde-3-phosphate dehydrogenase activity and increased concentrations of Nicotinamide adenine dinucleotide (NADH) and lactate.[4–6] As a conse-

quence of these changes, high-energy phosphate concentrations rapidly decline, heart rate and myocardial contractility decrease,[2,5,7,8] and respiratory and cardiac arrest ensue.

Providing a substrate that would enter the glycolytic pathway below PFK might increase anaerobic metabolism, provide high-energy phosphates, prolong the time to respiratory arrest, and increase the likelihood of resuscitation from cardiac arrest. FDP might be such a substrate because it increases the activity of both PFK[9–11] and pyruvate kinase.[12–14] Administration of FDP improves cardiovascular function and increases the number of animals that survive hemorrhagic,[15,16] septic,[17] and traumatic shock.[18] FDP is said to have increased the glycolytic activity of ischemic myocardia in one study,[19] but not in another.[20]

We determined whether administering FDP increased the likelihood of resuscitation from hypoxemia-induced cardiac arrest, and compared our results in FDP-treated rabbits with those in glucose- and saline-treated rabbits.

Methods

After receiving permission from the University of California, San Francisco committee on Animal Research, we studied 28 adult, male, 2.2–3.3 kg (2.98 ± 0.06 kg; mean ± SEM), white, New Zealand rabbits whose diet was unrestricted prior to the study. We infiltrated the skin with 1% lidocaine, cannulated an ear vein, and induced anesthesia with iv sodium pentobarbital (25 mg/kg). Then we inserted a 3.5-mm endotracheal tube through a tracheostomy, and introduced polyethylene catheters (PE 160) into the left ventricle (via the left common carotid artery) and into a femoral artery to enable us to measure left ventricular and systemic arterial pressures and arterial blood gases and pH. The 100% response time of the catheters, connecting tubing, and strain gauge to a step change in pressure was 0.1 s; the amplitude–frequency response of the system was flat to 15 Hz. We continuously monitored a three-lead electrocardiogram (ECG) and rectal temperature (Yellow Springs thermistor, Yellow Springs, OH). Body temperature was kept at 38.3 ± 0.03° C with a servocontrolled heating lamp.

During the control period, the rabbits breathed 100% oxygen from a Bain® circuit.[21] During the experimental period, they breathed a hypoxic gas mixture (inspired O_2 concentration [FI_{O_2}] = 0.04) from a second Bain® circuit whose concentration of oxygen was adjusted to 4% before

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the circuit was attached to the endotracheal tube. The total gas flow in both circuits was 6–7 l/min. We continuously measured the FI_{O_2} with a Miniox I® oxygen analyzer (Catalyst Research Corporation, Owings Mills, MD), which was calibrated with room air and 4% oxygen. These concentrations of oxygen were corroborated before and after each experiment by mass spectrometry. Because the oxygen analyzer was inserted between the Bain® circuit and the endotracheal tube connector, the inspired oxygen concentration may have been slightly less than 4%, but we did not detect a change in FI_{O_2} when we connected the Bain® circuit with low oxygen to the tracheal tube. We tested the respiratory circuit for leaks by closing the system, filling it with oxygen, and maintaining a pressure of 20 mmHg. Only circuits that maintained this pressure for 5 min were used. The FI_{O_2} of the circuit was constant ($FI_{O_2} = 0.04$) for at least 5 min before we attached it to the tracheostomy tube.

PROCEDURE

The rabbits spontaneously breathed 100% oxygen for 30–45 min while recovering from surgery. Animals in the FDP and glucose groups were assigned randomly to these groups, but saline-treated rabbits were studied separately after we completed the FDP–glucose study. Fifteen minutes before beginning the study, FI_{O_2} was reduced to 0.21. Five minutes before administering the hypoxic gas mixture, we gave 10 mg/kg of sodium pentobarbital. With the onset of hypoxemia, we gave 40 mg/kg of either 5% FDP (n = 10), 5% glucose (n = 11), or an equal volume of normal saline (n = 7) iv over 30 s and continuously infused the same sugar (2 mg · kg^{-1} · min^{-1}) or an equal volume of saline (0.12 ml/min) by Harvard® infusion pump. Ninety seconds after the onset of cardiac arrest (defined as a systemic arterial blood pressure of <5 mmHg and a left ventricular pressure change of <5 mmHg with each beat), we began external cardiac massage (rate 160–180 compressions/min; mean arterial pressure 20–25 mmHg); and mechanical ventilation (Baby-Bird® ventilator [FI_{O_2} 1.0; rate 40–45 breaths/min; peak inspiratory pressure 20–25 cmH$_2$O; PEEP 4 cmH$_2$O]).§ If the heartbeat and arterial pressure were not restored after 5 min of cardiopulmonary resuscitation (CPR), we gave 1 mEq/

