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TRACKING PLASMA LACTATE CONCENTRATION *IN VIVO* WITH A CATHETER-TIP L-LACTATE SENSOR

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Abstract

To circumvent the problems of repeated blood sampling for *in-vitro* analysis, a catheter-tip L-lactate sensor has been developed. The sensor was tested in anesthetized pigs (n=6). The sensor *in vivo* tracked the lactate concentration non-linearly, seeming to obey Michaelis-Menten kinetics. Calibration time was short, typically 1.5 min per lactate standard. Furthermore, time drift was small, typically -1.3% to -3.3% per hour of *in-vivo* use.

TRACKING PLASMA LACTATE CONCENTRATION *IN VIVO* WITH A CATHETER-TIP L-LACTATE SENSOR

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Introduction

Increased blood lactate levels occur in a variety of clinical and physiological circumstances. Lactacidemia is due most commonly to an imbalance between the metabolic needs and the oxygen supply of the tissues, and can, in most circumstances, be regarded as an index of the "anaerobic distress" of the organism. In clinical medicine, blood lactate levels are used in the diagnosis of lactic acidosis. In critically ill patients, blood lactate levels are the marker of the severity of the disease and are therefore an excellent prognostic indicator.[1] However, repeated lactate determinations represent a more reliable prognostic index than an initial value taken alone.[2] Also, changes in lactate concentration can provide an early and objective evaluation of the patient's response to therapy.

Current methods for the analysis of blood lactate concentrations require the withdrawal of blood samples from the patient at intervals, processing of the blood sample to prevent the production of lactate *in vitro* and measurement of lactate enzymatically. A finite time delay occurs between the withdrawal of the blood sample and the availability of the result (the blood lactate level at the time of the withdrawal of the blood sample). This interval may range from several minutes to several hours or longer, depending on the method used for lactate analysis and the way the laboratory's facilities are organized. A method that provides a continuous, instantaneous indication of blood lactate levels can provide vital information not now available to the clinician that can assist in accelerating and further refining the assessment of the patient's status and the efficacy of the therapeutic measures being used.

In this paper, we describe the effectiveness of a catheter-tip L-lactate sensor which is capable of tracking plasma lactate concentrations, and which could form the basis of a system which could provide such an on-line moment-to-moment index of the organism's anaerobic distress.

Sensor Preparation

Five sensors were fabricated by the method outlined by Lim.[3] This design is based upon a heart-pacing catheter with a platinum electrode and a silver/silver chloride electrode. The sensors were fabricated by covering the platinum anode with a membrane containing immobilized L-lactate oxidase. The completed sensors were stored at 6°C in the buffer solution (0 mM lactate) described in the calibration section. Before each experiment, the sensor was conditioned by polarizing it with the supporting electronics, described by Waite *et al.*,[4] while exposing it to 37°C buffer solution for at least three hours.

In-Vitro Calibration

L-Lactic acid (sodium salt) standards, with concentrations of 0, 1, 4, 7, and 10 mM, were prepared in deionized water for *in-vitro* calibration of the sensor. All standards comprised 90 mM potassium phosphate buffer (*p*H=7.40), 5.5 mM sodium benzoate, 1.3 mM Na_2EDTA, and 40 mM NaCl. All of these chemicals were obtained from Sigma Chemical Company, St. Louis, MO.

After the sensor was conditioned for a period of at least three hours and the output was adjusted to zero, the *in-vitro* calibration was performed. For the calibration, the sensor was placed in each of the standards (T=37°C), first in ascending, then in descending, order of concentration. This process was repeated. For each standard throughout the calibration, the sensor output was monitored every second until it stabilized, at which time the actual concentration, the sensor output (volts), and the elapsed stabilization time were recorded by the computer. The *in-vitro* data acquisition program recognized the stabilization point when the most recent value was within 0.1% of the average of the values from the previous 10 seconds.

Surgery and *In-Vivo* Data Collection

Six pigs, of various breeds (Table 1), weighing approximately 35 pounds each, were anesthetized by unassisted inhalation of a mixture of nitrous oxide and oxygen (1:1, v/v), containing Halothane (2-bromo-2-chloro-1,1,1,-trifluoroethane) at 1-2%. Aspirin (325 mg) was administered orally to the last four animals 12 hours before the experiment to inhibit thrombus formation on the sensor, which was noticed in the first two experiments. After the blood vessels were exposed, a calibrated lactate sensor and two heparinized Tygon cannulas were introduced into the venous circulation (Table 1). One cannula

was used for the infusion of a 20% sodium L-lactate/0.9% NaCl solution, while a second, placed in close proximity to the sensor, was used to withdraw blood samples for analysis. For additional protection against coagulation, all of the animals received a bolus injection of approximately 2000 units of sodium heparin immediately after the cannulas were in place. All of the animals, except the first, received an additional infusion of 500 units of sodium heparin every hour after a substantial clot was found on the sensor membrane in the first experiment.

Immediately after insertion of the lactate sensor, the *in-vivo* data acquisition program was started; the program recorded the sensor output every minute, in volts. Baseline blood samples were withdrawn and analyzed, with a YSI 1500 SPORT L-Lactate Analyzer. Then, with a Sage Instruments pump, infusion of the 20% lactate solution, at a rate of approximately 2.1 mL/min, was started. With the YSI analyzer, sampling and analysis of the blood continued throughout the experiment at 5- to 10-minute intervals. Lactate was infused until the concentration in the blood reached a prespecified elevated value. At this point, the infusion was stopped and the lactate concentration was allowed to fall into the baseline range. In some of the animals, the entire infusion process was repeated. At the end of the experiment, the animal was euthanized by increasing the Halothane concentration in the inspired gas and by an intravenous injection of Bio-tal (Thiamylal Sodium, 1g/10mL). The sensor was removed, rinsed, and recalibrated.

Discussion of Results

Results are shown in Figures 8-13.

F-ratios from linear regressions performed on the *in-vitro* calibration data are all highly significant ($p < 1.8*10^{-9}$). This indicates that all sensors were linearly dependent upon lactate concentration in the 0- to 10-mM range before and after the experiments; Figure 1 depicts a typical calibration curve. *In-vitro* sensor sensitivity, defined as the slope of the *in-vitro* calibration curve, ranged from 0.166 to 0.933 V/mM (Table 2). This relatively large range of sensor sensitivities necessitates the calibration of each sensor before use. The percent change in *in-vitro* sensor sensitivity, measured before and after the experiment, per hour of *in-vivo* use can be used as a measure of time drift for a given sensor. These values (Table 2) were typically negative, ranging from

-1.3 to -3.3% per hour of *in-vivo* use, with one exception; the sensitivity of sensor B107 increased 5.5% per hour of *in-vivo* use. The cause of the slight decrease in sensitivity experienced by most of the sensors can probably be attributed either to a lower rate of lactate diffusion through the membrane caused by a factor in blood that clogs the pores in the membrane or to a loss of enzyme activity, resulting from either normal denaturation of the enzyme or inhibition of the enzyme by a substance from blood. Further investigation of L-lactate oxidase inhibitors in porcine and human blood is in progress. The unexpected increase in sensitivity of sensor B107 presumably resulted from the fact that the sensor was inadvertently disconnected after the 3-hour conditioning period and only one hour was allowed for reconditioning before the experiment. Throughout the entire series of experiments, the average time that elapsed before the output stabilized in each standard, during the *in-vitro* calibration, was approximately 1.5 minutes. The stabilization times in the zero-lactate standards were excluded from this mean since a zero point is not necessary for calibration and, because the software recognized the stabilization point when the most recent value was within 0.1% of the average of the values from the previous 10 seconds, these times were long (0.1% of a value near zero is very small).

