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Lactate Infusions and Panic Attacks: Do Patients and Controls Respond Differently?

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Abstract. Ten patients with panic disorder or agoraphobia with panic attacks and 10 normal controls received infusions of normal saline (placebo) and sodium lactate in a single-blind design. The time course of changes in the dependent variables was closely monitored, and expectancy biases and demand characteristics were minimized. Lactate increased self-reported anxiety and heart rate equally in patients and controls. The only variables showing statistically different responses between the groups were systolic and diastolic blood pressure. Overall, in both groups, the effects of lactate were quite similar to states of natural panic or anxiety for both self-report measures and heart rate. Patients had a tendency to endorse somatic symptoms indiscriminately. Our data do not support response to lactate as a biological marker of proneness to panic attacks.

Key Words. Panic disorder, agoraphobia, anxiety, sodium lactate infusion, heart rate, blood pressure.

Agoraphobia with panic attacks and panic disorder are characterized by frequent panic attacks, i.e., discrete periods of apprehension or fear accompanied by such symptoms as dyspnea, palpitations, chest pain, and fear of dying (*DSM-III*, American Psychiatric Association, 1980). Infusions of sodium lactate are considered a useful tool in investigating the possible causes of panic attacks. Although the mechanism of lactate's effects is unclear (Ackerman and Sachar, 1974; Insel et al., 1984; Levin et al., 1984; Rainey et al., 1984*b*; Margraf et al., 1986), there is evidence that the incidence of lactate-induced panic attacks is much higher in patients prone to panic attacks than in normal controls (Pitts and McClure, 1967; Bonn et al., 1971; Fink et al., 1971; Kelly et al., 1971; Appleby et al., 1981; Rifkin et al., 1981; Liebowitz et al., 1984; Rainey et al., 1984*a*, 1984*b*). Usually, patients reported higher anxiety levels and more anxiety symptoms with lactate than controls, and also showed higher autonomic arousal

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(Freedman et al., 1984; Liebowitz et al., 1985). This has led to the conclusion that lactate infusions might be useful both as a diagnostic test and as a method of evaluating the effectiveness of treatment (Fink et al., 1971; Klein, 1981; Sheehan et al., 1985). Fyer et al. (1985) recently suggested that "lactate vulnerability may be a trait characteristic" (p. 143). Lactate studies have been advanced as the major support for the notion of panic disorder as a biological entity distinct from other anxiety disorders (Shader et al., 1982; Carr and Sheehan, 1984).

Recent studies, however, have reported that patients showed higher levels of anxiety and heart rate than controls even before the lactate infusion began (Freedman et al., 1984; Liebowitz et al., 1984, 1985; Rainey et al., 1984*a*, 1984*b*), which replicates earlier findings of Kelly et al. (1971). Moreover, higher levels of anxiety and heart rate were correlated with the propensity to panic under lactate (Liebowitz et al., 1984, 1985). Furthermore, a number of patients (5-36%) have reported panic attacks in response to placebo infusions (Kelly et al., 1971; Appleby et al., 1981; Liebowitz et al., 1983; Rainey et al., 1984*a*, 1984*b*), whereas controls never report panic to placebo. Thus, it is possible that differences between patients and controls in *baseline levels* rather than in *degree of responsiveness* explain the different levels of anxiety reached with lactate infusion (for a comprehensive review, see Margraf et al., 1986).

Earlier studies could not distinguish between effects of baseline differences and responsivity because they did not assess the dependent variables frequently enough. With few exceptions (Liebowitz et al., 1984; Rainey et al., 1984*b*), the degree of similarity of lactate effects and naturally occurring panic attacks has been neglected. The resolution of these issues has been hampered by a general methodological shortcoming—namely, the lack of control of nonspecific factors such as different expectations in the groups or different reactions to a laboratory setting. The main purpose of our study was to investigate whether patients and controls would respond differently to lactate infusions in a design that controlled experimenter influences and demand characteristics. Our methods included frequent assessment of anxiety, other mood states, heart rate, and blood pressure.

