Lactate Provocation of Panic Attacks

II. Biochemical and Physiological Findings

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• **Thirty-one of 43 patients with panic disorder or agoraphobia with panic attacks and none of 20 normal controls panicked in response to infusions of sodium lactate. Before receiving lactate, patients showed higher heart rates than controls and also signs of hyperventilation. During lactate infusion, patients who did not panic, nevertheless, developed higher lactate and pyruvate levels and greater ionized calcium and pH changes than controls. Lactate-induced panic attacks were regularly accompanied by biological changes consistent with hyperventilation and central noradrenergic activation and irregularly by elevation of plasma norepinephrine and cortisol levels. Panic attacks were not associated with changes in epinephrine or calcium levels or pH. Baseline arousal increased the likelihood of panic during lactate infusion. It is hypothesized that lactate-induced panic primarily involves central noradrenergic discharge with inconsistent peripheral manifestations.**

(*Arch Gen Psychiatry* 1985;42:709-719)

Sodium lactate infusions reliably induce panic in patients who experience spontaneous anxiety attacks, but not in normal controls.[1-4] Moreover, both pharmacological and phenomenological data support the similarity of lactate-induced and naturally occurring panic attacks.[1-4] These findings suggest that lactate acts, in a yet unidentified way, to trigger actual panic attacks in clinically vulnerable individuals. Therefore, lactate-induced attacks may provide insights into the antecedents and mechanisms of naturally occurring panic.

Pitts and McClure,[1] who pioneered lactate provocation of panic in 1967, originally hypothesized that lactate produced its panic by "complexing of ionized calcium at the surface of excitable membranes." Adding calcium to the lactate infusion considerably diminished the incidence and severity of resulting anxiety, which supported this theory. Other possible mechanisms, eg, induction of alkalosis, however, were not excluded by the initial experiments. Grosz and Farmer[5,6] postulated that the lactate dosages administered by Pitts and McClure were insufficient to depress ionized calcium levels significantly, and that metabolic alkalosis was the more likely precipitant of lactate-induced anxiety.

Pitts and Allen[7] later found that infusion of ethylenediaminetetraacetic acid, a powerful calcium chelator, produced symptoms of tetany in panic patients but did not induce panic attacks. They now hold that panic patients are specifically sensitive to β-adrenergic agonists (epinephrine, isoproterenol) or metabolic products of their action, eg, increased lactate levels.[7]

Interest in lactate challenge studies waned, to be rekindled by Kelly and co-workers' 1971 finding that panic patients successfully treated with monoamine oxidase inhibitors lost their lactate vulnerability as well.[8] However, it is not known whether patients who panic with sodium lactate infusions do so because lactate alters their body chemistry, eg, lactate level, pH, calcium level, differently than it does that of controls; because lactate's effects in normal subjects and patients are similar, except for an interaction with a central nervous system (CNS) vulnerability in patients; or because lactate is a powerful, nonspecific stressor that induces panic in people conditioned to perceive certain bodily sensations with alarm.

INVESTIGATION

We initiated a multidisciplinary longitudinal investigation of lactate provocation of panic to pursue these issues. This article compares the biochemical and physiological findings in patients with histories of panic attacks and normal controls, before and during lactate infusions. Clinical and behavioral findings were presented in a preceding article.[4]

The specific questions addressed are as follows.

Accepted for publication Aug 9, 1984.

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Baseline Questions

1. Can physiological or biochemical differences between patients and normal controls be detected before their receiving lactate?
2. Can differences between patients who go on to panic with lactate infusions and those who do not be detected before their receiving lactate?

Infusion Questions

3. What are the biochemical and physiological concomitants of a lactate infusion?
4. Are there differences between nonpanicking patients and normal controls in response to a lactate infusion?
5. What pattern of biochemical and physiological events characterize lactate-induced panic attacks? We will address this by comparing panicking and nonpanicking patients.

General Questions

6. What do the findings suggest with regard to the mechanism by which lactate induces panic attacks? Is there some peripheral event that triggers the panic? Is there some necessary antecedent level of peripheral disturbance for panic attacks to occur?
7. What do the findings imply for the pathophysiology of naturally occurring anxiety states?

SUBJECTS AND METHODS

Procedures and subject selection for the "lactate study" have been described in detail.[4] In brief, patients who met criteria for *DSM-III* panic disorder or agoraphobia with panic attacks, as well as normal controls, underwent an adaptation day of physiological monitoring, then returned to the laboratory the next day. Five percent dextrose in water was administered slowly intravenously (IV) for 28 minutes and then rapidly for two minutes. At this point 0.5M racemic sodium lactate, 10 mL/kg of body weight, heated to body temperature, was administered for a 20-minute period, unless the patient panicked, in which case the lactate infusion was stopped. On occasion, lactate infusions took longer than 20 minutes to complete, and infusions lasting up to 22 minutes are included in this article. Sequence and duration of infusions were known to the staff but not to patients. Written informed consent was obtained from each patient after detailed explanation of study procedures.

To determine whether and when a patient panicked during the infusion procedure, we relied on clinical observations and patients' self-report. To establish that a patient panicked, we required both the report of a crescendo of extreme apprehension or fear and the *DSM-III* physical symptoms for a panic attack—tachycardia, shortness of breath, sweating, faintness, etc. Physical symptoms alone did not suffice.

To assess the roles of autonomic discharge, acid-base balance, lactate metabolism, ionized calcium level, and stress responsivity in the lactate response, we measured three physiological and 11 biochemical variables. The physiological measures were heart rate and systolic and diastolic blood pressure. The biochemical variables were blood L-lactate and pyruvate levels; plasma ionized calcium, phosphate, prolactin, epinephrine, norepinephrine, and cortisol levels; and venous carbon dioxide pressure (P_{CO_2}), pH, and (calculated) bicarbonate level.

Biochemical and physiological variables were measured before the start of lactate infusion (zero time) and at five-minute intervals during lactate infusion (+5, +10, +15, +20). An additional sample was drawn at the point of lactate-induced panic, if it occurred. The *N*s vary across variables at any given time point because measurement of some variables was started after the project had begun. The *N*s vary within a given variable between baseline and infusion because an individual's infusion data were included only if measurements for every sampling period were obtained. Cortisol and prolactin levels were not measured in nonpanicking patients or normal controls at the +5- and +15-minute points during lactate administration.

Table 1.—Demographic and Clinical Data

	Patients		
	Lactate Panickers	Lactate Nonpanickers	Normal Controls
N	31	12	20
Mean age (SD), yr	31.9 (7.5)	31.1 (9.2)	29.6 (7.6)
Sex			
M, No. (%)	12 (38.7)	4 (33.3)	12 (60)
F, No. (%)	19 (61.3)	8 (66.7)	8 (40)
Diagnosis			
No. (%) with panic disorder	13 (41.9)	4 (33.3)	. . .
No. (%) with agoraphobia	18 (58.1)	8 (66.7)	. . .
Mean duration of illness (SD), yr	6.7 (6.1)	6.0 (5.7)	. . .
Mean age at onset (SD), yr	25.4 (8.7)	24.7 (6.8)	. . .

Biochemical and Physiological Measurements

L-Lactate and Pyruvate Determination.—Blood samples were placed on ice, two volumes of 8% perchloric acid added, and the mixture centrifuged in the cold. The L-lactate concentration in the extracts was determined after a 45-minute incubation at 37 °C with nicotinamide-adenine dinucleotide and L-lactate dehydrogenase (L-LDH) by measuring the absorbance increase at 340 nm in a spectrophotometer.

The concentrations of pyruvate were assayed by incubating the perchloric acid extracts with reduced nicotinamide-adenine dinucleotide (NADH) and L-LDH for five minutes at 37 °C. The decrease in absorbance at 340 nm was measured in a spectrophotometer. All reagents for these assays were purchased commercially.

Radioenzymatic Assay of Plasma Norepinephrine and Epinephrine.—The assay procedure was based on the incubation of small (0.050-mL) plasma samples with catechol-O-methyl transferase (COMT) and tritiated *S*-adenosyl-1-methionine to form tritiated methylated derivatives. The products, normetanephrine and metanephrine, were extracted, separated by high-pressure liquid chromatography (HPLC), periodated, reextracted into toluene, and counted in a liquid scintillation spectrometer.

The procedures for blood collection, incubation, and extraction were similar to those described by da Prada and Zurcher.[8] After HPLC, the effluents corresponding to the peaks of normetanephrine and metanephrine were collected in counting vials, oxidized, extracted in 10 mL of a hydrocarbon miscible scintillation cocktail (Betafluer), and counted.