Plots of the sensor output *vs.* the whole blood lactate concentration as determined by the YSI analyzer (Figures 2-7) reveal that the sensors behaved nonlinearly *in vivo;* presumably the result of inhibition of the enzyme by a substance from blood. Thus, the linear *in-vitro* calibration curves cannot be used to convert the *in-vivo* sensor output to meaningful lactate concentrations. However, the sensor output did track (change in the same direction as) the actual lactate concentration. Since most of the plots seem hyperbolic and the sensor is enzyme-based, the Michaelis-Menten equation,

$$\text{output}=V_{max}*[\text{lactate}]/(K_m+[\text{lactate}]),$$

was fitted to the data. The Michaelis-Menten equation is useful as a model inasmuch as this system has a theoretical maximum output, V_{max}, which depends upon the amount of enzyme present in the membrane and is approached asymptotically as the substrate (lactate) concentration increases. K_m is the lactate concentration at which the output is half-maximal.[5] The Michaelis-Menten equation was fitted to the data by the non-linear regression method of Oestreicher and Pinto.[6] The 95% confidence intervals for V_{max} and K_m, which were calculated by multiplying the standard errors from the

regression program by the appropriate *t*-value (0.975, n-2 dof), are reported in Table 3. We used the Michaelis-Menten equation and the estimated values of V_{max} and K_m to represent the data graphically (Figures 2-7). The equation was solved for lactate concentration,

$$[\text{lactate}]=\text{output}*K_m/(V_{max}-\text{output}),$$

and was used to convert the *in-vivo* sensor output values to lactate concentrations. These values were then plotted against time; on the same plots are the lactate concentrations that were determined *in vitro* (Figures 8-13). The lactate values calculated from the sensor output data correlate well with the actual blood lactate values. Excluding calculated lactate values that fell outside the valid domain of the model, the maximum standard error for these data (Table 3) was 2.289 mM (12.1% of full scale). Clearly, the sensors tracked the concentration of lactate in the plasma over time. The output of some of the sensors (especially those placed near the heart) was confounded by occasional spikes. The cause of this "noise" was presumably either mechanical or electrical disturbance of the sensor caused by the activity of the heart, in the case of pigs 5 and 6, or by extreme shivering, as seen in the latter portion of the pig 3 experiment. In the future, sampling of the sensor output at a higher frequency and recording the mean of several values rather than sampling only one value per time interval should solve this problem, allowing the sensor to be used in almost any situation. A recursive digital low-pass filter,[7] which was designed to emulate a second-order Butterworth analog filter with a corner frequency of 0.1 times the sampling rate (1 min^{-1}), was used to attenuate spikes in the data.

Summary

A catheter-tip L-lactate sensor, which is capable of tracking plasma lactate concentrations *in vivo*, has been developed Many of the characteristics affecting the ultimate clinical usefulness of this sensor have been investigated, and the results seem promising. Time drift is small (typically between -1.3 and -3.3% per hour of *in-vivo* use) and may be improved by applying insight gained from the inhibition experiments, which we are conducting at this time. Calibration time is short (approximately 1.5 min required for stabilization in each non-zero standard) making bedside calibration of the sensors feasible. Previously published biocompatibility data indicate that the components of the sensors are not cytotoxic and are suitable for use *in vivo*.[4] Use of the

results of our enzyme-inhibitor-in-plasma experiments may allow *in-vitro* performance of the sensors to mimic *in-vivo* nonlinearity (perhaps by exposing the sensor to isolated inhibitor(s) prior to calibration), thereby simplifying (or eliminating) *in-vivo* calibration. The results of separate *in-vitro* experiments, which will be published as part of another manuscript, indicate that the effects of other variables, such as temperature, *p*H, oxygen tension, and ionic strength, are small in the physiological range when compared with the effect of lactate concentration. A microprocessor-based bedside analyzer has been constructed to facilitate calibration and subsequent lactate determination. Further investigation of non-destructive sterilization techniques for the sensors is in progress.

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6. Oestreicher EG, Pinto GF. Pocket computer program for fitting the Michaelis-Menten equation. Comput Biol Med. 1983;13:309-15.

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Table 1.

Pig no.	Breed	Aspirin (mg)	Sodium heparin (units)	Sensor no.	Sensor point of insertion	Withdrawal cannula point of insertion	Sensor and withdrawal cannula location	Infusion cannula location
1	Yorkshire	0	2000	B107	Left femoral vein	Right femoral vein	Inferior vena cava	Right cephalic vein
2	Yorkshire	0	2000 + 500/hr	B103	Left femoral vein	Right femoral vein	Inferior vena cava	Right cephalic vein
3	Duroc/ Hampshire	325	2000 + 500/hr	B106	Left femoral vein	Right femoral vein	Inferior vena cava	Right cephalic vein
4	Yorkshire	325	2000 + 500/hr	B106	Right jugular vein	Right jugular vein	* Superior vena cava	Left femoral vein
5	Duroc	325	2000 + 500/hr	B109	Right jugular vein	Right jugular vein	** Right atrium	Left cephalic vein
6	Hampshire	325	2000 + 500/hr	B108	Right jugular vein	Right jugular vein	** Right atrium	Left cephalic vein

** These sensors were advanced into the jugular vein until they reached an obstruction. The distance that they were inserted was consistent with our estimate of the distance to the heart. The low signal-to-noise ratio reinforces the conclusion that these sensors were in the right atrium.

* Although the exact position of the tip of this sensor was not known, the relatively high signal-to-noise ratio suggests that it was not in the heart. Since this sensor was advanced a lesser distance than the other jugular sensors and it did not strike an obstruction, we concluded it was in the superior vena cava.

Table 2.

Sensor no.	*In-vitro* sensor sensitivity before test (V/mM)	Pig no.	Total time used *in vivo* (min)	*In-vitro* sensor sensitivity after test (V/mM)	% change *in-vitro* sensitivity/ hour used *in vivo*
B107	0.166	1	203	0.197	5.5
B103	0.362	2	247	0.339	-1.5
B106	0.363	3	239	0.315	-3.3
B106	0.325	4	335	0.301	-1.3
B109	0.667	5	362	0.568	-2.5
B108	0.933	6	300	0.847	-1.9

Table 3.

Pig no.	Sensor no.	95% CI for Vmax, theoretical maximum output (V)	95% CI for Km, lactate concentration @ 1/2 Vmax (mM)	Standard error (mM)
1	B107	0.960 ± 0.063	1.798 ± 0.384	0.503
2	B103	1.449 ± 0.159	4.907 ± 0.943	0.971
3	B106	3.893 ± 0.851	8.139 ± 2.131	1.257
4	B106	3.194 ± 0.302	6.400 ± 1.163	1.720
5	B109	2.966 ± 0.325	3.022 ± 0.882	2.289
6	B108	4.039 ± 0.444	2.161 ± 0.611	1.662

Figure Legends

Figure 1: Sample *in-vitro* calibration curve.

Figure 2: *In-vivo* response curve for sensor B107 while in pig #1. Filled squares are sensor output observations (V) plotted against the corresponding blood lactate concentrations (mM) as determined by the YSI analyzer *in vitro*. The solid line is the best-fit Michaelis-Menten curve for the sensor output values. Dashed lines represent the 95% confidence interval for the Michaelis-Menten curve.

Figure 3: *In-vivo* response curve for sensor B103 while in pig #2. See Figure 2 legend for explanation of symbols.

Figure 4: *In-vivo* response curve for sensor B106 while in pig #3. See Figure 2 legend for explanation of symbols.

Figure 5: *In-vivo* response curve for sensor B106 while in pig #4. See Figure 2 legend for explanation of symbols.

Figure 6: *In-vivo* response curve for sensor B109 while in pig #5. See Figure 2 legend for explanation of symbols.

Figure 7: *In-vivo* response curve for sensor B108 while in pig #6. See Figure 2 legend for explanation of symbols.

Figure Legends (continued)

Figure 8: *In-vivo* tracking curve for sensor B107 while in pig #1. Empty squares are blood lactate concentrations (mM) as determined by the YSI analyzer *in vitro*. The dotted line is the lactate concentration (mM) calculated from the sensor output voltage using the Michaelis-Menten equation (solved for lactate concentration) and the estimated parameters from the corresponding best-fit curve shown in Figures 2-7.