Methods

Subjects. Ten female panic attack patients and 10 female control subjects were recruited from the community by newspaper advertisements. Three patients met *DSM-III* criteria for agoraphobia with panic attacks, four for panic disorder with limited phobic avoidance, and four for uncomplicated panic disorder as determined by the Structured Clinical Interview for *DSM-III*—Upjohn Version (SCID-UP) (Spitzer and Williams, 1983). Anyone who currently qualified for a diagnosis of a major affective disorder was excluded. To be accepted, patients had to be willing to discontinue any psychoactive medication 2 weeks before the lactate infusion and remain off medication until the end of the study. Control subjects had to be free of any history of psychiatric problems as determined by the SCID-UP and a general psychiatric interview, and not taking psychoactive medications. Plasma benzodiazepine levels from blood taken before the infusion indicated that all patients and controls were drug free. The groups were matched for age (mean 38.8 ± 10.5 for patients, 35.4 ± 6.7 for controls). All subjects were Caucasian. Subjects were in good physical health as determined by medical history, physical examination, and an electrocardiogram.

Procedure. To minimize interpersonal influences, subjects sat alone in a sound-attenuated, electrically shielded chamber. They could not see the laboratory personnel, but could

communicate with them by intercom at any time. Identical instructions were used for patients and controls. At exactly the time points specified in Table 1, a nurse came into the chamber, took the subject's blood pressure, and administered psychological tests. The nurse and the laboratory assistant did not know the subject's diagnosis. Four days before the lactate infusion, subjects had undergone a psychophysiological test battery in the same chamber. Besides familiarizing subjects with the laboratory environment, this session provided information on the time course of our measures in the same setting, but in the absence of an infusion.

As in most other lactate infusion studies, a single-blind procedure with a fixed sequence of infusions was used, similar to the procedure of the Columbia group (e.g., Liebowitz et al., 1984). The infusion period was divided into four parts. First, 0.5 normal saline was infused slowly for 15 minutes. Then, its rate was increased to what would be used for the lactate infusion. This condition was introduced to ensure the single blind and as a control for the effects of fast infusion rate per se. After 15 minutes of the fast saline infusion, 1.0 *M* racemic sodium lactate was infused at the rate of 15 m*M*/kg/hour for a maximum of 20 minutes. However, the lactate infusion was terminated before 20 minutes if subjects reported severe anxiety or panic and asked to stop. In any case, recording was continued for a 20-minute recovery period after the end of the lactate infusion, while saline was infused slowly to keep open the i.v. cannula. This concentration of lactate was previously used in several studies (Bonn et al., 1971, 1973; Freedman et al., 1984; Lapierre et al., 1984; Rainey et al., 1984*a*, 1984*b*). We chose this concentration rather than 0.5 *M* lactate to reduce the total fluid volume needed. The total amount of lactate, however, was equal to that used in almost all lactate infusion studies (for review, see Margraf et al., 1986).

Assessment of Lactate-Induced Changes. Three self-rating inventories of varying complexity were used for assessment of subjective state during the infusion: an Anxiety Rating Scale (AR), a Mood Scale (MS), and the State Form of the State-Trait Anxiety Inventory (STAI(S)) (Spielberger et al., 1970). All self-report inventories were given neutral names to reduce expectency bias. The AR and the MS use rating scales from 0 (labeled "none") to 10 (labeled "extreme"). The *AR* asks the subject to rate herself for "anxiety" and "excitement." The separate rating of excitement was included because patients and controls might differ in their ways of labeling arousal. The *MS* asks the subject to rate herself on 11 adjectives derived from the Profile of Mood States (McNair et al., 1981) and the Mood Adjective Checklist (Nowlis, 1965). The anxiety adjectives are "tense," "nervous," and "fearful," and the other adjectives are "depressed," "angry," "confused," "bored," "tired," "energetic," "comfortable," and "contented." The anxiety score is the sum of the scores on the three anxiety adjectives.