In a typical assay the values for blanks were less than 100 cells per meter (cpm) and the value for a 100-pg internal standard was 2,200 cpm. Thus, a sample concentration of 5 pg more than doubled the blank value. The values obtained for standards and plasma samples were similar to those reported by da Prada and Zurcher.[8]

Reagents were obtained commercially. The COMT was prepared from rat liver and partially purified as described by Gulliver and Tipton.[9]

Plasma Inorganic Phosphate.—A trichloroacetic acid extract of plasma was reacted with acid molybdate reagent, which was followed by the addition of a Fiske and Subba Row reducer. A blue color was formed that was proportional to phosphate concentration; the color was quantitated at 660 nm with a spectrophotometer. All reagents for the assay were purchased commercially.

Blood Ionized Calcium.—Blood ionized calcium concentrations were measured with a calcium electrode and a microprocessor ionalyzer. Blood samples (10-mL) were collected in heparinized evacuated tubes and allowed to reach ambient temperature. The samples were then placed in 30-mL beakers and stirred gently for exactly one minute to obtain the ionized calcium values.

Blood pH, P_{CO_2}, and Bicarbonate.—The values for pH and

Table 2.—Baseline Findings*

Variable	Lactate Panickers Mean	SD	N	Lactate Nonpanickers Mean	SD	N	Controls Mean	SD	N	Contrasts Overall	Pa vs NPa	Pa vs C	NPa vs C
L-Lactate, mg/dL	8.19	2.17	29	7.24	1.26	12	8.17	1.92	20	NS	...	...	...
Pyruvate, mg/dL	0.64	0.19	27	0.64	0.13	12	0.67	0.13	14	NS	...	...	...
Epinephrine, pg/mL	104.61	82.86	28	75.75	60.31	12	86.95	91.94	19	NS	...	...	...
Norepinephrine, pg/mL	292.28	171.50	29	238.67	91.26	12	240.84	100.56	19	NS	...	...	...
Cortisol, μg/dL	12.51	4.77	30	11.41	7.38	12	10.80	4.61	18	NS	...	...	...
Prolactin, ng/mL													
Men	9.97	2.75	12	6.08	1.66	4	6.63	2.7	10	NS	...	...	...
Women	11.43	8.34	18	15.06	7.03	8	12.91	4.35	8	NS	...	...	...
pH†	7.40	0.06	23	7.41	0.06	11	7.38	0.03	15	NS	...	...	...
P_{CO_2}, mm Hg	38.96	7.07	22	37.90	5.88	10	43.46	4.10	13	$F(2,42)=3.01$; $P\leq.06$	NS	$t(42)=2.11$; $P\leq.04$	$t(42)=2.17$; $P\leq.04$
Bicarbonate, mmole/L	23.21	3.48	22	22.38	2.59	10	24.97	1.83	13	$F(2,42)=2.53$; $P\leq.09$	NS	$t(42)=1.74$; $P\leq.09$	$t(42)=2.17$; $P\leq.04$
Calcium, mmole/L	1.09	0.16	13	1.00	0.11	7	1.03	0.08	6	NS	...	...	...
Phosphate, mg/dL	2.30	0.68	23	2.26	0.58	8	2.77	0.59	9	NS	...	...	...
Heart rate, beats/min	83.98	18.21	30	75.30	9.48	10	62.79	10.80	14	$F(2,51)=11.74$; $P\leq.0004$	$t(30)=1.94$; $P\leq.06$	$t(39)=4.82$; $P\leq.0001$	$t(21)=3.01$; $P\leq.007$
Systolic BP, mm Hg	117.56	17.36	27	112.18	14.35	11	109.86	12.47	14	NS	...	...	...
Diastolic BP, mm Hg	74.80	9.20	25	68.73	9.65	11	68.86	7.05	14	$F(2,47)=2.93$; $P\leq.06$	$t(47)=1.92$; $P\leq.06$	$t(47)=2.03$; $P\leq.05$	NS

*Pa indicates panickers; NPa, nonpanickers; C, controls; P_{CO_2}, carbon dioxide pressure; and BP, blood pressure.
†Means and SDs were calculated from individual pH values, but contrasts were based on individual H^+ concentrations.

P_{CO_2} were obtained with a blood microsystem and an acid-base analyzer. Blood samples in 1-mL syringes were freed from air bubbles and analyzed after drawing. Blood bicarbonate values were calculated from pH and P_{CO_2}.

Cortisol and Prolactin.—These assays were performed in the Behavioral Endocrinology Laboratory at the New York State Psychiatric Institute. A radioimmunoassay procedure was utilized.[10] Details of the assay are available on request.

Heart Rate.—Two standard chest electrodes were affixed to the subject and a continuous electrocardiographic recording obtained on a polygraph. The R-R intervals were measured for two minutes immediately surrounding each point of interest during the infusion and converted to beats per minute.

Blood Pressure.—Both systolic and diastolic blood pressures were recorded, using standard cuff technique.

Data Analyses

Because some patients did not panic during lactate infusion, we divided the study sample into three groups: patients who panicked with lactate (Pa); patients who did not panic with lactate (NPa); and normal controls, none of whom panicked with lactate (C). Contrasts of NPa and C groups permitted comparison of biochemical and physiological reactions to lactate in nonpanicking patients vs normal controls. Comparisons of Pa and NPa groups allowed identification of the predisposition to, or the consequences of, having a panic attack by comparing lactate panickers and nonpanickers with similar diagnoses.

Comparisons at baseline were made by one-way analysis of variance (ANOVA). If significant, they were followed by pooled variance t tests between groups. If heterogenous variances were detected, a Welch F statistic was computed for the ANOVA; if significant, it was followed by separate variance t tests between groups.[11]

Measurements made during the lactate infusion for nonpanicking patients and controls were analyzed by repeated-measures ANOVA (ANOVAR). A compound test of symmetry was applied to orthogonal components; when significant, a more conservative Greenhouse-Geisser probability was used for time, and group × time, analyses.[12]

To determine if any biological changes were specific for the lactate-induced panic attacks, ANOVA and analyses of covariance (ANCOVA) were used to compare the Pa, NPa, and C groups at each time point, followed by paired contrasts between groups. These analyses were complicated by the fact that infusions were terminated at the point of panic if patients panicked (to minimize subsequent patient discomfort) but run for the entire 20 minutes if they did not panic. To permit comparisons that controlled for amount of lactate received, panickers were divided into four groups: those that panicked between 2.5 and 7.5 minutes, between 7.5 and 12.5 minutes, between 12.5 and 17.5 minutes, and between 17.5 and 22 minutes. Biochemical and physiological measurements in these four groups made at the actual point of panic were then compared with the 5-, 10-, 15-, and 20-minute values, respectively, for the NPa and C groups. This method of analyzing point-of-panic findings is an approximation. It would be more exact to include only patients who panicked exactly at the 5-, 10-, 15-, and 20-minute points in the comparison. To maximize the sample size available for analysis, however, the grouping described was used.

Standard deviations are indicated in Tables 1 and 2.

This report is preliminary. To minimize type II errors, given our small sample sizes, a P value of less than or equal to .10 was selected as a criterion of statistical significance. All P values are two tailed.

RESULTS

Forty-three patients who met *DSM-III* criteria for either panic disorder or agoraphobia with panic attacks and 20 normal controls underwent infusions with 0.5M racemic sodium lactate. As described elsewhere,[4] 31 (72%) of the 43 patients but none of the controls experienced panic attacks during lactate infusion. The mean time to panic was 12.03 (SD = 5.85) minutes, with a range of three to 22 minutes.

Demographic data for Pa, NPa, and C groups are presented in Table 1. No significant group differences were noted in age or sex. The Pa and NPa groups did not differ with regard to diagnosis, duration of illness, or age at onset.