Figure 9: *In-vivo* tracking curve for sensor B103 while in pig #2. See Figure 8 legend for explanation of symbols.

Figure 10: *In-vivo* tracking curve for sensor B106 while in pig #3. See Figure 8 legend for explanation of symbols.

Figure 11: *In-vivo* tracking curve for sensor B106 while in pig #4. See Figure 8 legend for explanation of symbols.

Figure 12: *In-vivo* tracking curve for sensor B109 while in pig #5. See Figure 8 legend for explanation of symbols.

Figure 13: *In-vivo* tracking curve for sensor B108 while in pig #6. See Figure 8 legend for explanation of symbols.

FIG. 1

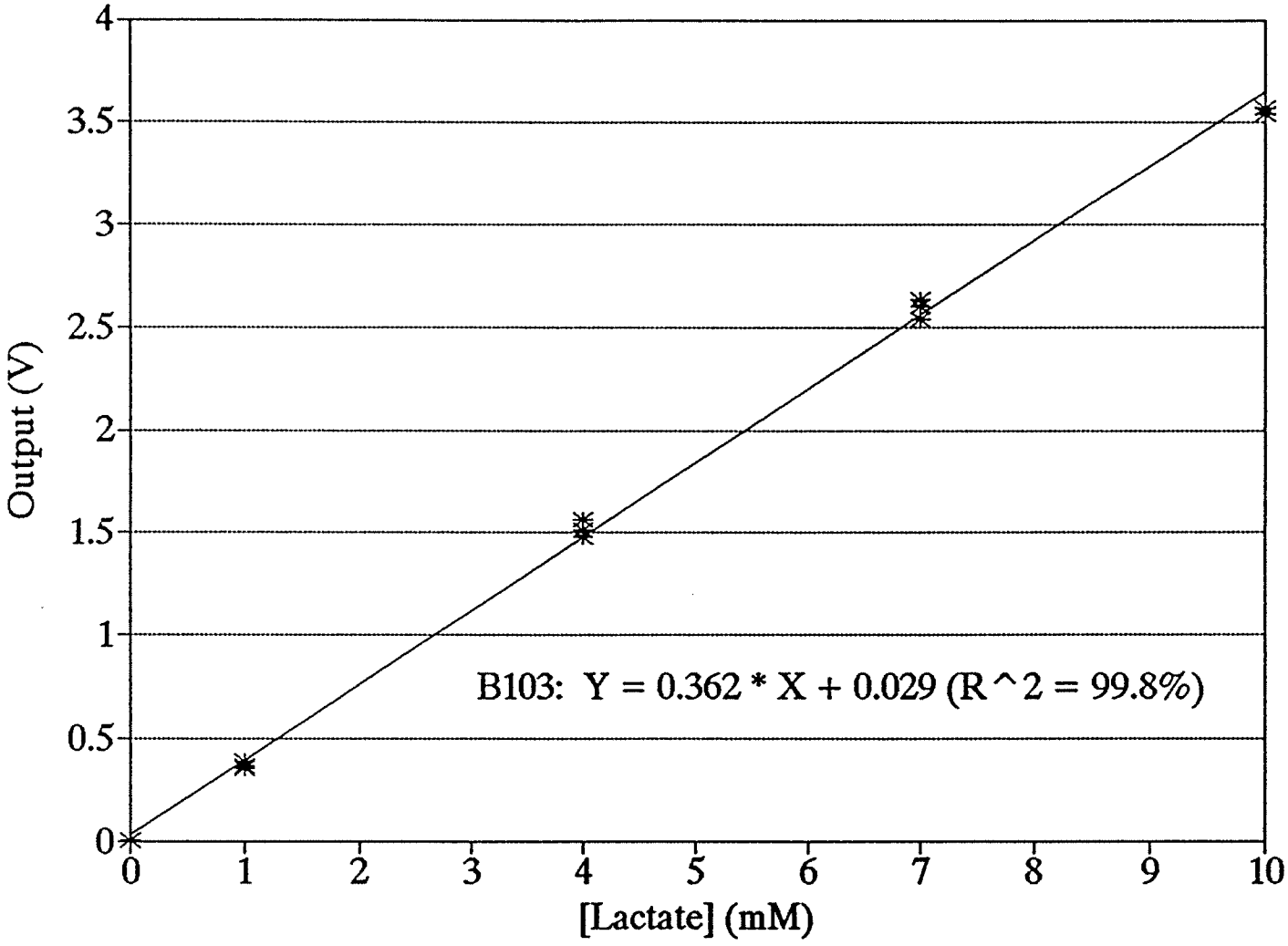
Output (V)
4
3.5
3
2.5
2
1.5
1
0.5
0
0
1
2
3
4
5
6
7
8
9
10
[Lactate] (mM)
B103: Y = 0.362 * X + 0.029 (R^2 = 99.8%)

