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Myocardial Substrate Utilization in Anaphylactic Shock (39136)

JOHN J. SPITZER

Department of Physiology, Louisiana State University Medical Center, New Orleans, Louisiana 70112

It has been found that myocardial substrate utilization is altered during acute hemorrhagic hypotension (1). Similar changes have also been observed following the administration of *E. coli* endotoxin (2). Thus, it seemed of interest to investigate another form of experimental shock with regard to the utilization of substrates by the myocardium. Therefore, anaphylactic shock has been produced in dogs in order to study myocardial substrate utilization and to compare the effect of this intervention to those observed following hemorrhage or following the administration of endotoxin.

Materials and methods. The experiments were performed on eight adult mongrel dogs. The animals were sensitized with 5 ml of horse serum intravenously and at the same time a mixture of 5 ml of horse serum plus 1 ml of Freund's adjuvant subcutaneously (3). Approximately 2 to 3 weeks later the animals were deprived of food for 16 hr and anesthetized with sodium pentobarbital given intravenously initially in a dose of 30 ml/kg and throughout the experiment as a constant infusion of 4 mg/kg/hr. Following tracheostomy each animal was respired with a Harvard Respiration Pump. Arterial blood samples were obtained by introducing a catheter into the femoral artery through a side branch. A catheter was also placed via the left external jugular vein and passed into the coronary sinus by manual control through a right thoracotomy incision. The position of the catheter was verified at the end of each experiment. The arterial blood pressure was monitored in a common carotid artery. Coronary blood flow was measured by the antipyrine saturation method described by Krasnow *et al.* (4), using [^{131}I]iodoantipyrine (Abbott Laboratories, Illinois). Cardiac output was determined by the dye dilution method (5).

An infusion of albumin-bound [1-^{14}C]palmitic acid was started at least 90 min prior to the first control blood sample and was continued throughout the experiment. After control blood samples (arterial and coronary sinus blood samples taken simultaneously), 5 ml of horse serum was injected intravenously. Additional pairs of blood samples were taken approximately 15, 60, and 120 min after the challenging dose of horse serum. With each pair of blood samples, measurements of coronary blood flow and cardiac output were carried out. No anticoagulant was used in the animals.

Each blood sample was anticoagulated *in vitro* with heparin and kept and handled in the cold. FFA, [^{14}C]FFA, lactate, glucose, oxygen, CO_2, and $^{14}CO_2$ were estimated as described previously (2). Both hematocrit and pH examinations were also performed on the arterial blood.

The following calculations were performed utilizing the experimental data (6):

(1) FFA flux or total body FFA turnover (μmole/min)

$$= \frac{\text{rate of palmitate } - \text{ }^{14}\text{C infusion (dpm/min)}}{\text{FFA}_a\text{SA (dpm/}\mu\text{mole)}}$$

(2) Myocardial O_2 consumption (μmole/min·100 g)

$$= \{O_{2a} - O_{2v}\ (\mu\text{mole/ml})\} \times \text{CSBF (ml/min·100 g)}$$

(3) Myocardial FFA oxidation (μmole/min·100 g)

$$= \frac{^{14}CO_{2v} - {}^{14}CO_{2a}\ (\text{dpm/ml})}{\text{FFA}_a\text{SA (dpm/}\mu\text{mole)}} \times \frac{\text{CSPF (ml/min·100 g)}}{1 - (\text{hematocrit}/100)}$$

(4) Myocardial lactate uptake (μmole/min·100 g)

$$= \{\text{lactate}_a - \text{lactate}_v\ (\mu\text{mole/ml})\} \times \text{CSBF (ml/min·100 g)}$$

(5) Percentage of CO_2 production from FFA

$$= \frac{\text{myocardial FFA oxidation} \times 17\ (\mu\text{mole/min·100 g})}{\{CO_{2v} - CO_{2a}\ (\mu\text{mole/ml})\} \times \text{CSBF (ml/min·100 g)}} \times 100$$

(6) Percentage of CO_2 production from lactate

$$= \frac{\text{myocardial lactate uptake} \times 3\ (\mu\text{mole/min·100 g})}{\{CO_{2v} - CO_{2a}\ (\mu\text{mole/ml})\} \times \text{CSBF (ml/min·100 g)}} \times 100.$$

Subscripts a and v represent arterial and coronary sinus plasma or blood. Statistical significance was determined using the Student's *t* tests.

Results. The hemodynamic changes during anaphylactic shock are shown in Table I. Mean arterial blood pressure decreased by almost 50% early after the challenging dose of horse serum and gradually returned towards normal in the course of 2 hr. The heart rate showed only a small change. Cardiac output decreased markedly and stayed depressed throughout the 2 hr of observation. Hematocrit increased and pH decreased significantly.

Alterations in myocardial FFA metabolism are shown in Table II. Myocardial blood flow decreased only transiently while arterial FFA concentration remained unchanged. Thus, the delivery of FFA to the myocardium was not significantly altered. Nor was the extraction fraction of FFA changed significantly throughout the experiment. However, myocardial FFA oxidation decreased significantly both 15 and 60 min after challenge. Total body FFA flux decreased considerably during the same two time periods.

Arterial lactate concentration increased significantly throughout the experimental period (Table III). Lactate extraction by the myocardium was not significantly altered, however myocardial lactate uptake

TABLE I. HEMODYNAMIC CHANGES DURING ANAPHYLACTIC SHOCK (N = 8).