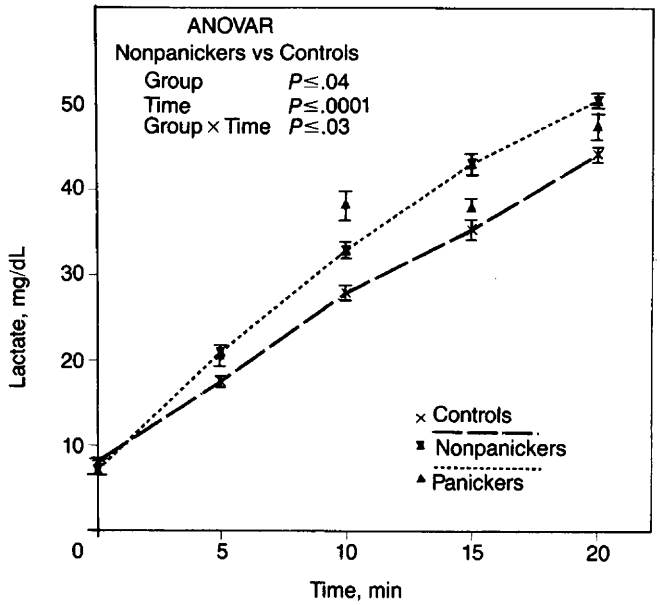
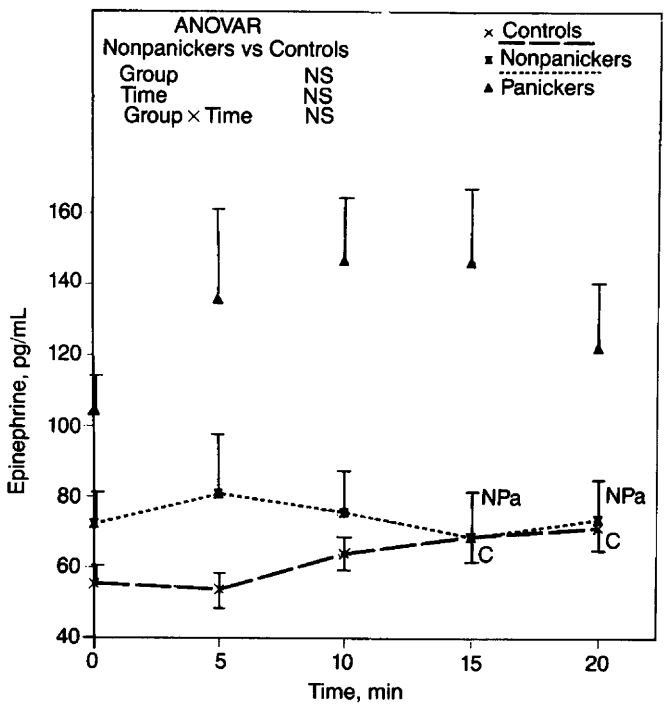


Fig 1.—Mean group lactate values (±SEM) for panicking patients (measured at point of panic) and for nonpanicking patients and normal subjects measured at five-minute intervals during lactate infusion. ANOVAR indicates repeated-measures analysis of variance.

Fig 2.—Mean group epinephrine values (±SEM) for panicking patients (measured at point of panic) and for nonpanicking patients and normal subjects measured at five-minute intervals during lactate infusion. NPa indicates nonpanicker SEM; C, control SEM; ANOVAR, repeated-measures analysis of variance.



Baseline Findings

Table 2 gives the biochemical and physiological measures just before lactate administration. Significant differences across the mutually exclusive groups (Pa, NPa, and C) were found for P_{CO_2} ($P \leq .06$), bicarbonate level ($P \leq .09$), heart rate ($P \leq .0002$), and diastolic blood pressure ($P \leq .06$). Therefore, paired group contrasts for these measures were performed.

Question 1.—Can preinfusion differences be found between patients and controls?

Both panickers and nonpanickers showed evidence at baseline of hyperventilation and autonomic arousal compared with normals. Both panickers and nonpanickers had a significantly lower preinfusion P_{CO_2} and bicarbonate level than normal subjects and a significantly higher heart rate. Panickers, but not nonpanickers, had a higher preinfusion diastolic blood pressure than controls (Table 2).

Question 2.—Can baseline differences be found between patients who go on to panic because of lactate infusion and those who do not?

Patients who panicked had a significantly higher heart rate and diastolic blood pressure than nonpanickers before receiving lactate (Table 2), suggesting greater baseline autonomic arousal in subsequent panickers.

Infusion Findings

Question 3.—What are the biochemical and physiological concomitants of a lactate infusion?

To examine the effects of lactate infusions per se, NPa and C were compared by ANOVAR. Included are biochemical and physiological measures taken before the start of lactate infusion (zero time) and at the 5-, 10-, 15-, and 20-minute points during the lactate infusion (see Figs 1 through 4 and Tables 3 and 4).

Lactate infusions were accompanied by significant increases for 20 minutes in lactate ($P \leq .0001$), pyruvate ($P \leq .0001$), and prolactin levels (men, $P \leq .001$; women, $P \leq .006$); pH ($P \leq .0001$); bicarbonate level ($P \leq .0001$); heart rate ($P \leq .0001$); and systolic blood pressure ($P \leq .0001$). Significant decreases were seen for cortisol level ($P \leq .0001$), P_{CO_2} ($P \leq .0001$), ionized calcium level ($P \leq .0001$), and phosphate level ($P \leq .0001$). Diastolic blood pressure and epinephrine and norepinephrine levels did not show significant changes during the infusion period.

Question 4.—Do nonpanicking patients and normal controls show biological differences in response to a lactate infusion?

The NPa and C groups were compared at 0-, 5-, 10-, 15-, and 20-minute points during lactate infusions by ANOVAR. Significant group × time interactions for lactate level ($P \leq .03$), pyruvate level ($P \leq .0003$), pH ($P \leq .02$), and calcium level ($P \leq .05$) were found (see Figs 1 through 4 and Tables 3 and 4). The NPa and C groups started out at similar levels for lactate, pyruvate, pH, and calcium before lactate administration, but the NPa group developed higher pH and lactate and pyruvate levels and lower ionized calcium levels than the control group.

Significant main effects between NPa and C groups were noted for lactate and pyruvate levels, P_{CO_2}, pH, bicarbonate level, and heart rate (Figs 1 through 4 and Tables 3 and 4). The higher heart rate ($P \leq .01$) and lower P_{CO_2} ($P \leq .02$) and bicarbonate level ($P \leq .06$) seen in the NPa group were due to maintenance of the differences that existed before lactate infusion. The higher lactate level ($P \leq .04$), pyruvate level ($P \leq .006$), and pH ($P \leq .06$) in the NPa group developed during the lactate infusion as shown by group × time analyses.

Question 5.—What pattern of biochemical and physiological events accompany a lactate-induced panic attack?

Tables 3 and 5 and Figs 1 through 4 compare biochemical and physiological measures at the point of panic with those obtained at comparable times in nonpanicking patients. For panickers, zero time values shown only on Figs 1 through 4 represent all patients, while 5-, 10-, 15-, and 20-minute values (Figs 1 through 4 and Table 3) represent only patients panicking at those time "points." By ANOVA and pairwise contrast of unadjusted means, panickers significantly exceeded nonpanickers at one or more measurement points for pyruvate level, epinephrine level, norepinephrine level, heart rate, systolic blood pressure, and diastolic blood pressure, and were lower than nonpanickers for P_{CO_2} and bicarbonate level.

However, differences at the point of panic could be due to the

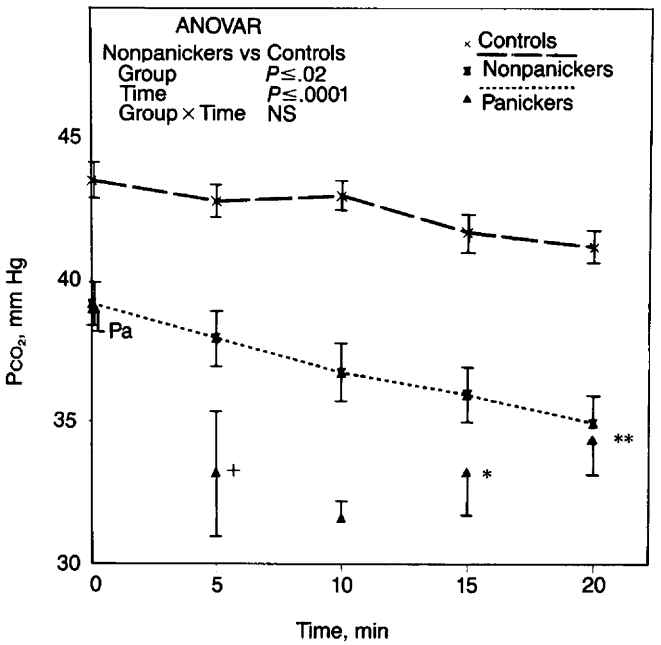


Fig 3.—Mean group carbon dioxide pressure (P_{CO_2}) values (±SEM) for panicking patients (measured at point of panic) and for nonpanicking patients and normal subjects measured at five-minute intervals during lactate infusion. For analysis of covariance comparing panicking patients and nonpanicking patients: +, $P \leq .10$; *, $P \leq .05$; **, $P \leq .01$. Pa indicates panicker SEM; ANOVAR, repeated-measures analysis of variance.