The electrocardiogram was continuously monitored and recorded. Heart rate was calculated from interbeat intervals (Graham, 1978). For statistical analysis, artifact-free 1-minute epochs beginning at specified time points were used. Blood pressure was measured by a brachial cuff and auscultation. Table 1 shows the assessment schedule for the lactate infusion session. If a subject asked to stop the infusion prematurely, a full set of measures (AR, MS, STAI, heart rate, and blood pressure) was obtained at that time (presumably the peak of anxiety). The same self-report and cardiovascular assessments were also applied on the first day that subjects came to the psychophysiological laboratory (without infusion).

Similarity of Lactate Effects and Natural Panic Attacks. During the week preceding the lactate infusion, subjects wore an ambulatory heart rate monitor and kept a panic attack diary in which they recorded the intensity of anxiety (on the same 11-point rating scale as in the AR) and the symptoms experienced during naturally occurring panic attacks. Twenty-five panic attacks were monitored (cf. Taylor et al., in press). Heart rates and anxiety ratings during these panic attacks were compared to the effects of lactate in the laboratory.

In addition, subjects were asked to compare the lactate experience with their usual panic attacks (patients) or most extreme anxiety (controls) on an 11-point Similarity Rating Scale from -5 (very dissimilar) to +5 (very similar). Furthermore, subjects described the effects of lactate on the Profile of Mood States (POMS) (McNair et al., 1981) and on a Symptom Questionnaire (Table 1). In the preceding test session, they had described a "usual panic attack"

Table 1. Assessment schedule

Event	Minute	AR	MS	STAI	HR	BP	SQ/POMS
Attaching electrodes		X	X	X			
Before i.v.		X	X				
Saline—slow infusion rate	0	X			X	X	
	5	X					
	10	X	X		X	X	
Saline—fast infusion rate	15	X					
	20	X					
	25	X	X		X	X	
Lactate	30	X					
	35	X					
	40	X	X		X	X	
	45	X					
	50	X	X	X	X	X	
Recovery	55	X					
	60	X	X		X	X	
	65	X					
	70	X	X		X	X	
Removing electrodes		X	X	X			X

The following abbreviations are used: AR (Anxiety Rating Scale), MS (Mood Scale), STAI (State Trait Anxiety Inventory, State Form), POMS (Profile of Mood States), SQ (Symptom Questionnaire), HR (heart rate), BP (blood pressure). The minutes indicate the relative time after start of the infusion. While HR was measured continuously, only mean HR for 1-minute epochs beginning at the time points shown in this table were used for statistical analysis.

(patients) or the "most extreme anxiety ever experienced" (controls) on these questionnaires and on the STAI(S). The Symptom Questionnaire comprises 53 descriptive words or short phrases, which are rated on a scale from 0 (not at all) to 4 (extremely). These items describe symptoms of five kinds. Eighteen items describe *DSM-III* symptoms ("Panic-*DSM-III*" Scale, PD Scale). Another 18 items represent other symptoms that have been used as symptoms of panic in the literature, e.g., "fluttery stomach" ("Panic-additional" Scale, PA Scale). Seven other items describe symptoms that might be associated with catecholamine secretion (CC Scale) and are not usually referred to as anxiety symptoms, e.g., "hair standing on end" (Charney et al., 1982). Three symptoms of hypocalcemia (e.g., "muscle cramps") that are not usually considered symptoms of anxiety were included as lactate infusions can induce hypocalcemia (HC Scale). To assess response bias, a "Somatic Control Scale" (SC Scale) was included that consists of seven items such as "ticklishness." The endorsement of these items is considered to represent a bias toward indiscriminate endorsement of somatic symptoms.