kg of NaHCO$_3$ and continued cardiac massage. We gave 0.01 mg/kg of epinephrine 2 min later and again 1 min later if restoration of spontaneous circulation did not follow administration of sodium bicarbonate. If the heart started beating and the arterial pressure was at least 75/40 mmHg 5 min after administering the second dose of epinephrine, and if the arterial pressure remained at these levels for 30 min, we considered resuscitation successful.

Arterial pressure, left ventricular end-diastolic pressure (LVEDP), ECG, and respiratory rate were continuously recorded on a Grass® polygraph. The data for all three groups were compared: 1) while the rabbits breathed room air; 2) after 2 and 4 min¶ of hypoxemia; 3) at respiratory arrest; 4) at cardiac arrest; 5) after 5 min of CPR; 6) 2 min after giving sodium bicarbonate; and 7) 5 min after successful resuscitation. Plasma potassium concentrations were measured before inducing hypoxemia and immediately after the onset of cardiac arrest. Finally, we determined the presence or absence of spontaneous breathing, and pupillary light and eyelid reflexes before the induction of hypoxemia and 5, 15, and 30 min after successful resuscitation. To determine whether the animals would breathe spontaneously, we briefly interrupted mechanical ventilation 5, 15, and 30 min after successful resuscitation.

At the end of each study, we killed the rabbits with an overdose of barbiturate, performed bilateral thoracotomies, and determined the presence or absence of thoracic trauma (mediastinal hemorrhage, pulmonary hemorrhage, pulmonary edema, multiple rib fractures, or pneumothorax). The data from three glucose-, two FDP-, and two saline-treated rabbits were excluded because they had severe pulmonary trauma that may have precluded resuscitation; none of these animals could be resuscitated.

Nine additional rabbits (three FDP-, three glucose-, and three saline-treated) were prepared and treated as described earlier. Plasma glucose concentrations (YSI Glucose Analyzer,® model 23A) were determined during the control period, at respiratory arrest, and 7 min after beginning CPR (just before administering epinephrine). The animals were then killed with an overdose of barbiturate. We calibrated the glucose analyzer before each measurement. Its output was not affected by FDP.

We compared the data by one-way analysis of variance, Newman-Keuls test, and chi-square with Yates correction for continuity. $P < 0.05$ was considered significant.

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§ In preliminary studies, we tried to blind the person (L.F.) doing cardiac massage to the treatment used (FDP or glucose), but it soon became apparent that this was impossible because there was such a large difference between the FDP and glucose groups with respect to the time from onset of hypoxemia to cardiac arrest. To circumvent this problem, we standardized the ventilation, maintained fixed chest compression rates, and kept the mean arterial pressures between 20 and 25 mmHg during resuscitation. These mean arterial pressures allowed us to resuscitate FDP-treated animals with a minimum of lung trauma.

¶ We made measurements after 4 min of hypoxemia because it allowed us to compare the effects of FDP, glucose, and saline on the measured variables before cardiac arrest occurred. Glucose-treated animals died shortly thereafter, while FDP- and saline-treated animals survived much longer. Glucose-treated rabbits had stopped breathing by this time.

Results

All animals had tachypnea within 10 s of administering 4% oxygen; the tachypnea was maximal 15–20 s later (78 ± 5 breaths/min in FDP-treated rabbits; 63 ± 9 breaths/min in glucose-treated rabbits; and 84 ± 9 breaths/min in saline-treated rabbits). The respiratory rate of glucose-treated and saline-treated rabbits progressively decreased thereafter, whereas (except for brief periods in some rabbits, see following) the respiratory rate of most FDP-treated rabbits exceeded 45 breaths/min for 15–17 min; thereafter, it progressively decreased. Hypoxemic, FDP-treated rabbits breathed for 20.9 ± 4.9 min, those given glucose breathed for 1.4 ± 0.2 min, (FDP vs. glucose, P < 0.001), and those given saline breathed for 10.3 ± 4 min, (FDP vs. saline, P < 0.06) (fig. 1). One saline-treated animal breathed for 29.8 min. The remaining six saline-treated rabbits breathed for 7.1 ± 2.8 min. We included all seven animals in our data analysis. Three rabbits in the FDP group had initial tachypnea but stopped breathing after 39–59 s of hypoxemia. In all three cases, the bolus of FDP was given in <20 s. In the remaining seven animals, we gave the bolus of FDP by infusion pump over 30 s. Four of these seven FDP-treated rabbits had tachypnea, but then breathed irregularly for 2.1 ± 0.7 min. Thereafter, they breathed rhythmically until the onset of respiratory arrest. The three remaining FDP-treated rabbits breathed regularly until respiratory arrest.