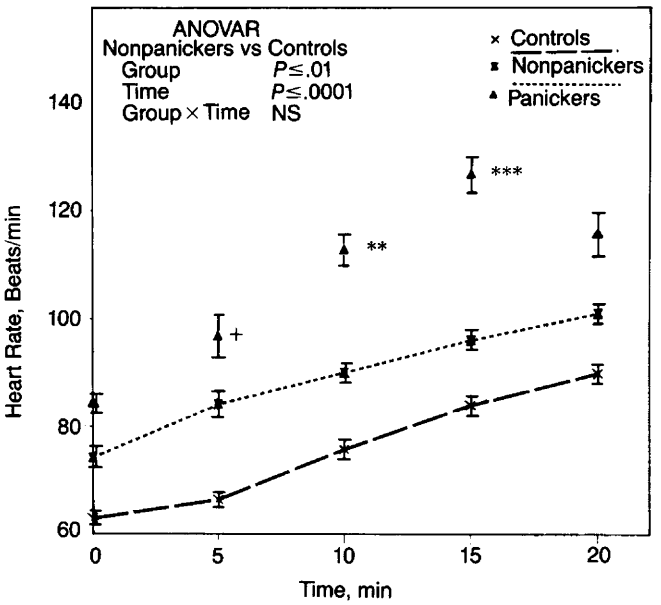


Fig 4.—Mean group heart rate values (±SEM) for panicking patients (measured at point of panic) and for nonpanicking patients and normal subjects measured at five-minute intervals during lactate infusion. For analysis of covariance comparing panicking patients and nonpanicking patients: +, $P \leq .10$; **, $P \leq .01$; ***, $P \leq .001$. ANOVAR indicates repeated-measures analysis of variance.

panic attack itself, to the biological alterations occurring during lactate infusion but anteceding the panic, or to differences anteceding the start of lactate infusion. To control for biological differences anteceding the start of lactate infusion, point-of-panic findings were contrasted with similarly timed results in the NPa group by ANCOVA, using preinfusion (zero time) values as covariates. Unless otherwise specified, paired contrasts between Pa and NPa groups were carried out only when the overall ANCOVA F of the three groups (Pa, NPa, and C) was significant.

Point-of-panic differences were found most frequently (in 75% of contrasts) for heart rate, P_{CO_2}, and bicarbonate level (Table 5 and Figs 1 through 4). Heart rate was elevated in panicking patients at the five-minute ($P \leq .06$), ten-minute ($P \leq .007$), and 15-minute ($P \leq .0003$) times (Fig 4). These heart rate increases usually occurred abruptly. The P_{CO_2} was lower in panicking patients than in comparably timed nonpanickers at the five-minute ($P \leq .07$), 15-minute ($P \leq .02$), and 20-minute ($P \leq .007$) times. This also appeared true for ten-minute panickers, but one panicking patient did not hyperventilate, resulting in nonparallel regression slopes between panickers and nonpanickers (Fig 3). Bicarbonate level was lower in ten-minute ($P \leq .05$) and 15-minute ($P \leq .07$) panickers; it was also lower in five-minute ($P \leq .07$) panickers, but the overall F for the three group (Pa, NPa, and C) ANCOVAs was not significant.

Point-of-panic differences were found somewhat less frequently (in 50% of contrasts) for norepinephrine and cortisol levels and diastolic blood pressure. Norepinephrine level was elevated in five-minute ($P \leq .05$) and 20-minute ($P \leq .10$) panickers, although at 20 minutes the three groups were not significantly different by ANCOVA. Cortisol level (measured only at ten- and 20-minute panic times) was elevated in ten-minute panickers ($P \leq .02$). Diastolic blood pressure was elevated in 15-minute ($P \leq .01$) and 20-minute ($P \leq .01$) panickers.

Ten-minute panickers had higher pyruvate levels than comparably timed nonpanickers ($P \leq .09$), but the reverse was true for 20-minute panickers ($P \leq .06$). By ANCOVA, no consistent differences in lactate level (Fig 1), epinephrine level (Fig 2), pH, phosphate level, or systolic blood pressure were found to accompany lactate-induced panic.

Because the differences found for epinephrine level and systolic blood pressure by ANOVA were not sustained when infusion findings were adjusted for baseline levels, they were substantially due to preinfusion differences between panickers and nonpanickers. Contrasts at the point of panic for prolactin and calcium level could not be carried out because of limited sample size.

Summarizing these findings, lactate-induced panic attacks were associated with heightened sympathetic arousal and hyperventilation. At the point of panic, patients regularly showed evidence of greater elevations in heart rate and greater decrements in P_{CO_2} and bicarbonate level than comparably timed nonpanickers. Elevations of norepinephrine and cortisol levels and diastolic blood pressure were less regularly associated with lactate-induced panic. No consistent changes in lactate, pyruvate, or epinephrine levels, pH, or systolic blood pressure were found specifically associated with lactate-induced panic.

To ensure that the findings were not due to panickers receiving lactate at a faster rate, early in the project we began to measure the amount of lactate remaining to be infused in patients who panicked before the 20-minute point. The rate of infusion for panickers was found to be virtually identical to that of nonpanicking patients and nonpanicking normal controls. For 18 panickers on whom data were available, a mean of 51% of the infusion time had elapsed before the point of panic. A mean of 50% of the lactate infusion had been administered during that time, showing they were on schedule.

COMMENT

Patient-Control Differences at Baseline

At baseline, patients had higher heart rates and lower P_{CO_2} and bicarbonate levels than normal controls. The higher heart rate in patients, which had previously been noted by Kelly et al,[3] appears to be, at least in part, an acute process, as the patient-control difference on the day before lactate infusion (to be discussed in subsequent reports) was less marked.

The most likely explanation for the lower P_{CO_2} and bicarbonate level is anxiety-induced hyperventilation, es-

Table 3.—Infusion Findings

Variable*	Time, min	Controls			Nonpanickers			Panickers		
		Mean	SD	N	Mean	SD	N	Mean	SD	N
L-Lactate	0	8.10	2.05	14	7.03	1.06	11	...	...	...
	5	17.46	4.00	14	20.89	6.56	11	20.57	6.06	6
	10	27.74	6.26	14	32.68	6.84	11	38.06	9.90	8
	15	34.94	8.47	14	42.56	8.29	11	37.55	6.13	7
	20	43.52	7.63	14	49.74	6.43	11	46.83	9.11	8
Pyruvate	0	0.68	0.14	14	0.63	0.13	11	...	...	...
	5	0.89	0.21	14	1.02	0.23	11	1.04	0.06	6
	10	1.38	0.29	14	1.66	0.24	11	1.95	0.54	8
	15	1.64	0.33	14	2.08	0.32	11	2.14	0.38	5
	20	2.02	0.34	14	2.60	0.35	11	2.27	0.41	8
Epinephrine	0	55.33	35.57	12	72.18	61.91	11	...	...	...
	5	53.67	37.07	12	80.64	114.03	11	135.57	138.24	7
	10	63.67	34.40	12	75.27	79.81	11	146.00	101.25	8
	15	68.50	46.67	12	68.25	86.25	11	145.17	105.86	6
	20	70.92	45.10	12	73.18	74.18	11	121.37	105.85	8
Norepinephrine	0	236.69	108.18	13	248.64	86.62	11	...	...	...
	5	218.92	113.52	13	254.00	104.70	11	418.29	195.43	7
	10	246.61	132.65	13	272.64	128.48	11	270.37	152.84	8
	15	226.31	134.18	13	279.91	131.13	11	311.67	155.79	6
	20	220.08	135.94	13	250.91	137.36	11	410.00	249.71	8
Cortisol	0	11.10	4.56	17	11.41	7.38	12	...	...	...
	5	...	...	...	...	...	...	9.57	3.43	7
	10	9.29	3.78	17	9.58	6.43	12	11.28	4.07	6
	15	...	...	...	...	...	...	12.60	4.30	6
	20	8.99	3.74	17	9.42	6.23	12	15.91	11.12	8
Prolactin										
Men	0	6.63	2.70	10	6.08	1.66	4	...	...	...
	10	6.19	1.95	10	5.93	2.38	4	12.30	0.99	2
	20	7.62	2.67	10	9.28	2.99	4	10.50	4.74	5
Women	0	13.36	4.50	7	15.06	7.03	8	...	...	...
	10	12.73	3.66	7	18.11	8.03	8	18.10	12.84	5
	20	17.13	7.41	7	26.24	12.30	8	18.10	6.13	3
Pco_2	0	43.42	4.27	12	39.11	4.73	9	...	...	...
	5	42.67	4.12	12	37.89	5.75	9	33.17	10.66	6
	10	42.83	3.59	12	36.67	6.14	9	31.60	2.79	5
	15	41.53	4.50	12	35.89	6.07	9	33.20	6.69	5
	20	41.00	3.81	12	34.89	5.73	9	34.33	5.82	6
pH	0	7.38	...	14	7.39	...	10	...	...	...
	5	7.39	...	14	7.44	...	10	7.45	...	6
	10	7.42	...	14	7.47	...	10	7.49	...	5
	15	7.45	...	14	7.50	...	10	7.50	...	5
	20	7.47	...	14	7.52	...	10	7.54	...	7
Bicarbonate	0	24.95	1.91	12	22.80	2.36	9	...	...	...
	5	25.13	1.69	12	24.65	1.40	9	22.07	3.62	6
	10	26.95	1.75	12	25.45	1.66	9	23.56	2.04	5
	15	27.61	2.60	12	26.22	1.91	9	25.24	3.21	5
	20	28.75	1.62	12	26.90	2.70	9	27.81	4.81	6
Calcium	0	1.08	0.09	3	1.06	0.08	4	...	...	...
	5	1.02	0.12	3	0.98	0.11	4	0.95	0	1
	10	0.99	0.13	3	0.90	0.13	4	1.10	0	1
	15	0.96	0.15	3	0.85	0.11	4	0.90	0.10	4
	20	0.91	0.13	3	0.83	0.08	4	0.92	0.14	4