Data Analysis. Repeated measures analysis of variance (ANOVA) with the Greenhouse-Geisser correction was used to calculate statistical significance. Different reactions of patients and controls to lactate would be seen as significant interactions between the factors Time (changes over the time points) and Group (patients vs. controls). Significant main effects or interactions were further evaluated for significant differences by paired and nonpaired *t* tests. Since some patients stopped the lactate infusion before the full 20 minutes, there were missing data. Three alternatives were used in order to include subjects with missing data in the analysis. First, time points that were not available for all subjects were excluded. Second, the last measurements taken during the lactate infusion were used as estimates for missing time points. Third, extrapolations from the changes occurring during the first half of the lactate infusion were used as estimates for missing time points.

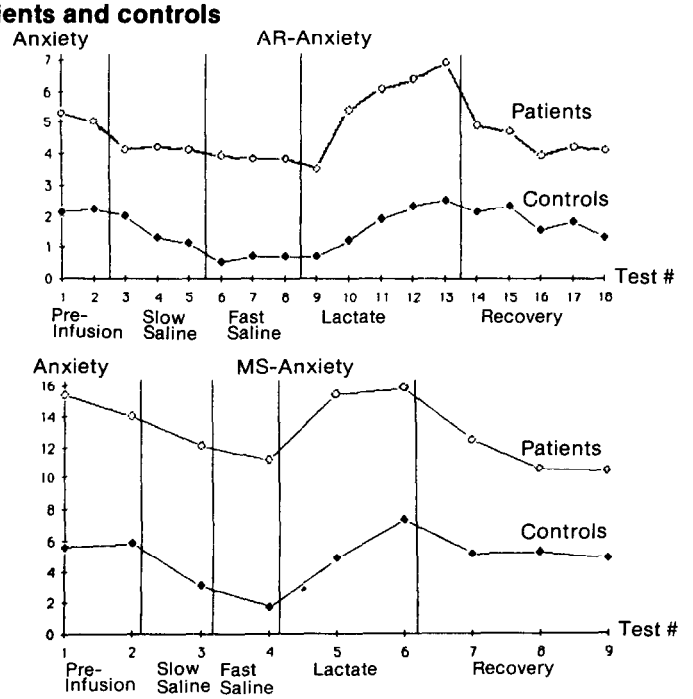
For comparing the incidence of panic attacks in the groups, we used Fisher's exact probability test. For the comparison of lactate- and placebo-induced panic attacks, we used the McNemar test for the significance of changes. Statistical analyses were done on the raw scores of the STAI(S) and the POMS. For the scales of the Symptom Questionnaire, a severity score was calculated by adding the ratings for all items. If not mentioned otherwise, the results reported here meet the significance level of 0.05. All significance levels are two-tailed.

Results

Length of Lactate Infusions. Four patients asked to stop the infusion because of intolerable anxiety. In one of these cases, the request came in the last minute of the infusion so that this subject actually completed the infusion. For the other three patients, lactate was stopped after 8, 10, and 11 minutes. For another patient, the infusion had to be stopped after 13 minutes because of S-T depression in the electrocardiogram. This patient had not asked us to stop. In one patient and one control subject, it took 25 instead of 20 minutes to infuse the full lactate dose because the flow rate of the infusion was limited by the resistance of the vein in which the needle was placed.

Subjective Anxiety. All three measurements of subjective anxiety (AR-anxiety, MS-anxiety, STAI(S)) showed the same pattern of results: overall higher anxiety in the patients compared to the controls, but parallel and approximately equal increases during the lactate infusion. Fig. 1 shows the mean for AR-anxiety and MS-anxiety. At