Heart rates of FDP-treated rabbits decreased during the first 2 min of hypoxemia, but then increased and exceeded 75% of the control value (>190 beats/min) until just before cardiac arrest (table 1). Heart rates of glucose-treated and saline-treated rabbits progressively decreased while breathing 4% oxygen. Heart rates of glucose- and saline-treated rabbits slowed during hypoxemia, but were significantly higher (P < 0.05) than those of FDP-treated animals at respiratory arrest. Systolic and diastolic blood pressures were more nearly normal in hypoxemic FDP-treated rabbits than in glucose- or saline-treated animals. Four minutes after the onset of hypoxemia, systolic pressures were higher in the FDP-treated group than they were in either the glucose- (P < 0.005), or saline-treated (P < 0.05) groups. At respiratory arrest, the systolic and diastolic arterial blood pressures were higher in glucose- and saline-treated rabbits than in FDP-treated rabbits, possibly because FDP-treated rabbits were much more acidotic than those in the other two groups. Acidosis may have caused more myocardial depression in the FDP group. Cardiac arrest occurred after 23.4 ± 4.4 min of hypoxemia in the FDP group, after 5.5 ± 0.2 min of hypoxemia in the glucose group (FDP vs. glucose, P < 0.001), and after 13.2 ± 3.8 min in the saline group (FDP vs. saline, P < 0.05) (fig. 1). However, the time from respiratory arrest to cardiac arrest did not differ among
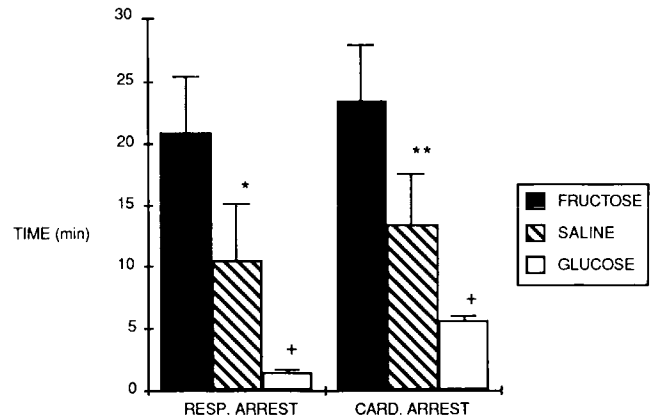

FIG. 1. The effects of fructose-1,6-diphosphate, saline, and glucose administration on the time from onset of hypoxemia to respiratory and cardiac arrest in severely hypoxemic rabbits. *P < 0.06, compared with FDP; **P < 0.05, significantly different from FDP; +P < 0.001, significantly different from FDP.

the three groups (2.5 ± 0.5 min, FDP; 4.1 ± 0.2 min, glucose; 2.9 ± 0.4 min, saline). All rabbits had an extremely slow heart rate and wide QRS complexes on ECG during cardiac arrest. Two saline-treated rabbits had grand mal seizures 10 and 11 min after the onset of hypoxemia. A third saline-treated rabbit had twitching of its hind limbs 2 min after the onset of hypoxemia.