Continued on p 715.

Table 3.—Infusion Findings (cont)

Variable*	Time, min	Controls			Nonpanickers			Panickers		
		Mean	SD	N	Mean	SD	N	Mean	SD	N
Phosphate	0	2.72	0.61	8	2.45	0.25	7	...	...	...
	5	2.55	0.51	8	2.29	0.31	7	2.12	0.91	6
	10	2.44	0.49	8	2.18	0.23	7	2.07	0.38	5
	15	2.39	0.51	8	2.03	0.32	7	1.81	0.84	5
	20	2.25	0.47	8	1.92	0.36	7	1.90	0.46	7
Heart rate	0	62.79	10.80	14	74.06	10.33	8	...	...	...
	5	66.29	12.09	14	84.00	13.56	8	96.75	21.78	8
	10	75.64	14.41	14	89.81	11.44	8	112.67	17.01	9
	15	83.78	12.58	14	95.81	10.44	8	126.50	16.01	6
	20	89.68	12.76	14	100.69	9.83	8	115.50	21.69	7
Systolic BP	0	108.31	12.08	13	112.75	11.41	8	...	...	...
	5	114.08	13.64	13	117.75	13.16	8	109.71	14.53	7
	10	120.46	13.98	13	120.50	14.92	8	123.11	19.70	9
	15	123.00	13.38	13	124.25	14.64	8	129.43	18.25	7
	20	122.92	14.09	13	120.00	14.42	8	134.25	10.28	8
Diastolic BP	0	69.33	7.10	12	70.75	8.81	8	...	...	...
	5	70.17	6.35	12	73.00	9.26	8	69.43	9.07	7
	10	71.33	7.69	12	70.75	5.65	8	74.56	11.91	9
	15	69.67	10.01	12	70.00	8.07	8	84.33	6.98	6
	20	69.33	7.92	12	68.75	8.00	8	84.00	9.44	8

*P_{CO_2} indicates carbon dioxide pressure; BP, blood pressure.

pecially because the same effect has been seen subsequently with arterial blood gases. Secondary renal compensation then normalized pH by enhanced excretion of bicarbonate in the patient group.[13] Because the P_{CO_2}, bicarbonate level, and heart rate differences between patients and controls remained when lactate panickers were excluded from the analyses, the baseline differences between patients and controls were not features of impending panic, but rather reflected altered psychobiological processes in the patient group as a whole.

Baseline Differences Between Lactate Panickers and Nonpanickers

A previous article noted that patients who panicked during lactate infusion manifested greater preinfusion anxiety and fearfulness than did nonpanicking patients, suggesting that lactate panickers were in some way primed to panic before receiving lactate.[4] Consistent with this possibility are the findings of a higher (but within normal range) baseline heart rate and diastolic blood pressure in panicking compared with nonpanicking patients. In addition, baseline epinephrine, norepinephrine, cortisol, and prolactin (in male patients) levels and systolic blood pressure were all higher in panickers than in either comparison group, although these differences were not statistically significant in the sample sizes reported herein.

Preinfusion arousal could represent the early phase of an actual panic attack. Patients with clinical panic attacks may have some CNS instability that, when fully activated, is associated with a panic attack, but when partially activated gives rise to a feeling of apprehension and to moderate cardiovascular stimulation. If so, patients with a partially activated CNS instability would be more likely to panic with lactate, but not all would do so, which is what we found. This is also consistent with the experience of patients, early in pharmacological treatment, of mild surges of apprehension and physical discomfort that no longer peak into full panic attacks.

Alternatively, the greater preinfusion arousal in the panicker group may be due to nonspecific apprehension rather than representing an early phase of panic. If apprehension per se increases the likelihood of patients panicking with lactate, then at least some patients who do not panic with standard lactate infusion should panic with infusions preceded by anxiety-provoking procedures.

Effects of Lactate Infusions Independent of Panic

As evidenced in individuals who did not panic, infusions of 0.5M racemic lactate have a number of metabolic, physiochemical, and nonspecific effects. In a separate series of ten panic patients given standard 20-minute infusions, mean hematocrit value dropped from 48.3% (SD = 8.5) to 43.0% (SD = 5.2), reflecting hemodilution.

Although the lactate infusate was buffered to a pH of 6.6, subjects developed a mild metabolic alkalosis through metabolism of lactate to bicarbonate.

The serum ionized calcium level was depressed by direct complexing with lactate, by increased protein binding secondary to alkalinization, and by hemodilution. Hemodilution, respiratory alkalosis, and decreased renal tubular reabsorption secondary to a hypertonic fluid load contributed to lowering phosphate level.[14] The fall in P_{CO_2}, the opposite of what would be expected from respiratory compensation for significant metabolic alkalosis, reflected hyperventilation, which was of greater magnitude in patients than controls. Our phosphate and bicarbonate findings are close to those previously reported by Bonn et al.[15,16]

The rise in serum lactate level, similar to previous findings,[15,16] resulted from the infusion of a large lactate

Table 4.—Infusion Effects: Nonpanickers vs Controls*

Variable	Group Effects	Time Effects	Group × Time Effects
Lactate	NPa>C†	Increase‡	NPa>C†
Pyruvate	NPa>C§	Increase‡	NPa>C‡
Epinephrine	NS	NS	NS
Norepinephrine	NS	NS	NS
Cortisol	NS	Decrease‡	NS
Prolactin (men)	NS	Increase‡	NS
Prolactin (women)	NS	Increase‡	NS
Calcium	NS	Decrease‡	C>NPa†
Phosphate	NS	Decrease‡	NS
Pco_2	C>NPa†	Decrease‡	NS
pH	NPa>C‖	Increase‡	NPa>C†
Bicarbonate	C>NPa‖	Increase‡	NS
Heart rate	NPa>C†	Increase‡	NS
Systolic BP	NS	Increase‡	NS
Diastolic BP	NS	NS	NS

*NPa indicates nonpanickers; C, controls; Pco_2, carbon dioxide pressure; and BP, blood pressure.
†$P \leq .05$.
‡$P \leq .001$.
§$P \leq .01$.
‖$.05 \leq P \leq .10$.