FIG. 2

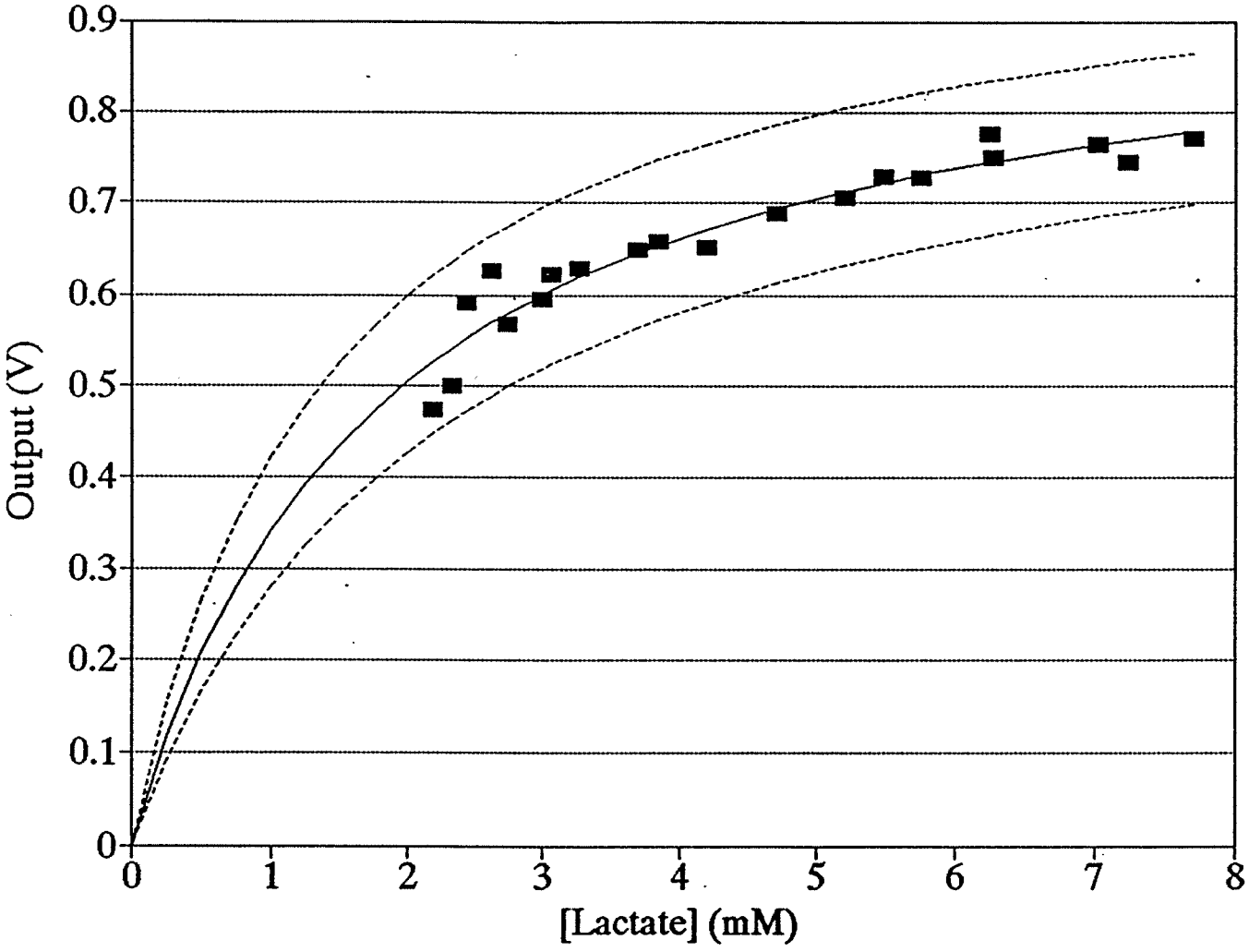

FIG. 3

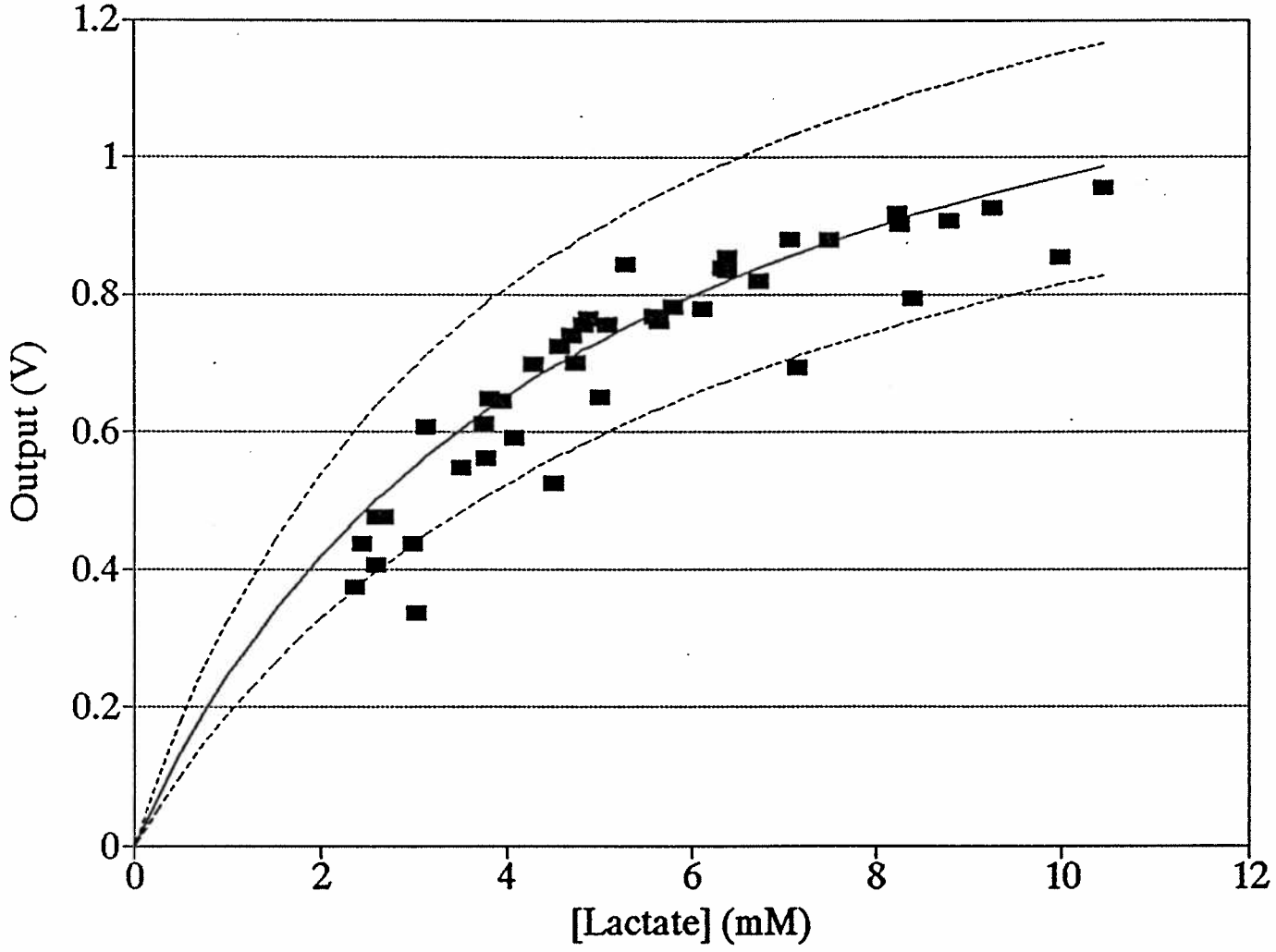

FIG. 4

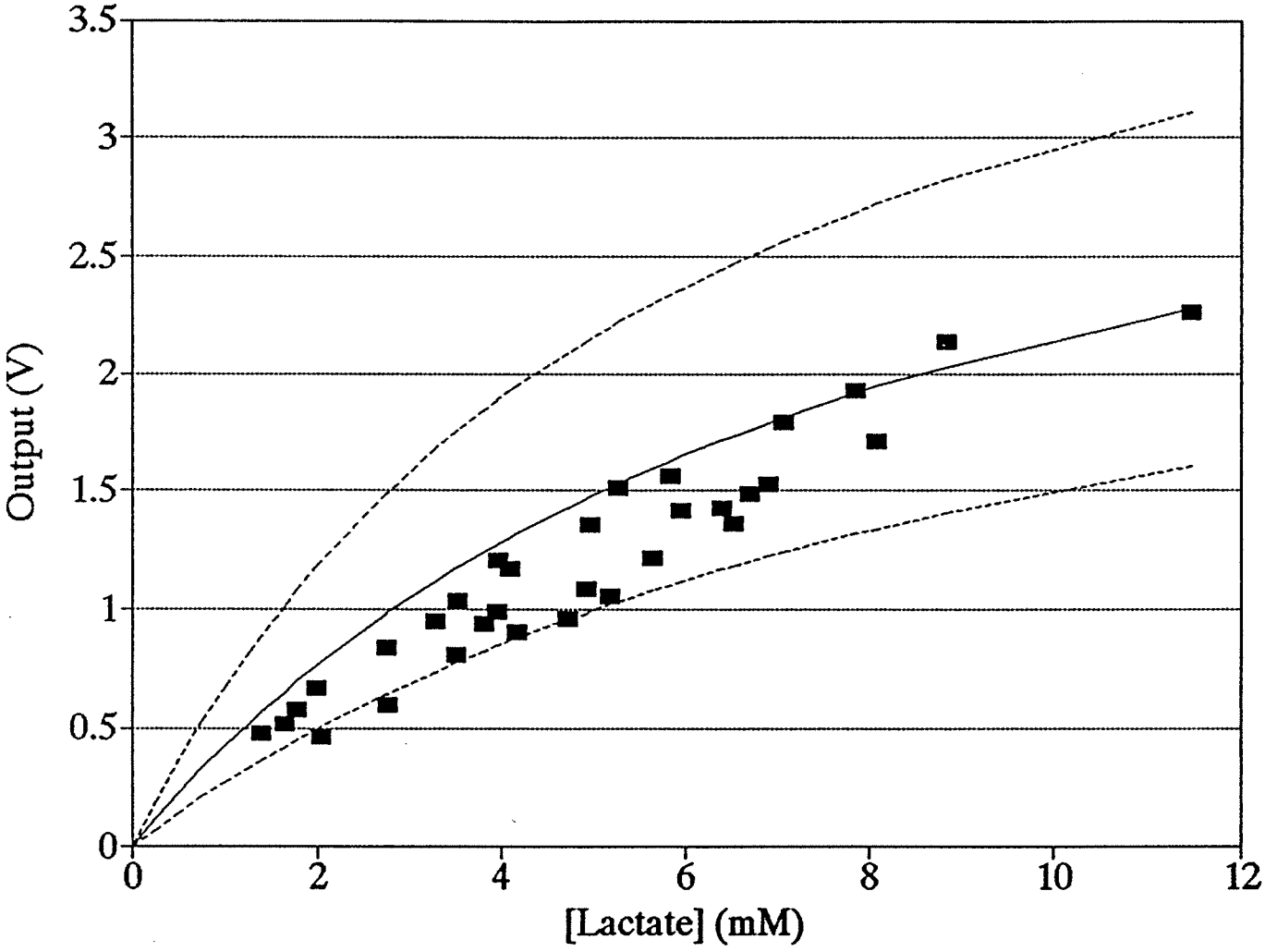

