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Contract N00014-76-C-0229

Project NR 105-516

TECHNICAL REPORT NO. 111

MYOCARDIAL SUBSTRATE UTILIZATION IN EXPERIMENTAL SHOCK

J. J. Spitzer and L. B. Hinshaw

Prepared for Publication

in

Circulatory Shock

Department of Physiology,
Louisiana State University Medical Center,
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INTRODUCTION

It has been demonstrated by numerous investigations that under control postprandial conditions the myocardium may utilize a variety of substrates. Quantitatively, the most important of these are fatty acids and lactate. Under control conditions close to two-thirds of the myocardial energy is derived from oxidation of free fatty acids (FFA) and about one-third from the utilization of lactate. Since the arterial concentration of several metabolites changes during shock, and because of the dependence of myocardial substrate utilization on arterial concentration, it seemed desirable to study the alterations in myocardial substrate utilization during experimentally produced shock.

The results obtained in several shock models are summarized in this presentation. The following interventions were utilized to produce shock-like conditions experimentally: (a) administration of an LD_{90} Escherichia coli endotoxin; (b) acute severe hemorrhage, (c) anaphylactic shock caused by horse serum administration, (d) severe hypotension caused by physostigmine infusion, (e) hyperlactacidemia caused by lactate infusion, and (f) prolonged hypoperfusion of the coronary arteries.

MATERIALS AND METHODS

Dogs anesthetized with sodium pentobarbarbital were used for all of the studies. In all experiments (with the exception of the coronary hypoperfusion studies) a systemic artery and the coronary sinus were catheterized for simultaneous blood sampling (1). Continuous infusion of albumin-bound, [1-^{14}C] palmitate was administered 60 to 90 min before and throughout the experimental procedure. No anticoagulant was employed in the animals (with

the exception of the coronary hypoperfusion studies). By simultaneously sampling arterial and coronary sinus blood and determining coronary sinus blood flow (by the [^{125}I] iodoantipyrine method (2)) the uptake and oxidation of FFA and myocardial removal of lactate and oxygen were determined (1).

Details of the methodology dealing with the endotoxin experiments, hemorrhagic hypotension, lactate infusion, and the coronary hypoperfusion studies have already been published (3-6). Anaphylaxis was produced in dogs by intravenous injection of horse serum which followed by 3 weeks the sensitization of the animals with horse serum. Physostigmine was infused intravenously and the dosage was adjusted to produce approximately 50% decrease of the mean arterial blood pressure. Details of the latter two groups of studies will be published.

RESULTS AND DISCUSSION

Administration of E. coli Endotoxin

After the administration of E. coli endotoxin in anesthetized dogs the following hemodynamic changes were obtained: mean arterial blood pressure decreased markedly (by 45%), heart rate decreased, and coronary sinus blood flow showed a tendency to decrease (Table 1). At the same time arterial FFA concentration did not change significantly, whereas the extraction ratio (E) $\left(\frac{\text{arteriovenous concentration}}{\text{arterial concentration}} \times 100\right)$ decreased significantly. Myocardial FFA uptake and oxidation decreased (Table 2). During endotoxic shock the arterial lactate concentration was markedly elevated, lactate extraction ratio was decreased, and lactate removal by the myocardium was significantly increased (Table 3). Thus, the major changes can be summarized by stating that the contribution of FFA oxidation to myocardial oxidative metabolism decreased and the contribution of lactate increased after the administration of E. coli endotoxin (Table 4). At the same time

TABLE 1. Hemodynamic changes after E. coli endotoxin (n=6)[a]

	Control[b]	Change after[c] 100-140 min	Change after[c] 170-250 min
Mean arterial blood pressure (mm Hg)	122 ±6	-57[d] ±6	-35[d] ±11
Heart rate (beats/min)	201 ±10	-28[e] ±11	-38[d] ±12
Coronary sinus blood flow (ml/100 g · min)	106 ±11	-15 ±9	-16 ±11

[a] Data reproduced from Spitzer et al. (3) by courtesy of the American Journal of Physiology.
[b] Mean ± SE.
[c] Mean difference ± SE.
[d] $p<0.01$.
[e] $p<0.05$.

TABLE 2. Changes in myocardial FFA metabolism after E. coli endotoxin (n=6)[a]

	Control[b]	Change after[c] 100-140 min	Change after[c] 170-250 min
Arterial FFA (μmole/ml)	0.659 ±0.093	-0.001 ±0.107	0.001 ±0.128
FFA E%	53.0 ±4.6	-19.3[d] ±4.8	-20.2[d] ±2.7
FFA uptake (μmole/100 g · min)	23.5 ±4.1	-11.0[d] ±3.4	-12.3[d] ±1.8
FFA oxidation (μmole/100 g · min)	19.3 ±2.5	-13.4 ±3.6	-7.7 ±4.6

[a] Data reproduced from Spitzer et al. (3) by courtesy of American Journal of Physiology.
[b] Mean ± SE.
[c] Mean difference ± SE.
[d] $p<0.01$.