Rabbits given FDP had lower pHs (table 2) than rabbits given glucose (7.20 ± 0.05 vs. 7.45 ± 0.02, P < 0.001) or saline (7.20 ± 0.05 vs. 7.41 ± 0.04, P < 0.005) and larger base deficits (−14 ± 4 [FDP] vs. 0 ± 1 [glucose], P < 0.005; −14 ± 4 [FDP] vs. −8 ± 3 [saline], P < 0.05) at respiratory arrest, presumably because respiratory arrest occurred later in the FDP-treated rabbits. The pHs were also lower (7.11 ± 0.03 [FDP] vs. 7.30 ± 0.04 [glucose], P < 0.005; and 7.11 ± 0.03 [FDP] vs. 7.27 ± 0.03 [saline], P < 0.01) at cardiac arrest in FDP-treated animals. At respiratory arrest, the average Pa_{CO_2} of all three groups was lower than control values (table 2); the oxygen saturation and oxygen contents of arterial blood (Ca_{O_2}) were similar for all three groups at respiratory arrest (table 3). In the FDP-treated group, the serum potassium concentration rose from a control value of 3.3 ± 0.2 mEq/l to 6.2 ± 0.44 (P < 0.001) at cardiac arrest; it rose from 3.8 ± 0.3 to 6.1 ± 0.1 (P < 0.01) in the glucose-treated group; and from 3.7 ± 0.2 to 6.4 ± 0.9 (P < 0.02) in the saline-treated group. Both the rise in serum potassium and the absolute values were similar in all three groups. Blood glucose concentrations before hypoxemia, at respiratory arrest, and during resuscitation (before epinephrine administration) are shown in figure 2. The glucose concentrations before hypoxemia were similar for all three groups. Plasma glucose concentrations were higher during resuscitation than during the control period (350 ± 30

TABLE 1. Hemodynamic Changes in Severely Hypoxemic Rabbits Treated with FDP (n = 10), Glucose (n = 11), or Normal Saline (n = 7)

Time after Induction of Hypoxemia	Heart Rate (beats/min)			Arterial Pressure								
				Systolic (mmHg)			Diastolic (mmHg)			Left Ventricular End Diastolic (mmHg)		
	F	G	S	F	G	S	F	G	S	F	G	S
Control	263 ± 8	287 ± 6	301 ± 9	150 ± 5	149 ± 6	154 ± 6	82 ± 5	82 ± 5	76 ± 6	0.0 ± 0.1	2 ± 1	2 ± 1
2 min	177 ± 22	211 ± 19	242 ± 33	159 ± 11	138 ± 9	116 ± 10	69 ± 8	60 ± 5	54 ± 6	12 ± 4	17 ± 3	20 ± 6
4 min	203 ± 19	163 ± 14	201 ± 45	111 ± 13	56 ± 6†	74 ± 17*	50 ± 7	28 ± 4	37 ± 8	8 ± 3	14 ± 2	13 ± 4
Respiratory arrest‡	191 ± 19	256 ± 9*	248 ± 20*	92 ± 18	137 ± 9	102 ± 12	45 ± 11	72 ± 8	56 ± 10	8 ± 2	12 ± 4	20 ± 6

Respirations were spontaneous.
Values are means ± 1 SEM.
F = fructose-1,6-diphosphate (FDP); G = glucose; S = saline.
* $P < 0.05$, significantly different from FDP.

† $P < 0.005$, significantly different from FDP.
‡ Time from onset of hypoxemia to respiratory arrest: 20.9 ± 4.9 min, FDP; 1.4 ± 0.2 min, glucose; and 10.3 ± 4 min, saline.

vs. 142 ± 10 mg/dl [hypoxemic *vs.* normoxemic values], $P < 0.005$, FDP; 352 ± 16 *vs.* 154 ± 14 mg/dl, $P < 0.001$, glucose; 262 ± 23 *vs.* 154 ± 8 mg/dl, $P < 0.001$, saline) or at respiratory arrest (350 ± 30 *vs.* 200 ± 25 mg/dl, $P < 0.01$, FDP; 352 ± 16 *vs.* 180 ± 21 mg/dl, $P < 0.001$, glucose; 262 ± 23 mg/dl *vs.* 149 ± 4 mg/dl, $P < 0.005$, saline).

All FDP-treated rabbits without pulmonary trauma were successfully resuscitated from cardiac arrest, breathed spontaneously, and had pupillary light and eyelid reflexes 30 min after successful resuscitation (table 4). Only two of 11 glucose-treated rabbits and one of 7 saline-treated rabbits were successfully resuscitated. Both surviving glucose-treated animals breathed spontaneously. One had normal pupillary light reflexes 30 min after resuscitation. Two additional glucose-treated rabbits recovered their heartbeat and arterial pressure but died within 10 min of CPR cessation. The remaining glucose-treated rabbits could not be resuscitated. The one successfully resuscitated saline-treated rabbit breathed spontaneously and had pupillary light and eyelid reflexes 30 min after resuscitation. A second saline-treated rabbit recovered his

heartbeat and blood pressure, but died 5 min after stopping CPR. Neither the two glucose-treated rabbits nor the one saline-treated rabbit that died shortly after CPR was stopped had evidence of spontaneous breathing, pupillary light reflexes, eyelid reflexes, or pulmonary trauma.**

All rabbits received $NaHCO_3$ during cardiac resuscitation. One of ten FDP-treated rabbits, ten of 11 glucose-treated rabbits, and seven of seven saline-treated rabbits received two doses of epinephrine during resuscitation.