FIG. 5

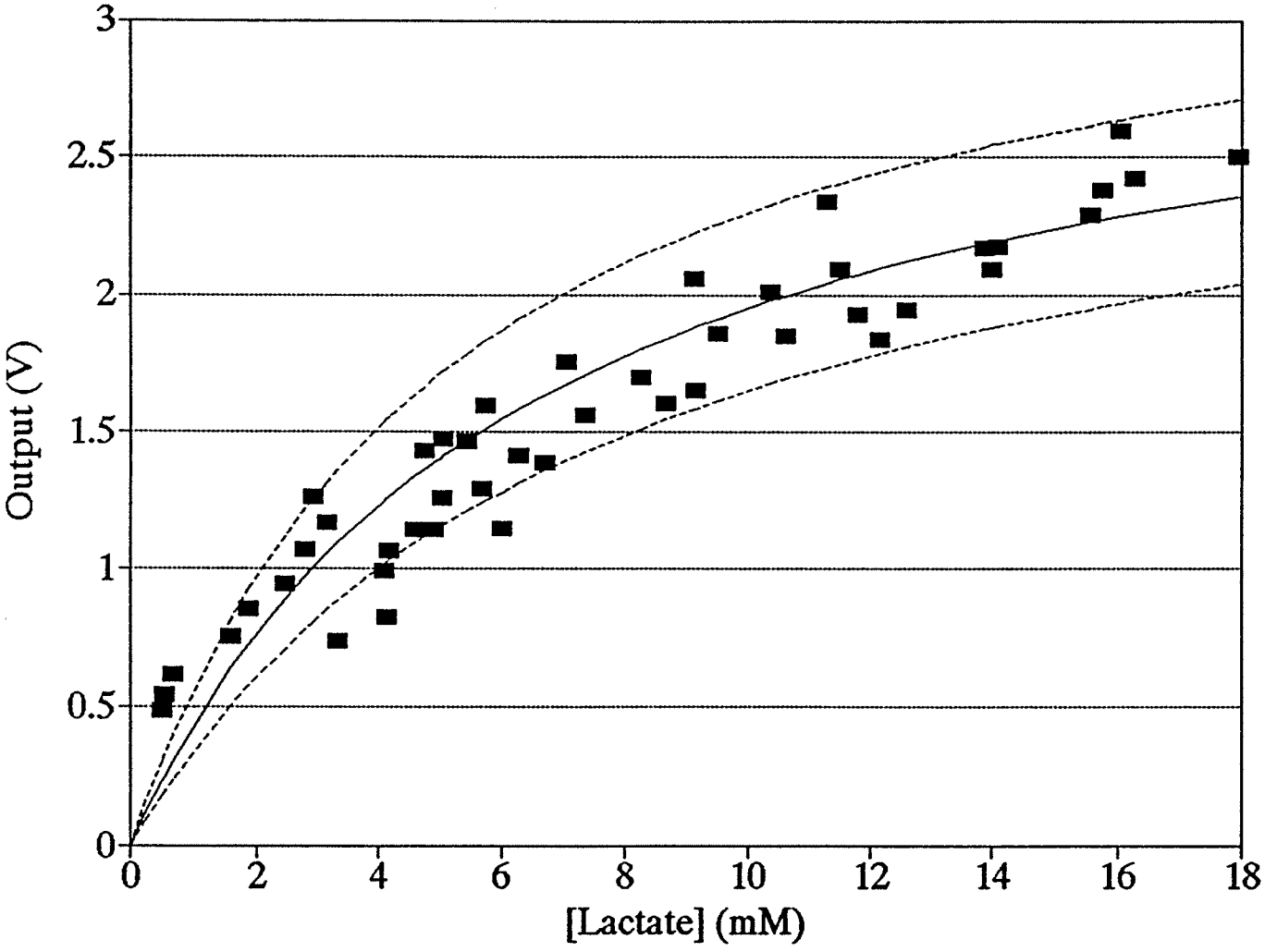

FIG. 6

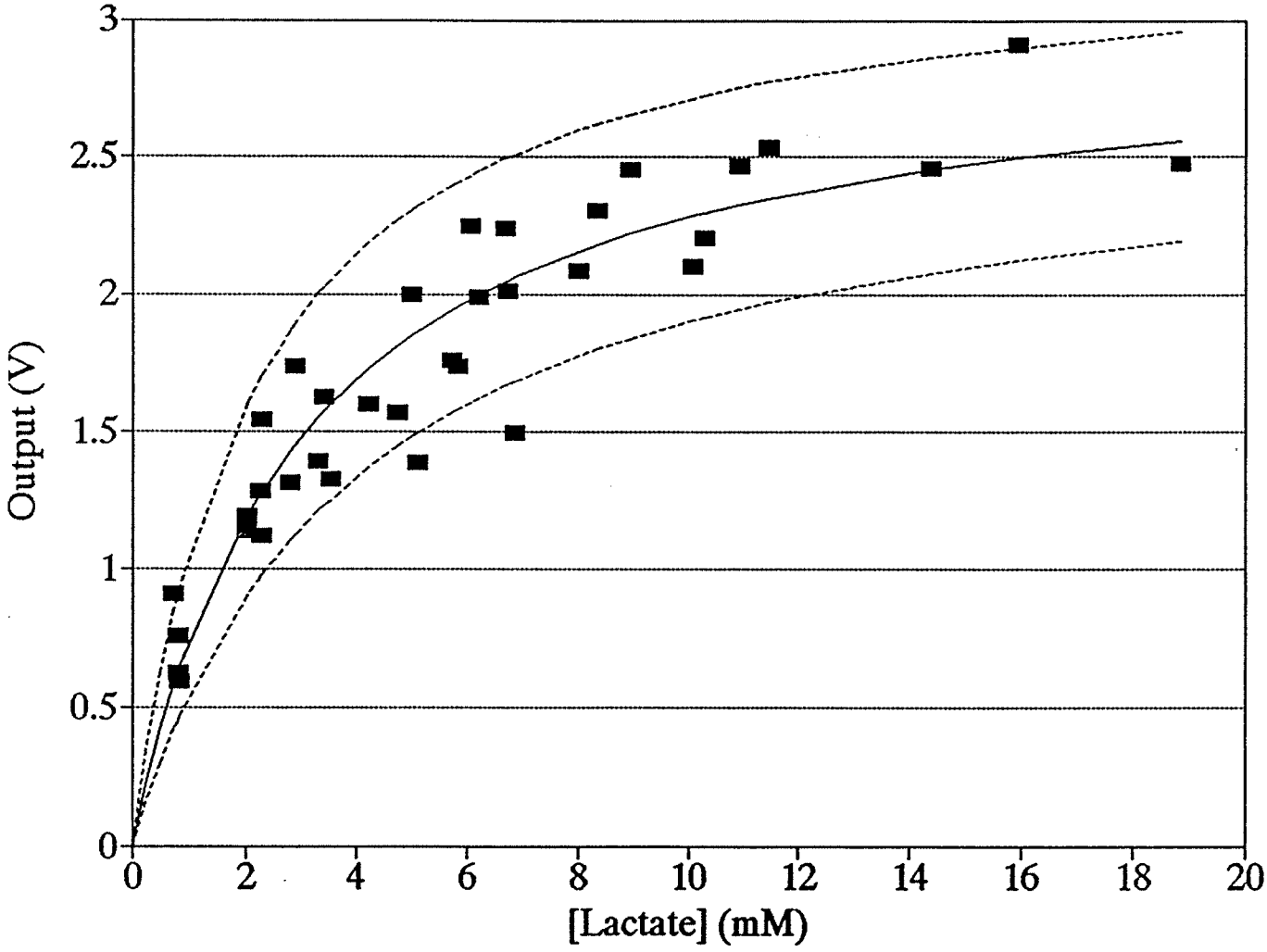

FIG. 7

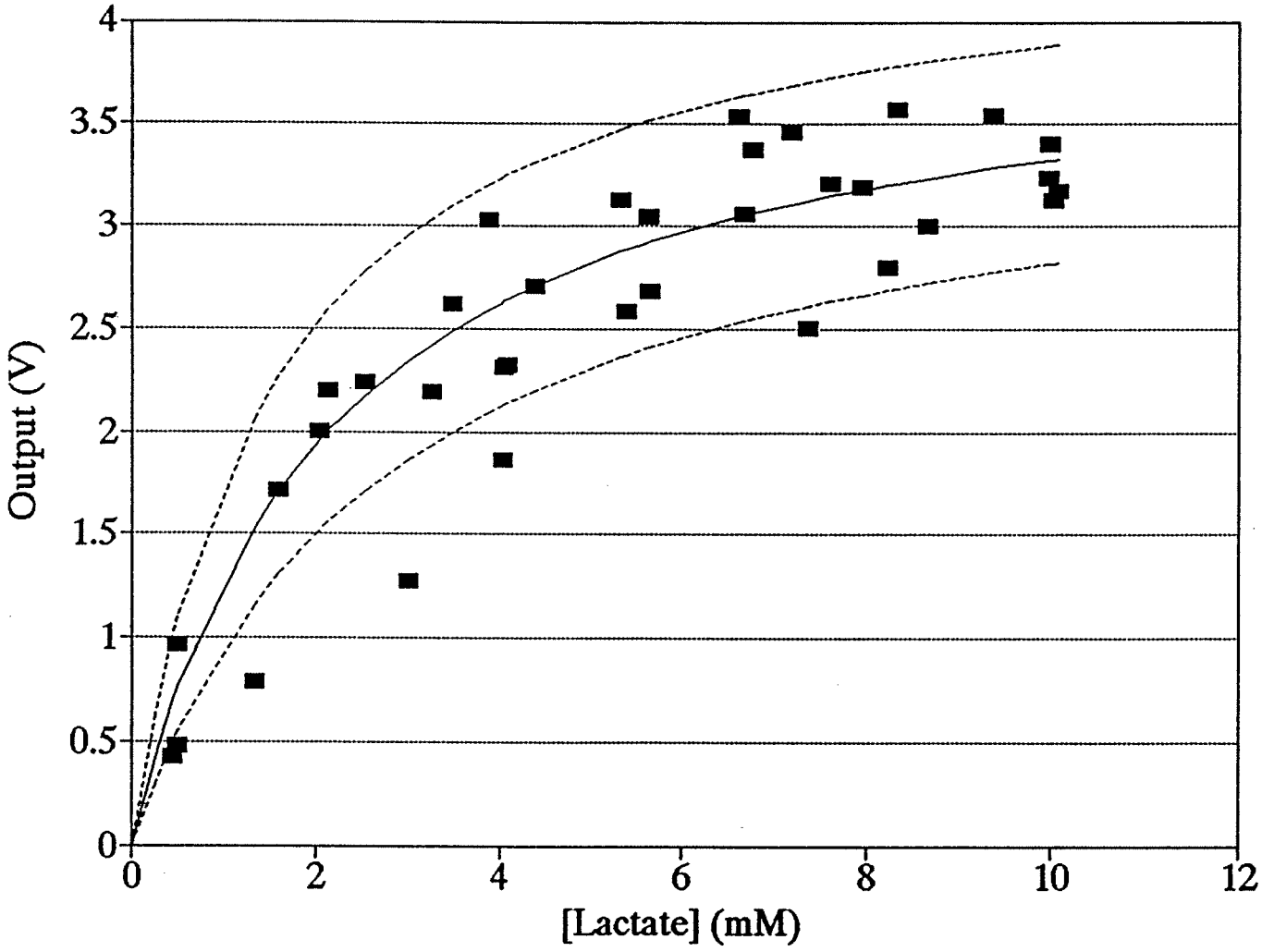