Table 5.—Point-of-Panic Effects: Significant Findings*

Variable	Time, min	Pa vs NPa†
Pyruvate	10	Pa>NPa‡
	20	NPa>Pa‡
Norepinephrine	5	Pa>NPa§
	20	Pa>NPa‡‖
Cortisol	10	Pa>NPa§
Pco_2	5	NPa>Pa‡
	15	NPa>Pa§
	20	NPa>Pa¶
Bicarbonate	5	NPa>Pa‡‖
	10	NPa>Pa§
	15	NPa>Pa‡
Heart rate	5	Pa>NPa‡
	10	Pa>NPa¶
	15	Pa>NPa#
Diastolic BP	15	Pa>NPa¶
	20	Pa>NPa¶

*Analyses of covariance (ANCOVA). Pco_2 indicates carbon dioxide pressure, BP, blood pressure.
†Pa indicates panickers; NPa, nonpanickers. Means adjusted for baseline scores.
‡$.10 \leq P \leq .05$.
§$P \leq .05$.
‖Overall F for ANCOVA comparing Pa, NPa, or control groups not significant; pairwise contrast included to explore trends in the data.
¶$P \leq .01$.
#$P \leq .001$.

load, the oxidation of which caused the elevation of pyruvate level.

The rise in heart rate and systolic blood pressure seen in all subject groups may have reflected anxiety or some specific physiological process induced by the lactate. Similar heart rate findings were reported by Bonn et al.[15,16]

The prolactin increase could be due to stress or to the hypertonic fluid load, because both have been shown to result in increases of this hormone.[17,18] If stress is involved, a concomitant rise in cortisol level should have occurred. Minor secretory bursts of cortisol may have occurred, but have been outweighed by the effect of hemodilution. Hypocalcemia may also have limited the stress-induced cortisol increase, because corticotropin release has been shown to be calcium dependent.[19]

Contrary to what occurs peripherally, the brain lactate concentration may not dramatically increase during a lactate infusion. At physiological pH, lactate is largely ionized and depends on active transport to cross the blood barrier.[20,21] The system is easily saturable, and elevations of the plasma lactate level above the usual concentrations are not readily transferred to the brain.[20,21] In dogs, there is a five- to six-hour lag in elevation of the cerebrospinal fluid lactate level following blood lactate increases from 2 to 8 mmole/L.[21] Because lactate levels begin to fall soon after a 20-minute lactate infusion is completed, there may not be sufficient time for significant amounts of lactate to be transported into the brain. If so, the initial metabolic or physiochemical lactate effects in the chain that produces panic must occur peripherally rather than centrally.

Nonpanicking Patient-Control Differences In Response to Lactate Infusion

Comparison of nonpanicking patients and normal controls during the infusions revealed further biological differences between the two groups that could not be attributed to lactate-induced panic.

The higher pH developed by the nonpanicking patients reflected continued hyperventilation and/or a decreased ability to buffer the alkalinizing effects of the lactate infusion, perhaps due to an already lowered bicarbonate status at baseline. Because the ionized calcium level is pH dependent, the lower level seen in the patients was probably secondary to higher pH.

The high lactate and pyruvate levels developed by the patient group suggest some yet unidentified difference in lactate distribution, clearance, or metabolism in panic disorders. Because both lactate and pyruvate levels were increased, a decreased capacity to convert lactate into pyruvate, as might occur if there were a bias toward anaerobic glycolysis, seems unlikely. Respiratory alkalosis, however, can cause an increase in blood lactate levels, and the greater alkalosis developed by the patient group during the infusion may have contributed to its higher lactate and pyruvate levels.

Patient-control differences in blood volume could have resulted in differences in volume of lactate distribution. The groups did not differ in height or weight, and, therefore, not in estimated surface area, which is considered a good index of blood volume in our mostly lean subjects. There are differences in percent body fat between men and women and within sexes depending on diet, activity levels, fitness, and strength, and subsequent analyses in larger samples will control for these variables. Whatever the cause, our data are consistent with the findings of higher lactate levels after exercise in anxiety patients than in normal controls.[22-25]

Point-of-Panic Findings and Possible Mechanisms

Our principal findings were that lactate-induced panic attacks were regularly accompanied by elevated heart rate and lowered Pco_2 and bicarbonate level. Knott et al[26]

previously noted heart rate increases of similar proportions in six lactate panickers. Elevation of norepinephrine and cortisol levels and diastolic blood pressure were seen less regularly in our study. No consistent change in lactate, pyruvate, or epinephrine level, pH, phosphate level, or systolic blood pressure was found to accompany lactate-induced panic.

Too few calcium measurements during panics were available for analysis. However, contrasts of subsequently studied patients did not show panicking patients to have lower ionized calcium levels than nonpanickers. This suggests that hypocalcemia per se does not cause panic attacks in clinically vulnerable patients. It is still possible, however, that lowered calcium level is panicogenic in patients already primed for panic. Pitts and McClure,[1] as well as Fink et al,[2] found that adding calcium to lactate infusions lowered the incidence of panic. This finding, which requires further replication, is compatible with but does not prove a panicogenic role for hypocalcemia. It is also possible that added calcium simply offsets the effects of lactate on a noncalcium system.

Patients who panicked with lactate did not develop greater alkalosis than nonpanicking patients, suggesting that no absolute pH threshold exists beyond which clinically vulnerable patients will panic. Raising the pH in itself does not appear panicogenic. In a separate study, induction of marked respiratory alkalosis by room air hyperventilation-induced panic attacks in only three of 12 panic patients, eight of whom had panicked with lactate infusions.[27]

Our peripheral catecholamine findings are surprising in several respects. Rapid elevations in circulating epinephrine levels have been considered a likely mechanism of clinical panic attacks. We found little evidence of such epinephrine increase during lactate-induced panic. Epinephrine levels higher than generally found in our patients or controls (greater than 150 pg/mL) were found to accompany only 32% (10/31) of our patients who had lactate-induced panic, and six of these patients also had elevated baseline epinephrine levels. This finding is strikingly different from the twofold or greater increase in plasma epinephrine level found to regularly accompany public-speaking anxiety.[28] Our findings suggest a predisposing or epiphenomenal rather than causal role for epinephrine increase in lactate-induced panic.

Norepinephrine has generally not been found to be anxiogenic in infusion studies.[29,30] The elevated plasma levels found to accompany lactate-induced panic during two of our measurement periods presumably reflect heightened peripheral sympathetic activity with synaptic spillover. Moreover, greater elevations were regularly seen when our patient stood up 25 minutes after completion of the lactate procedure and were not associated with panic symptoms. Because patients are capable of experiencing recurrent panic attacks within brief periods, plasma norepinephrine increase alone does not appear panicogenic. It is almost certainly a consequence rather than a cause of lactate-induced panic.

It is also possible, though unlikely, that discrete point-of-panic catecholamine bursts were missed by our blood collection procedures. Plasma catecholamines have half-lives of only one or two minutes.[31] On occasion, the collection of a point-of-panic sample was delayed for two to three minutes by venospasm. To offset the problem of short catecholamine half-life, continuous rather than periodic sampling has been recommended.[32] It is our experience, however, that point-of-panic venospasm will interfere with any type of venous sampling, at least if traditional-length catheters are used. To overcome this problem (and to obtain more accurate blood gas measurements), arterial blood samples (via an indwelling catheter) are now being drawn for all biochemical measures.

Pitts and Allen[7] have argued that panic patients are hypersensitive to all β-adrenergic agonists. This is supported by the recent finding that isoproterenol may induce panic attacks in patients with panic disorder more frequently than in normal controls.[33] Arguing against a direct β-adrenergic mechanism for lactate's induction of panic is our finding that pretreatment of patients with intravenous propranolol, 0.2 mg/kg, did not prevent lactate-induced panic despite evidence of peripheral β-adrenergic blockade.[34] It has been questioned whether lactate may impair β-adrenergic blockade,[35] although we find this unpersuasive. The failure of β-blockers, in preliminary trials, to block clinical panic attacks[36-39] also strongly argues against peripheral epinephrine surge as the mechanism underlying panic attacks.

The physiological changes often seen at the point of panic, ie, elevated heart rate and diastolic blood pressure, are observed with central sympathetic activation.[39,40] The locus ceruleus (a principal CNS noradrenergic nucleus) has been suggested as a mediator of fear responses in primates[41] and rodents.[42] That the locus ceruleus plays a role in human panic attacks is suggested by the reported increase in plasma 3-methoxy-4-hydroxyphenylglycol in phobic anxious patients during in vivo exposure.[43] Also, oral clonidine hydrochloride, a locus ceruleus inhibitor, was administered on a chronic basis in two studies and found to block panic attacks at least transiently.[44,45] In addition, stress has been shown to increase electrophysiological activity in single-unit locus ceruleus recordings in live animals.[46]

A role for central noradrenergic pathways as a specific substrate for panic must still be considered speculative. Clonidine may not be specific for noradrenergic systems, because it reverses the nonadrenergically mediated rhinorrhea and lacrimation attendant to narcotic withdrawal,[47] and because the effects of clonidine overdose can be reversed by administration of naloxone hydrochloride.[48] Also, locus ceruleus activity in animals is enhanced by a variety of nonanxiogenic sensory stimuli. Cooper et al[46] hypothesized that this noradrenergic nucleus serves a global orienting function rather than as a specific organizing center for anxiety. While heart rate increase seems to accompany lactate-induced panic consistently, elevations in blood pressure were more inconsistent than would be expected if locus ceruleus discharge was necessary for the panic experience. Also, plasma MHPG increases have not been found to accompany lactate-induced panic[49] nor caffeine-induced panic.[50]

Hyperventilation has been suggested as a cause of panic attacks. Our data affirm that hyperventilation routinely accompanies lactate-induced panic. In a separate study, however, lactate panickers did not regularly panic during prolonged hyperventilation in room air,[27] suggesting that hyperventilation is more likely a reflection rather than a cause of panic attacks.