The pHs were lower and the base deficits larger in FDP-treated rabbits (table 5) than they were in either of the other two groups 5 min after we began CPR, 2 min after administering $NaHCO_3$, and 5 min after reestablishing a heart beat. These differences were probably due

** Including the data from the seven animals that had pulmonary trauma does not alter the statistical significance of either the time to respiratory arrest (18.1 min ± 4.4 min, FDP; 1.5 ± 0.2 min, glucose [FDP *vs.* glucose, $P < 0.001$]; 8.8 ± 3.2 min, saline [FDP *vs.* saline, $P < 0.05$]; or the number of animals that could be successfully resuscitated (FDP *vs.* glucose, $P < 0.001$; FDP *vs.* saline, $P < 0.001$).

TABLE 2. Blood Gases, pH, and Base Deficit in Severely Hypoxemic Rabbits Treated with FDP (n = 10), Glucose (n = 11), or Normal Saline (n = 7)

Time of Measurement	P_{aO_2} (mmHg)			P_{aCO_2} (mmHg)			pH			Base Deficit (mEq/l)		
	F	G	S	F	G	S	F	G	S	F	G	S
Control	84 ± 5	88 ± 8	84 ± 6	36 ± 2	38 ± 1	34 ± 1	7.41 ± 0.02	7.41 ± 0.01	7.44 ± 0.01	−1 ± 1	0 ± 1	0 ± 1
4 min of hypoxemia	15 ± 1	12 ± 2	16 ± 1	34 ± 5	45 ± 5	29 ± 7	7.39 ± 0.04	7.34 ± 0.05	7.50 ± 0.08	−4 ± 1	−2 ± 1	−2 ± 1
Respiratory arrest¶	20 ± 2	16 ± 1	16 ± 1	27 ± 4	34 ± 2	23 ± 4	7.20 ± 0.05	7.45 ± 0.02§	7.41 ± 0.04‡	−14 ± 4	0 ± 1‡	−8 ± 3*
Cardiac arrest**	18 ± 2	12 ± 2	10 ± 1	33 ± 6	46 ± 5	36 ± 6	7.11 ± 0.03	7.30 ± 0.04‡	7.27 ± 0.03†	−17 ± 3	−5 ± 1§	−9 ± 2*

Respirations were spontaneous.
Values are means ± 1 SEM.
F = fructose-1,6-diphosphate (FDP); G = glucose; S = saline.
* $P < 0.05$, significantly different from FDP; † < 0.01, significantly different from FDP.
‡ $P < 0.005$, significantly different from FDP; § < 0.001, significantly

different from FDP.
¶ Time from onset of hypoxemia to respiratory arrest: 20.9 ± 4.9 min, FDP; 1.4 ± 0.2 min, glucose; 10.3 ± 4 min, saline.
** Time from onset of hypoxemia to cardiac arrest: 23.4 ± 4.4 min, FDP; 5.5 ± 0.2 min, glucose; and 13.2 ± 3.8 min, saline.

TABLE 3. Pa_{O_2}, Hemoglobin Concentration, Per Cent Oxygen Saturation, and Arterial Oxygen Content at Respiratory Arrest in Severely Hypoxemic Rabbits Treated with FDP (n = 10), Glucose (n = 11), or Normal Saline (n = 7)

	Pa_{O_2} (mmHg)	Hb (g/dl)	Sa_{O_2} (%)	Ca_{O_2} (ml/100 ml)
FDP	20 ± 2	12.9 ± 0.3	15.6 ± 1.4	2.9 ± 0.3
Glucose	16 ± 1	12.3 ± 0.1	16 ± 2.0	2.8 ± 0.3
Saline	16 ± 1	12.4 ± 0.4	14.9 ± 1.4	2.7 ± 0.3

Values are means ± 1 SEM.
FDP = fructose-1,6-diphosphate; Hb = hemoglobin; Ca_{O_2} = arterial oxygen content.

to the fact that FDP-treated rabbits survived severe hypoxemia longer than the other animals.