FIG. 8

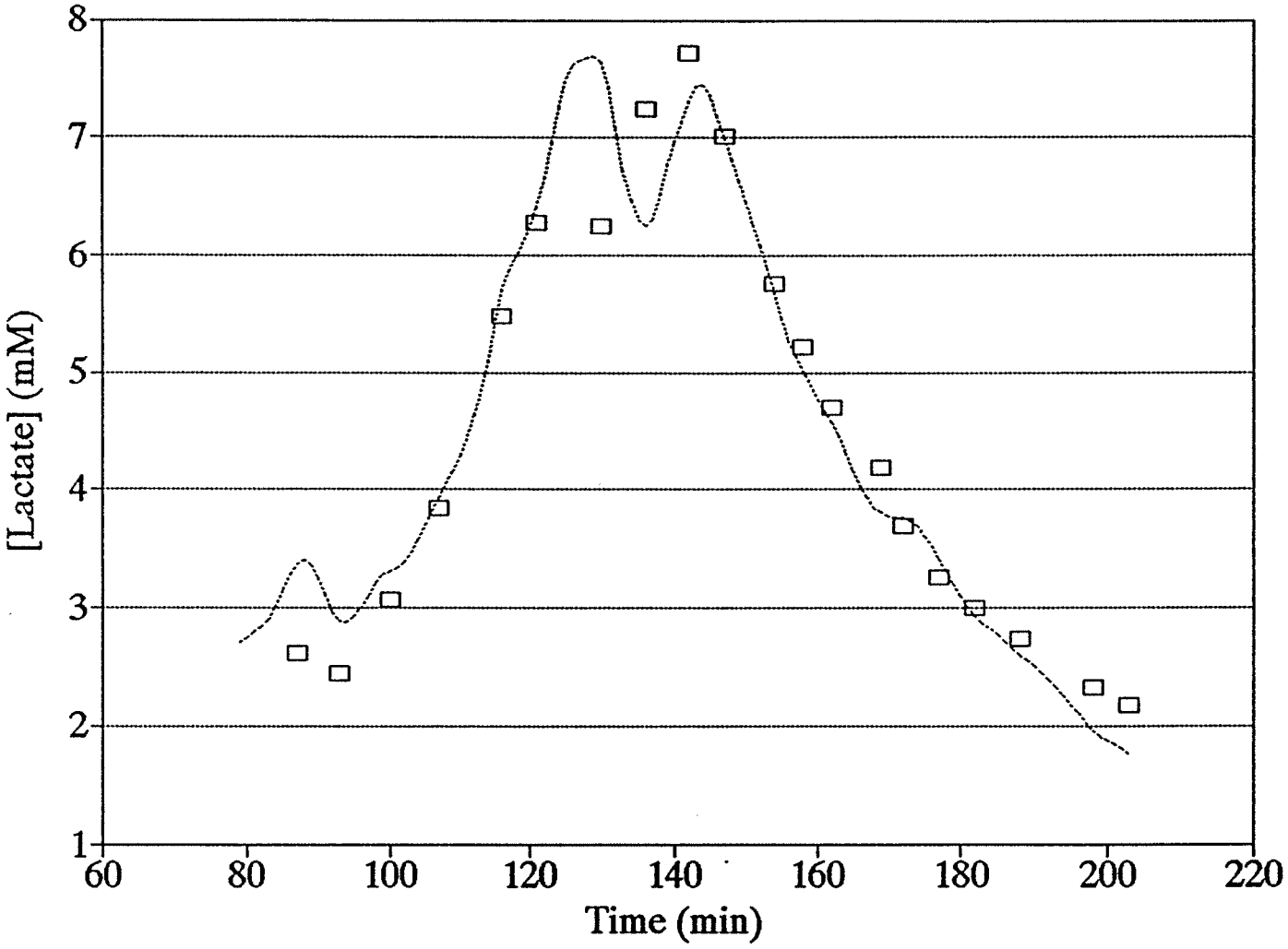

FIG. 9

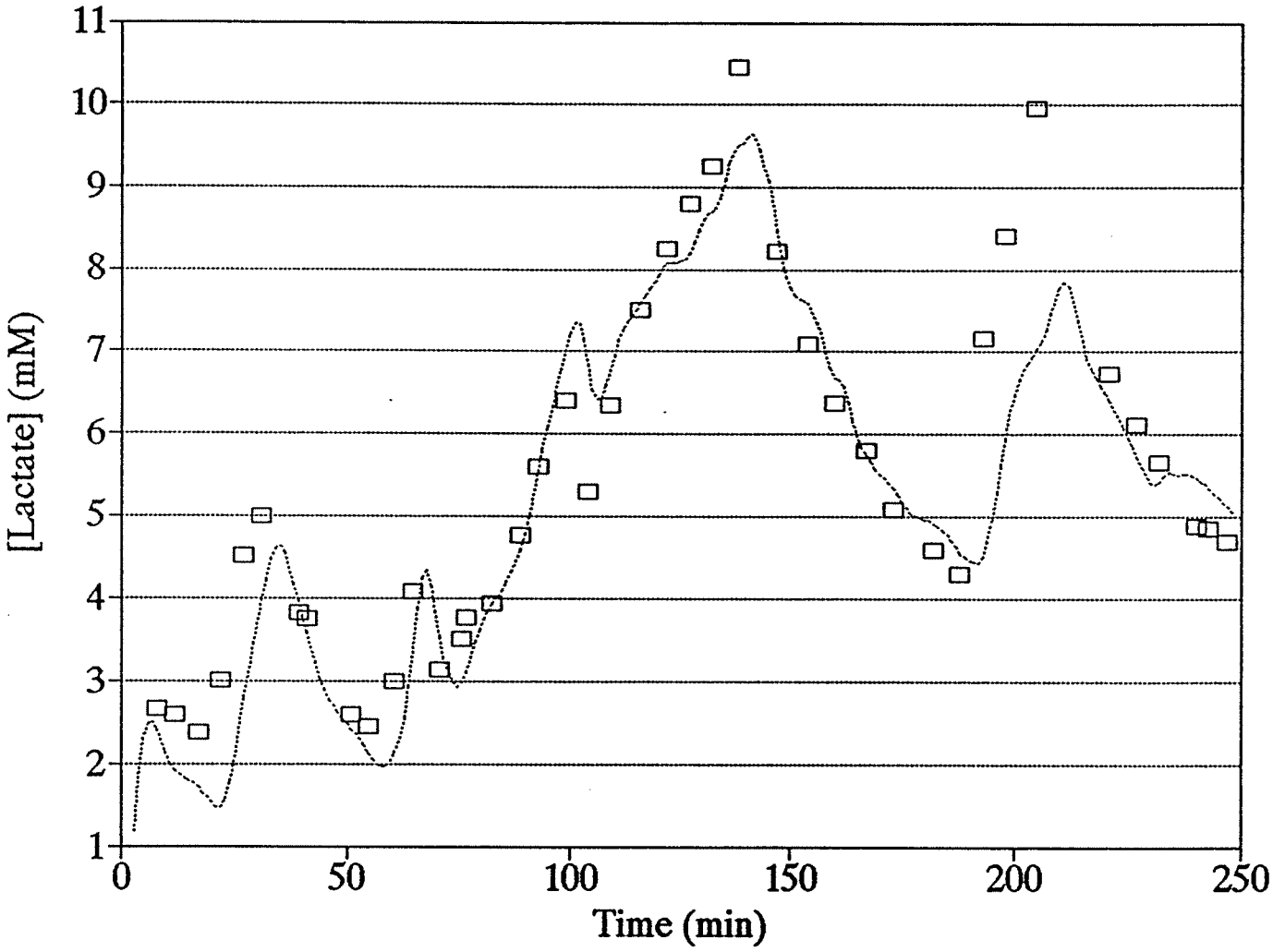

FIG. 10

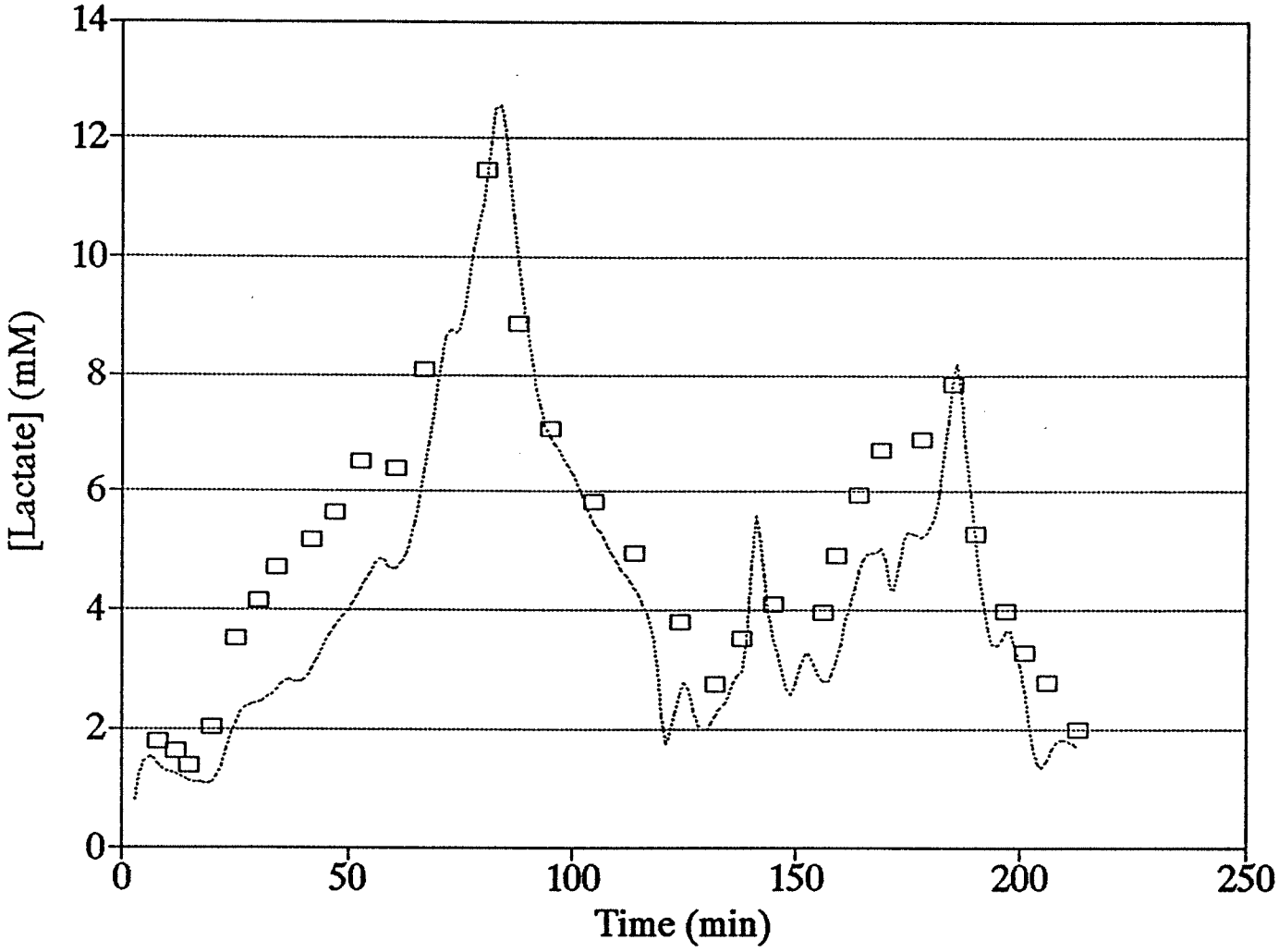