Surprisingly, however, lactate panickers did regularly panic after breathing air containing 5% carbon dioxide.[27] Cohen and White[22] also observed anxiogenic effects in neurocirculatory asthenics (a nosological forerunner of panic disorder) from rebreathing 4% CO_2. Recently, CO_2 has been shown to be a locus ceruleus stimulant,[51] which might be the mechanism of CO_2-induced panic. Also linking CO_2 and lactate is their common effect on stimulating cerebral blood flow.[52] Because breathing 4% to 5% CO_2 drives respi-

ration, it is also possible that CO_2 panic is secondary to the feeling that one's breathing is out of control, an experience that panic patients, but not controls, might find intolerable. D. Klein, MD, hypothesized that patients with clinical panic attacks may have a pathologically lowered threshold in a "suffocation alarm mechanism" that is triggered by CO_2 (oral communication, Nov 4, 1983).

Carbon dioxide and lactate challenges could conceivably operate via the common mechanism of increased CNS CO_2. Lactate metabolism produces CO_2, which, unlike bicarbonate, freely crosses the blood-brain barrier. Lactate infusions could produce transient cerebral tissue CO_2 elevation, even though peripheral P_{CO_2} falls because of hyperventilation. This hypothesis must be tested by direct measurement.

Carr and Sheehan[53] linked lactate and CO_2 by hypothesizing a "central chemoreceptor hypersensitivity" for panic patients. According to this theory, pH or CO_2 changes that would have little or no effect on normal subjects produce significant excitatory effects on brain-stem chemoreceptors in panic patients, with secondary excitation of central sympathetic neurons.

The nonspecific stress hypothesis holds that lactate produces panic in patients who, through previous panic experiences, have become conditioned to perceive certain bodily sensations with alarm.[54] Weighing against this notion are the reported failure of ethylenediaminetetraacetic acid,[7] mental arithmetic,[3] glucose tolerance test–induced hypoglycemia,[50] or the cold pressor test[55] to provoke panic in clinically vulnerable patients, despite the prominent physiological changes evoked by these challenges. Our study does not directly test this hypothesis. The course during lactate infusion indicates, however, that many patients perceive symptoms of tremor and paresthesias well before the onset of panic.

Lactate infusions may also cause panic by alteration in the body's NAD^+/NADH ratio. It is NAD^+, the oxidized form of NAD, that is a widely important, necessary coenzyme for the oxidative metabolism of carbohydrates, lipids, and amino acids. In the absence of oxygen (anaerobic conditions), the conversion of pyruvate to lactate replenishes the body's store of NAD^+. This allows energy production by glycosis to continue even under anaerobic conditions.[56] Under normal circumstances, lactate is only produced from pyruvate and is transformed only into pyruvate. During a lactate infusion, there is a huge increase in lactate that, contrary to normal physiology, has not been generated from pyruvate. Therefore, the NAD^+/NADH ratio is shifted in favor of NADH.

Standard lactate infusions are racemic and contain an equal mix of L and D isomers of lactate; however, only L-lactate is converted to pyruvate. If D-lactate proves panicogenic, then the shift in the NAD^+/NADH ratio can be excluded as a possible mechanism.

To conclude, our data do not support depression of ionized calcium or induction of alkalosis as sufficient to cause panic during lactate infusions. That either or both serve to trigger panic attacks in already predisposed patients, however, remains possible.

Peripheral catecholamine surge also does not appear to be the mechanism by which lactate causes panic, although high circulating epinephrine levels may play a predisposing role. Heightened cardiovascular activity is present during most panic attacks, as is evidence of hyperventilation. Stimulation of central noradrenergic centers, either directly or through an unidentified intermediary, is the most likely explanation of these findings, although conclusive evidence is as yet lacking. Since lactate-induced panic occurs frequently in patients who suffer clinical panic attacks but rarely, if at all, in normal controls, lactate must be interacting with deranged regulatory mechanisms in the patient group. However, definitive elucidation of the mechanism underlying lactate-induced panic awaits further experimentation.

One initial concern in the study had been the lack of objective indices for lactate-induced panic. Our data suggest that abrupt increase in heart rate and hyperventilation may serve as markers for the panic experience during lactate infusion. This is consistent with the observation of Lader and Mathews[57] that a rapid increase in heart rate accompanied spontaneous panic attacks in three patients undergoing laboratory testing.

Implications for Understanding Clinical Anxiety States

Clinical panic attacks may involve a combination of baseline arousal followed by triggering. Patient reports of "good days" during which they feel less panic prone and "bad days" during which they are more fearful of venturing forth may reflect fluctuations in baseline arousal. Situations that are unfamiliar, stressful, or from which easy or unobtrusive exits are difficult increase the likelihood of (but do not insure) panic attacks, perhaps by raising baseline arousal. Being accompanied by a trusted figure seems to lower both baseline apprehension levels and panic vulnerability for many patients. If lowering apprehensiveness decreases the probability of experiencing panic, the common antidemoralizing benefits of the various psychotherapies should produce some benefit.[58]

Apprehensiveness is neither a necessary nor sufficient condition for panic and some overriding trigger mechanism remains to be discovered.

This investigation was supported in part by grants MH903-1163C and MHCR903C006 and Research Scientist Development Award MH-00416 (Dr Gorman) from the National Institute of Mental Health.

We thank Isidore Edelman, MD, for his suggestions; Rachel Gittelman, PhD, for her review; Barry Cohen, MS, for data analytic assistance; and Ethel Danielson for her laboratory assistance.

References

1. Pitts FN Jr, McClure JN Jr: Lactate metabolism in anxiety neurosis. *N Engl J Med* 1967;277:1328-1336.

2. Fink M, Taylor MA, Volavka J: Anxiety precipitated by lactate. *N Engl J Med* 1970;281:1429.

3. Kelly D, Mitchell-Heggs N, Sherman D: Anxiety and the effects of sodium lactate assessed clinically and physiologically. *Br J Psychiatry* 1971;119:129-141.

4. Liebowitz MR, Fyer AJ, Gorman JM, Dillon D, Appleby IL, Levy G, Anderson S, Levitt M, Palij M, Davies SO, Klein DF: Lactate provocation of panic attacks: I. Clinical and behavioral findings. *Arch Gen Psychiatry* 1984;41:764-770.

5. Grosz HJ, Farmer BB: Blood lactate in the development of anxiety symptoms. *Arch Gen Psychiatry* 1969;21:611-619.

6. Grosz HJ, Farmer BB: Pitts' and McClure's lactate-anxiety study revisited. *Br J Psychiatry* 1972;120:415-418.

7. Pitts FN, Allen RE: Biochemical induction of anxiety, in Fann WE, Karacan I, Pokorny AD, Williams RL (eds): *Phenomenology and Treatment of Anxiety.* New York, Prentice-Hall Inc, 1979, pp 125-140.

8. Da Prada M, Zurcher G: Simultaneous radioenzymatic determination of plasma and tissue adrenalin, noradrenalin, and dopamine within the femtomole range. *Life Sci* 1976;19:1161-1174.

9. Gulliver PA, Tipton KF: The purification and properties of pig liver catechol-O-methyl transferase. *Eur J Biochem* 1978;88:439-444.

10. Murphy BEP: Some studies of the protein-binding of steroids and their application to the routine micro and ultramicro measurement of various binding radio assay. *J Clin Endocrinol Metabol* 1967;27:973.

11. Dixon WJ, Brown MB: *BMDP 79: Biomedical Computer Programs P Series.* Berkeley, Calif, University of California Press, 1979.