Discussion

These studies show that FDP administration, compared with glucose or saline administration, prolongs the time to respiratory arrest in hypoxemic rabbits and increases the number of animals that can be resuscitated from hypoxemia-induced cardiac arrest. More FDP-treated rabbits maintained stable heart rates and arterial blood pressures, breathed spontaneously, had normal pupillary and eyelid reflexes 30 min after resuscitation, and breathed longer when hypoxemic than glucose- or saline-treated rabbits. One possible explanation for these differences is that exogenous FDP enters cells and is metabolized by glycolysis.[15,22,23] However, two reports have questioned whether exogenous FDP can enter cells.[20,24] A second possibility is that exogenous FDP does not enter cells but interacts with cell membranes to increase intracellular FDP and thereby stimulate glycolysis.[25–27] By either of these mechanisms, FDP would increase the concentration of ATP and sustain cell function better than glucose. While anaerobic metabolism of FDP and glucose produces 4 mol of ATP each, anaerobic metabolism of FDP makes twice as much ATP available as anaerobic metabolism of glucose, because FDP metabolism does not require phosphorylation.[15,17] FDP administration increases ATP production in blood *in vitro*[28] and *in vivo*.[29] A third possibility is that FDP increases the amount of ATP produced by glycolysis. ATP produced by glycolysis more effectively preserves membrane functions (*e.g.*, ion pumps) than ATP produced by mitochondria.[5,30,31] Giving FDP before occluding the hepatic artery and portal vein results in near normal hepatocyte morphology in rats.[32] FDP administration also provides histologic and functional protection from an ischemic renal insult.[33] More effective maintenance of cell integrity and function during hypoxemia and cardiac arrest would explain why the myocardia of FDP-treated rabbits were more responsive to exogenous
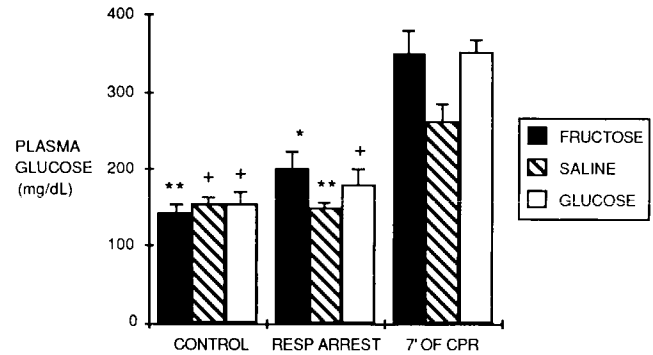

FIG. 2. Plasma glucose concentrations during severe hypoxemia and resuscitation in rabbits treated with fructose-1,6-diphosphate, glucose, or saline. $*P < 0.01$, significantly different from 7 min of CPR; $**P < 0.005$, significantly different from 7 min of CPR; $+P < 0.001$, significantly different from 7 min of CPR.

epinephrine than the myocardia of glucose- or saline-treated rabbits, even though FDP-treated rabbits were more acidotic. Only one glucose- and no saline-treated rabbit could be resuscitated with one dose of epinephrine. Seven of 11 glucose- and five of seven saline-treated animals could not be resuscitated with two doses of epinephrine. Nine of ten FDP-treated rabbits had their heart beat and arterial pressure restored with one dose of epinephrine. A fourth possible reason why we could resuscitate more FDP-treated rabbits is that FDP provides more cerebral protection than glucose. This possibility is consistent with the fact that FDP administration prolongs the time to EEG flattening with anoxia in cats and increases the reoxidation of cytochrome a, a_3 in brain during reoxygenation.[34] It is also suggested by the fact that our FDP-treated rabbits breathed longer during hypoxemia and that more of them had normal pupillary and eyelid reflexes after resuscitation from cardiac arrest than animals in the other two groups.