FIG. 11

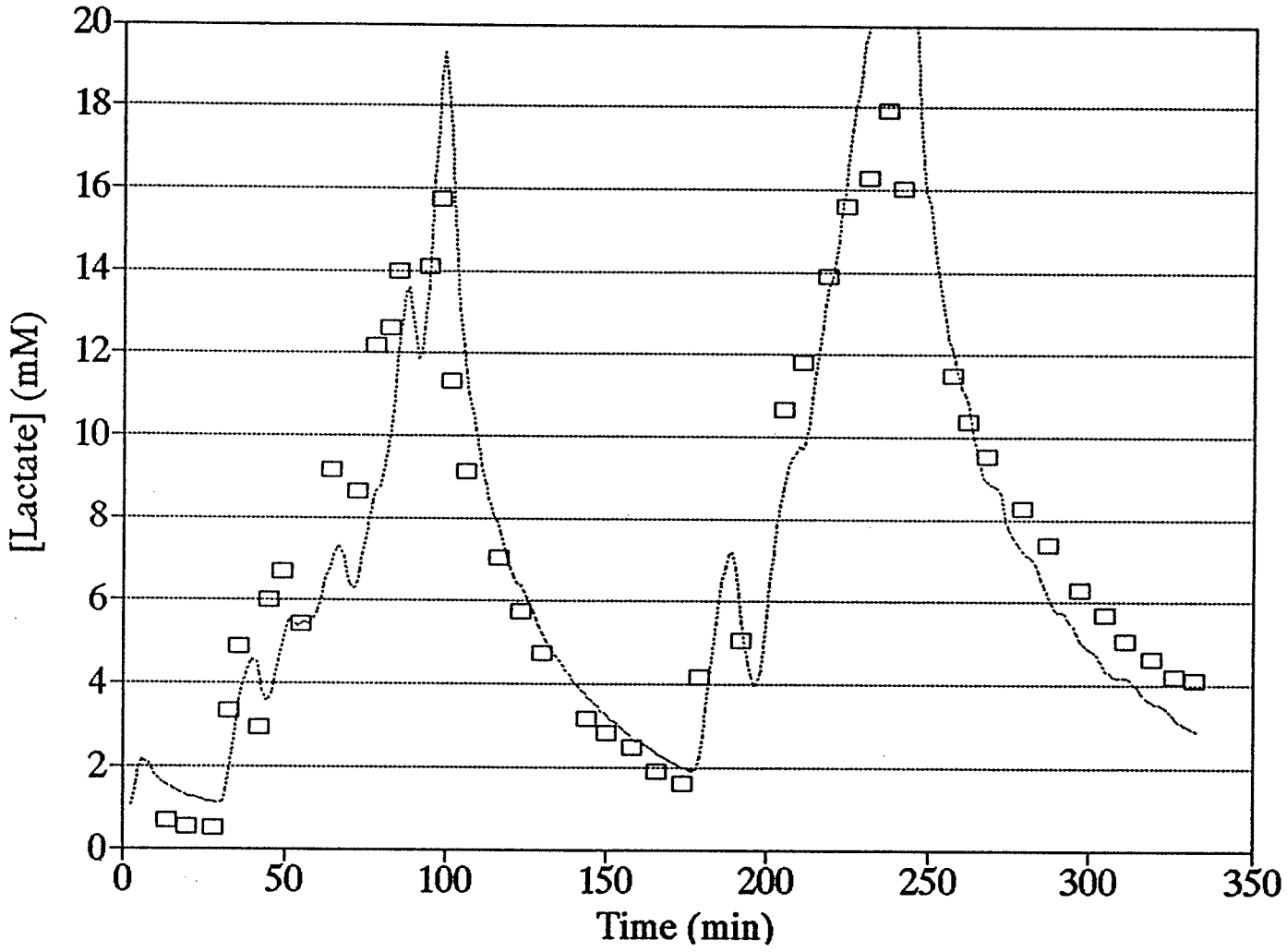
[Lactate] (mM)
20
18
16
14
12
10
8
6
4
2
0
0
50
100
150
200
250
300
350