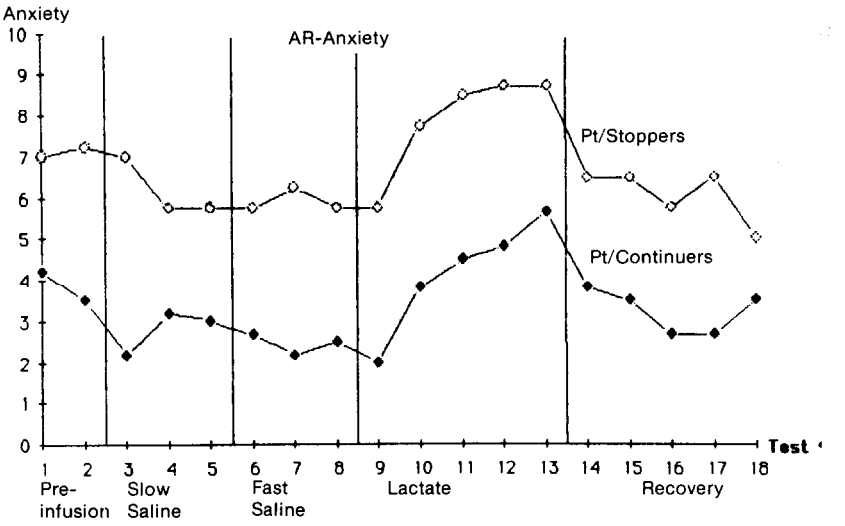
Fig. 1. AR-anxiety and MS-anxiety scores during the lactate infusion session for patients and controls



The range of AR-anxiety is 0-10, and the range of MS-anxiety is 0-30. The last ratings given during the lactate infusion are used as estimates for missing time points in 4 patients who stopped the infusion before 20 minutes had elapsed.

all time points during the session, patients who stopped the lactate infusion before the full 20 minutes had higher anxiety scores than patients who did not discontinue the infusion ($p < 0.05$ for AR-anxiety) as shown in Fig. 2.

Fig. 2. AR-anxiety scores during the lactate infusion session for patients who completed the lactate infusion (PT/Continuers, $n = 6$) and patients who did not complete the lactate infusion (PT/Stoppers, $n = 4$)



The last ratings given during the lactate infusion are used as estimates for missing time points.

ANOVAs for both anxiety measures showed highly significant Group ($p < 0.001$ for the AR, $p < 0.01$ for the MS) and Time effects ($p < 0.001$ for the AR, $p < 0.01$ for the MS). Time × Group interactions were far from significant. The F ratios for the interactions ranged from 0.86 to 1.28 on the basis of the three different ways of dealing with missing data described above. AR-anxiety and MS-anxiety increased significantly with the lactate infusion. The increase in the rate of infusion (fast drip of saline) alone did not elicit anxiety. Interestingly, the very first ratings when subjects came to our laboratory did not differ significantly from those at the end of the lactate infusion.

The results for the STAI(S) are shown in Table 2. In an ANOVA, we compared the scores of the groups at three assessments (Time) during two laboratory sessions (Day), the preceding session without infusion and the lactate infusion session. Patients had higher anxiety scores ($p < 0.01$ for the Group factor) on both occasions. The anxiety increases on the infusion day contrast to an anxiety decrease on the day without infusion ($p < 0.001$ for the Day factor and $p < 0.001$ for the Day × Time interaction). Again, all interactions with the Group factor were far from the significant (F ratios smaller than 0.9).

Other Mood States. The results for AR-excitement on the lactate infusion day parallel those for AR-anxiety in time course ($p < 0.02$ for Time effect). Patients had significantly higher scores than controls ($p < 0.05$ for Group effect). Descriptors of other mood states followed different patterns. There were no group differences, and the time course was clearly distinct from that of the anxiety and excitement ratings.

Table 2. Results of the STAI(S)