TABLE 3. Changes in myocardial lactate uptake after E. coli endotoxin (n=6)[a]

	Control[b]	Change after[c] 100-140 min	Change after[c] 170-250 min
Arterial lactate (μmole/ml)	1.312 ±0.239	+3.464[d] ±0.668	+3.666[d] ±0.853
Lactate E%	37.9 ±5.9	-14.4[e] ±4.8	-16.9[d] ±5.6
Lactate uptake (μmole/100 g · min)	48.5 ±10.5	+39.3[d] ±12.6	+38.0[d] ±11.5
Arterial glucose (μmole/ml)	5.73 ±5.9	-1.51[e] ±0.56	-2.13[d] ±0.32

[a]Data reproduced from Spitzer et al. (3) by courtesy of American Journal of Physiology.
[b]Mean ± SE.
[c]Mean difference ± SE.
[d]$p<0.01$.
[e]$p<0.05$.

TABLE 4. Contributions of FFA and lactate to myocardial CO_2 production (n=6)[a]

	Control[b]	Change after[c] 100-140 min	Change after[c] 170-250 min
FFA (%)	76 ±12	-53[d] ±13	-20 ±11
Lactate (%)	30 ±4	+35[e] ±12	+34[e] ±12
Myocardial RQ	0.78 ±0.04	+0.16[e] ±0.06	+0.09 ±0.06

[a]Data reproduced from Spitzer et al. (3) by courtesy of American Journal of Physiology.
[b]Mean ± SE.
[c]Mean difference ± SE.
[d]$p<0.01$.
[e]$p<0.05$.

myocardial respiratory quotient (RQ) was significantly elevated reflecting the shift from fatty acid oxidation to lactate utilization.

It should be noted that the oxidation of FFA was directly determined from the conversion of ^{14}C-labeled CO_2. At the same time lactate uptake rather than direct oxidation was determined in these studies. Equating oxidation with the uptake of lactate by the myocardium implies the assumption that all of the lactate removed was oxidized by this organ. This seems to be the case, as shown by earlier studies of Griggs et al. (7) and also by our own unpublished observations which indicate that 92 to 97% of the lactate removed is oxidized by the myocardium.

It may be noted that after the administration of endotoxin, the arterial glucose concentration decreased. We have noted such hypoglycemia in our earlier studies (8) and it has been demonstrated subsequently by Hinshaw et al. (9) that hypoglycemia may contribute to lethality after endotoxin shock.

It is of interest to re-emphasize two additional points (3): there was no evidence of myocardial hypoxia in these investigations, and the observed alterations of myocardial substrate utilization occurred very soon after the administration of endotoxin and preceded the changes of myocardial function by several hours.

Hemorrhagic Hypotension

Changes of myocardial substrate utilization after an acute severe hemorrhage were very similar to those noted during endotoxic shock. Under these conditions the mean arterial blood pressure decreased by 45%. After hemorrhage, FFA ceased to be the major metabolite oxidized by the myocardium. The contribution of lactate to myocardial energy metabolism increased markedly (Table 5).

TABLE 5. Contributions of FFA, triglyceride fatty acid (TGFA), and lactate to myocardial CO_2 production (n=9)[a]

	Control[b]	After hemorrhage	Change[c]
FFA (%)	58.5 ±11.7	18.4	-40.1[d] ±7.9
TGFA (%)	9.1 ±2.6	2.9	-6.2 ±3.7
Lactate (%)	33.1 ±10.3	68.5	+35.4[e] ±15.3

[a]Data reproduced from Spitzer and Spitzer (4) by courtesy of American Journal of Physiology.
[b]Mean ± SE.
[c]Mean difference ± SE.
[d]$p<0.01$.
[e]$p<0.05$.

TABLE 6. Changes in myocardial lactate metabolism during anaphylactic shock (n=4)

		Change after challenge		
	Control[a]	5-15 min	35-65 min	70-130 min
Arterial lactate (μmole/ml)	0.789 ±0.216	+1.568 ±0.466	+3.227 ±0.452	+3.118 ±0.901
Lactate extraction (%)	24.3 ±3.5	+2.6 ±3.7	+0.2 ±3.6	+0.7 ±2.8
Lactate uptake (μmole/min · 100 g)	19.2 ±5.7	+27.0 ±13.8	+68.8 ±19.0	+69.0 ±31.2
Myocardial RQ	0.80 ±0.02	-0.03 ±0.06	+0.19 ±0.05	+0.15 ±0.03

[a]Mean ± SEM.