FDP-treated rabbits were more acidotic than glucose- and saline-treated rabbits at cardiac arrest, presumably because FDP-treated rabbits were hypoxemic longer and possibly because FDP metabolism produced more lactic

TABLE 4. Effects of FDP, Glucose, and Saline on the Ability to Resuscitate Adult Rabbits from Cardiac Arrest

	Resuscitation Outcome*		
	FDP	Glucose	Saline
Successful resuscitation	10/10	2/11‡	1/7‡
Spontaneous breathing†	10/10	2/11‡	1/7‡
Pupillary light reflex†	10/10	1/11‡	1/7‡
Eyelid reflex†	10/10	0/11‡	1/7‡

FDP = fructose-1,6-diphosphate.
* This includes all animals without pulmonary trauma at necropsy.
† 30 min after successful resuscitation.
‡ $P < 0.001$, significantly different from FDP.

TABLE 5. Blood Gases, pH, and Base Deficit during and after Cardiopulmonary Resuscitation (CPR) from Hypoxemia-induced Cardiac Arrest in Rabbits Treated with FDP, Glucose, or Normal Saline*

Time of Measurement	Pa_{O_2} (mmHg)			Pa_{CO_2} (mmHg)			pH			Base Deficit (mEq/l)		
	F	G	S	F	G	S	F	G	S	F	G	S
After 5 min of CPR	149 ± 33	174 ± 45	232 ± 45	34 ± 6	36 ± 4	18 ± 5	6.96 ± 0.05	7.25 ± 0.03§	7.28 ± 0.06§	-21 ± 3	-11 ± 1‡	-16 ± 2
2 min after NaHCO₃	191 ± 51	207 ± 46	260 ± 52	39 ± 5	42 ± 6	28 ± 8	7.06 ± 0.04	7.32 ± 0.04§	7.33 ± 0.07‡	-17 ± 2	-3 ± 1§	-10 ± 3†
5 min after resuscitation	323 ± 54	333 ± 103	410 ± 18	34 ± 5	33 ± 9	21 ± 7	7.03 ± 0.06	7.33 ± 0.06	7.36 ± 0.15	-19 ± 3	-8 ± 1	-12 ± 2

Values are means ± 1 SEM.
Five minutes after resuscitation n = 10 (F); n = 4 (G); and n = 2 (S). Included are the animals that could be resuscitated, even for a brief period.

† $P < 0.05$, significantly different from FDP.
‡ $P < 0.005$, significantly different from FDP.
§ $P < 0.001$, significantly different from FDP.

acid. Despite differences in the duration of hypoxemia and severity of acidosis, plasma potassium concentrations were similar in all three groups at cardiac arrest. Therefore, differences in potassium concentration cannot explain why we could resuscitate more FDP-treated rabbits.

Glucose-treated rabbits became apneic shortly after the onset of hypoxemia. Saline-treated rabbits breathed longer than glucose-treated rabbits but not as long as those given FDP. Pa_{CO_2} did not decrease as much as we expected with the level of hypoxemia and tachypnea present in our rabbits. It is possible that the barbiturate anesthesia blunted the expected increase in alveolar ventilation. Other possible reasons for the relatively high Pa_{CO_2} include increased work of breathing, cerebral depressant effects of hypoxemia, and increased anatomic dead space. Barbiturate anesthesia also may have protected against the effects of hypoxemia and cardiac arrest to some degree. This would not, however, explain our results because all three groups received the same amount of barbiturate.

FDP-treated rabbits breathed longer during hypoxemia than glucose- and saline-treated rabbits, possibly because FDP stimulated the respiratory center or because it provided a substrate that could be used by the muscles of respiration (diaphragm, intercostal muscles). This is speculative. The differences in the ability to maintain respiration throughout hypoxemia were not caused by differences in oxygenation because the per cent hemoglobin saturation and the arterial oxygen content were similar in all three groups at respiratory arrest (table 3).

Hyperglycemia worsens central nervous system damage during cerebral asphyxia and ischemia.[35-38] Our findings might, therefore, be interpreted as reflecting a detrimental effect of glucose rather than a beneficial effect of FDP. However, this is unlikely because the plasma glucose concentrations at respiratory arrest and after 7 min of resuscitation were similar in FDP- and glucose-treated rabbits. Furthermore, plasma glucose levels, although higher during resuscitation than during the control period, were

similar in both groups of rabbits. More FDP-treated rabbits were resuscitated and had better recovery of neurologic function (spontaneous ventilation, normal pupillary and eyelid reflexes) 30 min after resuscitation than glucose-treated animals, despite the fact that both groups had high plasma glucose concentrations. This suggests that FDP protects against some of the detrimental effects of hyperglycemia during hypoxemia.

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