Time (min)

FIG. 12

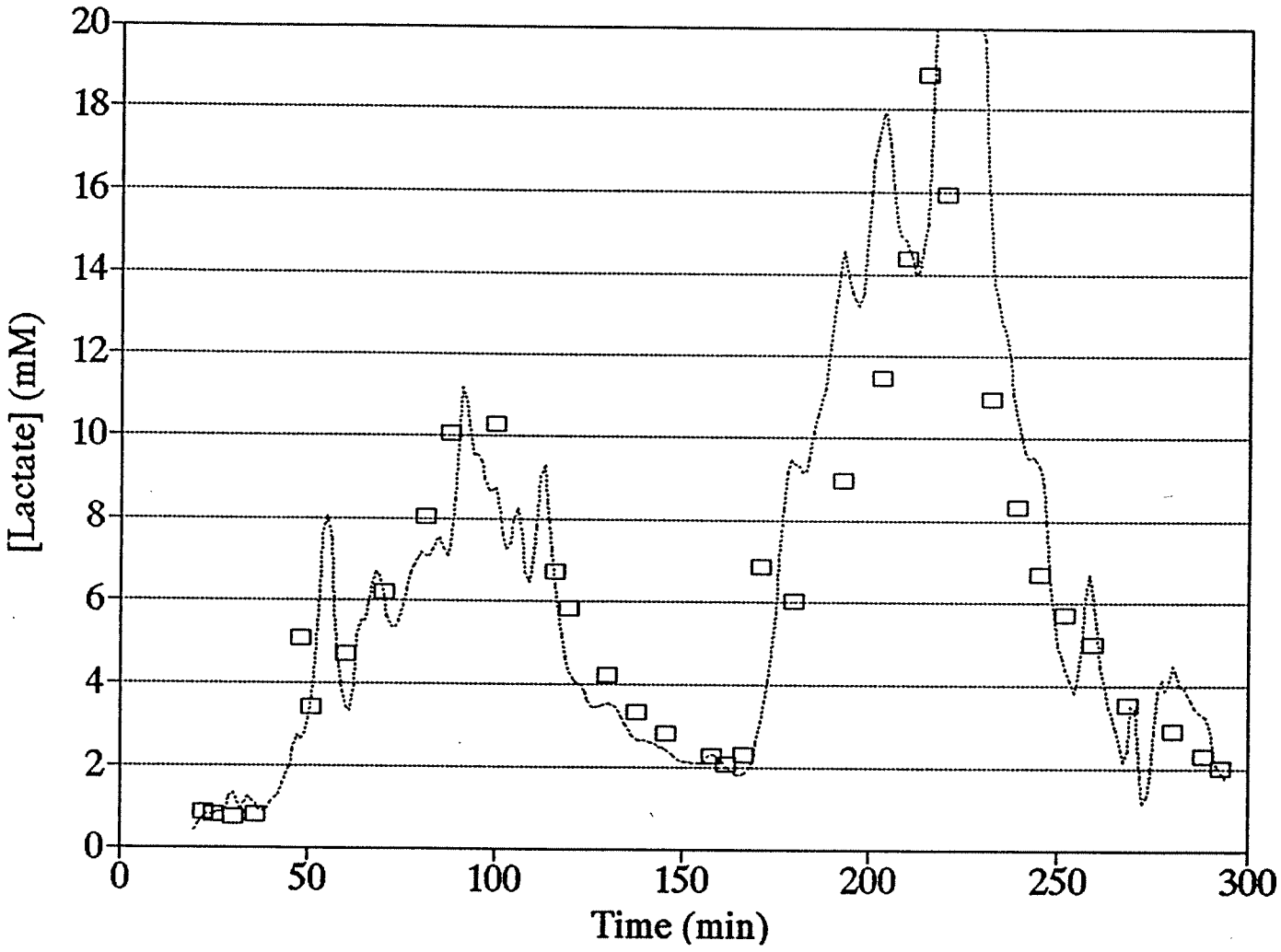
[Lactate] (mM)
20
18
16
14
12
10
8
6
4
2
0
0
50
100
150
200
250
300
Time (min)

FIG. 13