Anaphylactic Shock

This condition was evoked by a challenging dose of horse serum given intravenously to dogs that had been sensitized with the same agent 3 to 4 weeks before the experiments. In these preliminary studies (thus the small number of experiments) the hemodynamic changes were comparable with those which occurred during the other two experimental conditions, e.g., mean arterial blood pressure decreased by 43%, cardiac output by 39%. Arterial lactate concentration again increased markedly after challenge and the uptake of this metabolite by the myocardium was elevated. Myocardial RQ also increased significantly (Table 6).

Infusion of Physostigmine

A group of experiments was performed in which physostigmine was administered in sufficient quantity to decrease the arterial blood pressure by approximately 50% (the decrease in mean arterial blood pressure was 55%). Under these conditions, the metabolic alterations were very similar to those that were obtained by studying the above three models. The percentage contribution of lactate to CO_2 production increased from 27% to 75%, and the myocardial RQ also increased (Table 7).

At this point, this question may be asked: what are the possible factors responsible for the changes in myocardial substrate utilization that are common among the various shock models? At least two of these may be noted, increased arterial lactate concentration and decreased coronary perfusion. Both of these conditions were, therefore, subjected to further studies.

Hyperlactacidemia due to Lactate Infusion

When L(+)-lactate was administered intravenously into normal dogs in sufficient amounts to raise the arterial concentration markedly, it was found that the changes in myocardial substrate utilization resembled those observed

TABLE 7. Effect of physostigmine infusion on myocardial metabolism (n=9)

		Infusion	
	Control[a]	60-105 min	120-165 min
FFA oxidation (μmole/min · 100 g)	15.6 ±3.5	3.6[b] ±0.7	5.0[c] ±1.9
Lactate uptake (μmole/min · 100 g)	35.3 ±8.3	49.2 ±9.8	39.3 ±11.7
Contribution to myocardial CO_2 production by FFA%	70.8 ±13.1	44.0 ±12.8	34.2[c] ±9.6
Lactate (%)	26.5 ±5.7	75.1[b] ±7.1	49.9[c] ±10.1
Myocardial RQ	0.79 ±0.04	0.93[c] ±0.05	0.91[c] ±0.05

[a]Mean ± SEM.
[b]$p<0.01$.
[c]$p<0.05$.

Table 8. Effect of prolonged coronary hypotension on myocardial metabolism (n=10)[a]

	1st Control[b]	4 hr hypotension (change)	2nd Control[c]
FFA oxidation (μmole/min)	2.3 ±0.6	+0.5 ±1.1	4.1 ±1.3
Lactate uptake (μmole/min)	38.9 ±3.7	-20.1[c] ±4.1	31.6 ±6.3
O_2 uptake (μmole/min)	194 ±13	-56[c] ±8	195 ±14
Myocardial RQ	0.95 ±0.01	-0.06[c] ±0.02	0.87 ±0.04

[a]Data reproduced from Spitzer et al. (6) by courtesy of American Journal of Physiology.
[b]Mean ± SEM.
[c]$p<0.01$.

during experimental shock, although only minor changes in mean arterial blood pressure (-11%) were seen. The metabolic changes are seen in Figure 1 and indicate the decreased contribution of lactate utilization to myocardial CO_2 production. Myocardial RQ changes are also in accordance with these changes.

Coronary Hypoperfusion Studies

Experimentally produced hypoperfusion of the coronary vessel was the final condition investigated. For this preparation the method of Hinshaw et al. (10) was utilized in which the donor dog perfused *in vitro* the left ventricle of another dog's heart. The metabolic conditions during the control period (with afterload of 100 mmHg) were compared with those obtained during the hypoperfusion (at an afterload of 50 mmHg) for 4 hours. Studies of substrate utilization under these conditions indicated that myocardial FFA oxidation did not change significantly, although oxygen consumption, lactate utilization, and RQ decreased (Table 8). Thus, the contribution of lactate to myocardial energy metabolism decreased under these conditions.

In conclusion, these studies point out the alterations of substrate utilization by the myocardium during experimentally produced shock. These changes consisted of an increase in the importance of lactate with the simultaneous decrease of the importance of FFA as oxidizable substrates. The data further emphasize the key role that arterial lactate concentration plays in regulating substrate utilization by the myocardium.

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UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)

UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER
OKLAHOMA CITY, OKLAHOMA

2a. REPORT SECURITY CLASSIFICATION

UNCLASSIFIED

2b. GROUP

UNCLASSIFIED

3. REPORT TITLE

MYOCARDIAL SUBSTRATE UTILIZATION IN EXPERIMENTAL SHOCK

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

Technical Report

5. AUTHOR(S) (First name, middle initial, last name)

J. J. Spitzer and L. B. Hinshaw

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
19 July 1976	11	10

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
N00014-76-C-0229	111
8b. PROJECT NO. NR 105-516	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
8c.	
8d.	

10. DISTRIBUTION STATEMENT

Distribution of this report is unlimited

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
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DD FORM 1 NOV 68 1473 (PAGE 1)

S/N 0101-807-6811

Security Classification

A-31408

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