		Change (mean ± SEM)		
	Control	5–15 min after challenge	35–65 min after challenge	70–130 min after challenge (N = 6)
Mean arterial blood pressure (mm Hg)	110 ± 10	−58 ± 10[a]	−30 ± 10[a]	−18 ± 13
Heart rate (per min)	163 ± 8	−24 ± 10[b]	−15 ± 9	−13 ± 9
Cardiac output (ml/min)	2572 ± 422	−1117 ± 400[b]	−894 ± 219[a]	−878 ± 246[a]
Hematocrit (%)	41.2 ± 2.8	+2.9 ± 2.0	+5.2 ± 1.5[a]	+3.3 ± 1.6[b]
pH	7.43 ± 0.01	−0.08 ± 0.05	−0.17 ± 0.04[a]	−0.11 ± 0.03[a]

[a] $P < 0.01$.
[b] $P < 0.05$.

TABLE II. CHANGES IN MYOCARDIAL FFA METABOLISM DURING ANAPHYLACTIC SHOCK (N = 8).

		Change (Mean ± SEM)		
	Control	5–15 min after challenge	35–65 min after challenge	70–130 min after challenge (N = 6)
Myocardial blood flow (ml/min·100 g)	103 ± 11	−27 ± 9[a]	−15 ± 9	−4 ± 15
Arterial FFA (μmole/ml)	0.587 ± 0.113	+0.027 ± 0.040	−0.028 ± 0.081	+0.076± 0.047
FFA extraction (%)	45.4 ± 3.5	+4.4 ± 7.0	−10.8 ± 7.8	−3.6 ± 8.1
FFA oxidation (μmole/min·100 g)	29.7 ± 9.0	−11.9 ± 5.4[b]	−17.0 ± 8.3[b]	−9.3 ± 12.8
Total body FFA Flux (μmole/min)	533 ± 155	−243 ± 99[b]	−205 ± 80[b]	−163 ± 95

[a] $P < 0.01$.
[b] $P < 0.05$.

TABLE III. CHANGES IN MYOCARDIAL LACTATE METABOLISM AND ARTERIAL GLUCOSE CONCENTRATION DURING ANAPHYLACTIC SHOCK (N = 8).

		Change (mean ± SEM)		
	Control	5–15 min after challenge	35–65 min after challenge	70–130 min after challenge (N = 6)
Arterial lactate (μmole/ml)	1.02 ± 0.18	+1.98 ± 0.32[a]	+2.4 ± 0.60[a]	+1.38 ± 0.50[b]
Lactate extraction (%)	37.2 ± 6.1	−4.9 ± 3.3	−0.1 ± 2.5	−5.5 ± 5.4
Lactate uptake (μmole/min·100 g)	36.9 ± 7.3	+43.4 ± 13.0[a]	+50.3 ± 18.2[b]	+22.0 ± 9.7[b]
Arterial glucose (μmole/ml)	6.8 ± 0.5	+2.0 ± 0.8[b]	−0.4 ± 0.6	−0.7 ± 0.6

[a] $P < 0.01$.
[b] $P < 0.05$.

increased markedly and the changes were significant throughout the period of the experiment. Arterial glucose concentration increased only during the early time period.

Discussion. Substrate utilization by the myocardium was studied following the production of anaphylactic shock. The major changes observed under these conditions included the decreased oxidation of FFA by the myocardium and the increased uptake of lactate by this organ. These changes were reminiscent of those obtained during the development of two other experimentally produced forms of shock: posthemorrhagic hypotension (1) and administration of *E. coli* endotoxin (2). Changes observed during anaphylaxis particularly closely correlated with the endotoxic condition, the only difference being that anaphylactic shock in the dog appears to have a short duration and reversal to control conditions occurred faster than following endotoxin administration. It is noteworthy that myocardial blood flow underwent only relatively small changes and arterial FFA concentration did not change significantly throughout the experiments. Since FFA oxidation decreased markedly, this indicated that the usually observed correlation between arterial FFA concentration and FFA oxidation was not present under these experimental conditions. Arterial lactate concentrations increased markedly following the production of anaphylactic shock, which was accompanied by a greatly increased lactate uptake by the myocardium. It may be seen in Table IV that the calculated contribution of FFA to the oxidative metabolism of the myocardium was 76% under control conditions and it diminished considerably during the height of the anaphylactic shock (35–65 min after the challenging dose). Lactate contributed 23% to myocardial oxidative metabolism during control conditions and this contribution increased considerably at the height of anaphylactic shock.

TABLE IV. FRACTIONAL CONTRIBUTION OF FFA AND LACTATE TO MYOCARDIAL ENERGY UTILIZATION (N = 8).[a]

		Change		
	Control	5–15 min after challenge	35–65 min after challenge	70–130 (N = 6) min after challenge
CO_2 production due to:				
FFA oxidation	76	48	38	60
Lactate uptake	23	66	62	43

[a] Since these are calculated (rather than experimentally determined) variables only mean values are presented in table.

In conclusion, the data obtained in anaphylactic shock indicate that myocardial substrate utilization is altered under these conditions. Fatty acid oxidation by the myocardium decreased considerably and lactate uptake increased markedly. These changes are quite similar to those observed previously in two other experimentally produced shock models, namely, hemorrhagic and endotoxic shock.

Summary. Changes in myocardial substrate utilization were studied in anesthetized dogs following the production of anaphylactic shock. Mean arterial blood pres-

sure, cardiac output, and pH decreased significantly during this form of shock. Myocardial FFA oxidation was greatly diminished especially within the first hour following challenge and lactate uptake more than doubled during the same time. Thus, it is concluded that myocardial substrate utilization shifted away from FFA and towards lactate during anaphylactic shock and these changes resembled those observed following an acute, severe hemorrhage, or the administration of *E. coli* endotoxin.

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