12. Geisser S, Greenhouse SW: On methods in the analysis of profile data. *Psychometrika* 1959;24:95-112.

13. Davenport HW: *The ABC of Acid-Base Chemistry.* Chicago, University of Chicago Press, 1974.
14. Walton RJ: Effect of intravenous sodium lactate on renal tubular reabsorption of phosphate in man. *Clin Sci* 1979;57:125-127.
15. Bonn JA, Harrison J, Rees WL: Lactate-induced anxiety: Therapeutic applications. *Br J Psychiatry* 1971;119:468-471.
16. Bonn JA, Harrison J, Rees WL: Lactate infusion in the treatment of 'free-floating' anxiety. *Can J Psychiatry* 1973;18:41-46.
17. Noel GL, Suh HK, Stone JG, Frantz AG: Human prolactin and growth hormone release during surgery and other conditions of stress: Prolactin and HGH in surgery and stress. *J Clin Endocrinol* 1972;35: 840-851.
18. Buckman MT, Peake GT: Osmolar control of prolactin secretion in man. *Science* 1973;181:755-757.
19. Axelrod J, Reisine TD: Stress hormones: Their interaction and regulation. *Science* 1984;224:452-459.
20. Nemoto EM, Severinghaus JW: Stereospecific permeability of rat blood-brain barrier to lactic acid. *Stroke* 1974;5:81-84.
21. Pardridge WM, Oldendorf WH: Transport of metabolic substrates through the blood-brain barrier. *J Neurochem* 1977;28:5-12.
22. Cohen ME, White PD: Life situations, emotions and neurocirculatory asthenia (anxiety neurosis, neurasthenia, effort syndrome). *Res Publ Assoc Nerv Ment Dis* 1950;29:832-869.
23. Jones M, Mellersh V: Comparison of exercise response in anxiety states and normal controls. *Psychosom Med* 1946;8:180-187.
24. Linko E: Lactic acid response to muscular exercise in neurocirculatory asthenia. *Ann Med Intern Fen* 1950;39:161-176.
25. Holmgren A, Strom G: Blood lactate concentration in relation to absolute and relative work load in normal men and in mitral stenosis, atrial septal defect and vasoregulatory asthenia. *Acta Med Scand* 1959;163: 185-193.
26. Knott V, Chaudhry R, Lapierre YD: Panic induced by sodium lactate: Electrophysiological correlates. *Prog Neuropsychopharmacol* 1981;5: 511-514.
27. Gorman JM, Askanazi J, Liebowitz MR, Fyer AF, Stein J, Kinney JM, Klein DF: Hyperventilation and panic attacks. *Am J Psychiatry* 1984;141: 857-861.
28. Dimsdale JE, Moss J: Plasma catecholamines in stress and exercise. *JAMA* 1980;243:340-342.
29. Frankenhaeuser M, Jarpe G: Psychophysiological reactions to infusions of a mixture of adrenaline and noradrenaline. *Scand J Psychol* 1962;3:21-29.
30. Vlachakis ND, DeGuia D, Mendlowitz M, Antram S, Wolf RL: Hypertension and anxiety: A trial with epinephrine and norepinephrine infusion. *Mt Sinai J Med* 1974;41:1615-1625.
31. Cohen G, Holland B, Sha J, Goldenberg M: Plasma concentrations of epinephrine and norepinephrine during intravenous infusions in man. *J Clin Invest* 1959;38:1935-1941.
32. Dimsdale JE, Moss J: Short-term catecholamine response to psychological stress. *Psychosom Med* 1980;42:493-497.
33. Rainey JM, Frohman CE, Freedman RR, Pohl RB, Ettedgui E, Williams M: Specificity of lactate infusion as a model of anxiety. *Psychopharmacol Bull* 1984;20:45-49.
34. Gorman JM, Levy GJ, Liebowitz MR, McGrath P, Appleby IL, Dillon DJ, Davies SO, Klein DF: Effects of acute β-adrenergic blockade on lactate-induced panic. *Arch Gen Psychiatry* 1983;40:1079-1082.
35. Scebat A, Castan L, Renais R, Chiche J, Fernandez F, Gerbaux A: Action d'une perfusion de lactate de soude sur les effets hemodynamiques de beta-bloquants. *Arch Mal Coeur* 1978;71:306-313.
36. Heiser JF, Defrancisco D: The treatment of pathological panic states with propranolol. *Arch Gen Psychiatry* 1976;133:1389-1394.
37. Kathol RG, Noyes RN Jr, Slymen DJ, Crowe RR, Clancy J, Kerber R: Propranolol in chronic anxiety disorders: A controlled study. *Arch Gen Psychiatry* 1980;37:1361-1365.
38. Noyes R Jr, Anderson DJ, Clancy J, Crowe RR, Slymen D, Ghobneim MM, Hinrichs J: Diazepam and propranolol in panic disorder and agoraphobia. *Arch Gen Psychiatry* 1984;41:287-292.
39. Holmberg G, Gershon S: Autonomic and psychic effects of yohimbine hydrochloride. *Psychopharmacologia* 1961;2:93-106.
40. Garfield SL, Gershon S, Sletten I, Sundland DM, Ballou S: Chemically induced anxiety. *Int J Neuropsychiatry* 1967;3:426-433.
41. Redmond DE: New and old evidence for the involvement of a brain norepinephrine system in anxiety, in Fann WE, Karacan I, Pokorny AD, Williams RL (eds): *Phenomenology and Treatment of Anxiety.* New York, Prentice-Hall Inc, 1979, pp 153-203.
42. Gray JA: The neuropsychology of anxiety. *Br J Psychol* 1978;69: 417-434.
43. Ko GN, Elsworth JD, Roth RH, Rifkin BG, Leigh H, Redmond DE: Panic-induced elevation of plasma MHPG levels in phobic-anxious patients. *Arch Gen Psychiatry* 1983;40:425-430.
44. Hoehn-Saric R, Merchant AF, Keyser ML, Smith VK: Effects of clonidine on anxiety disorders. *Arch Gen Psychiatry* 1981;38:1278-1282.
45. Liebowitz MR, Fyer AJ, McGrath P, Klein DF: Clonidine treatment of panic disorder. *Psychopharmacol Bull* 1981;17:122-124.
46. Cooper JR, Bloom FE, Roth RH: *The Biochemical Basis of Neuropharmacology,* ed 4. New York, Oxford University Press, 1982.
47. Gold MS, Redmond DE, Kleber HD: Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. *Am J Psychiatry* 1979;136:100-102.
48. Kulig K, Duffy J, Rumack BH, Mauro R, Gaylord M: Naloxone for treatment of clonidine overdose. *JAMA* 1982;247:1697.
49. Sheehan DV, Carr DB, Surman OS, Nolan JM, Fisher JF, Claycomb JB: Sodium lactate infusion as a model for the biological investigation of panic. Syllabus and scientific proceedings of the American Psychiatric Association 137th Annual Meeting, Los Angeles, May 5-11, 1984.
50. Uhde TW, Boulenger JP, Siever L, Vittone B, Jimerson DC, Post R: Panic disorder: Drug challenge strategies. Syllabus and scientific proceedings of the American Psychiatric Association 137th Annual Meeting Los Angeles, May 5-11, 1984.
51. Elam M, Yoa T, Thoren P, Svensson TH: Hypercapnia and hypoxia: Chemo-receptor–mediated control of locus ceruleus neurons and splanchnic, sympathetic nerves. *Brain Res* 1981;222:373-381.
52. Mathew RJ, Feldman L, Stuyck KH: *The Biology of Anxiety.* New York, Brunner/Mazel Inc, 1982.
53. Carr DB, Sheehan DV: Panic anxiety: A new biological model. *J Clin Psychiatry* 1984;45:323-330.
54. Ackerman SH, Sachar EJ: The lactate theory of anxiety: A review and reevaluation. *Psychosom Med* 1974;36:69-81.
55. Grunhaus L, Gloger S, Birmacher B, Palmer C, Ben-David M: Prolactin response to the cold pressor test in patients with panic attacks. *Psychiatry Res* 1983;8:171-177.
56. Orten JM, Neuhaus OW, Lotz JE: *Human Biochemistry.* St Louis, CV Mosby Co, 1982.
57. Lader M, Mathews A: Physiological changes during spontaneous panic attacks. *J Psychosom Res* 1983;14:377-382.
58. Klein DF, Zitrin CM, Woerner MG, Ross DC: Treatment of phobias: II. Behavior therapy and supportive therapy: Are there any specific ingredients? *Arch Gen Psychiatry* 1983;40:139-145.