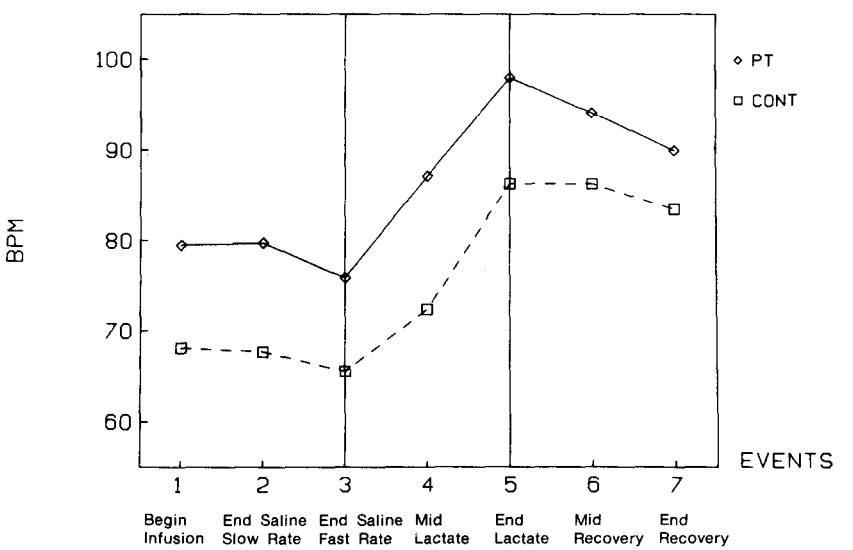
	Previous session without infusion			Lactate infusion session			Usual panic/anxiety
	1	2	3	1	2	3	
Patients							
Mean	49.5	44.9	44.8	55.5	62.5	58.0	71.1
SD	10.0	11.8	15.0	12.3	12.6	10.9	7.1
Controls							
Mean	34.4	30.2	32.2	35.3	49.0	44.0	62.0
SD	8.9	4.8	6.7	9.7	12.8	12.0	12.2

The possible range of State Trait Anxiety Inventory (STAI) scores is from 10 to 80; 1 refers to the beginning of the laboratory sessions; 2 refers to the middle of the session on the previous test day and to the end of the lactate part of the infusion on the second test day; and 3 refers to the end of the laboratory sessions.

Comparison to the Pre-infusion Test Day. During the previous laboratory session without infusion, patients and controls also differed in their anxiety levels ($p < 0.001$ for AR-anxiety and MS-anxiety). On all our anxiety measures (AR-anxiety, MS-anxiety, and STAI(S)), and on AR-excitement, patients had higher scores. The time course of change on the 2 days, however, was clearly distinct. Anxiety decreased on the day without infusion in both groups ($p < 0.05$ for AR, $p < 0.001$ for MS-anxiety).

Physiological Changes. Fig. 3 shows the average heart rate (HR) for 1-minute epochs representing the different parts of the infusion. Inspection of the patient and

Fig. 3. Heart rates for patients (PT) and controls (CONT) during the lactate infusion session



Mean heart rates during the 1-minute epochs selected for statistical analysis are presented in beats per minute (bpm). Note that for 4 of 10 patients the end of lactate occurred before 20 minutes had elapsed.

control averages for the continuously recorded heart rate (10-second averages) had shown smooth and gradual changes. Thus, the HR means at the times chosen a priori for statistical analysis were representative of the total data set. Furthermore, inspection of the individual HR records showed gradual increases for all controls and all but two patients. In two patients, we found abrupt surges in HR representing sinus tachycardia. These changes occurred during lactate, but also during baseline and recovery periods. The ANOVA showed significant Time ($p < 0.001$) and Group ($p < 0.05$) effects. Patients had higher HR than controls. Lactate increased HR significantly in both groups by about 20 beats per minute (bpm). The increase in infusion drip rate itself did not lead to increases in HR. The lack of a Time × Group interaction confirms the visual impression that the rise in HR from placebo to lactate was equal by the end of lactate for patients and controls. F ratios for the interaction of the Time and Group factors ranged between 1.0 and 1.5 using the different ways of dealing with missing data described above.

At baseline, patients for whom the lactate infusion had to be stopped before the full 20 minutes did not differ in HR from the other patients. However, their HR increased at a faster rate with the lactate infusion (increase of 20 bpm within the first 10 minutes of lactate) than did HR of other patients and controls. After lactate had been stopped, their HR decreased by 15 bpm during the 20-minute recovery period, whereas for other patients and controls HR decreased only by 3 bpm. This led to a significant Time × Group interaction ($p < 0.05$) in an ANOVA comparing the three groups.

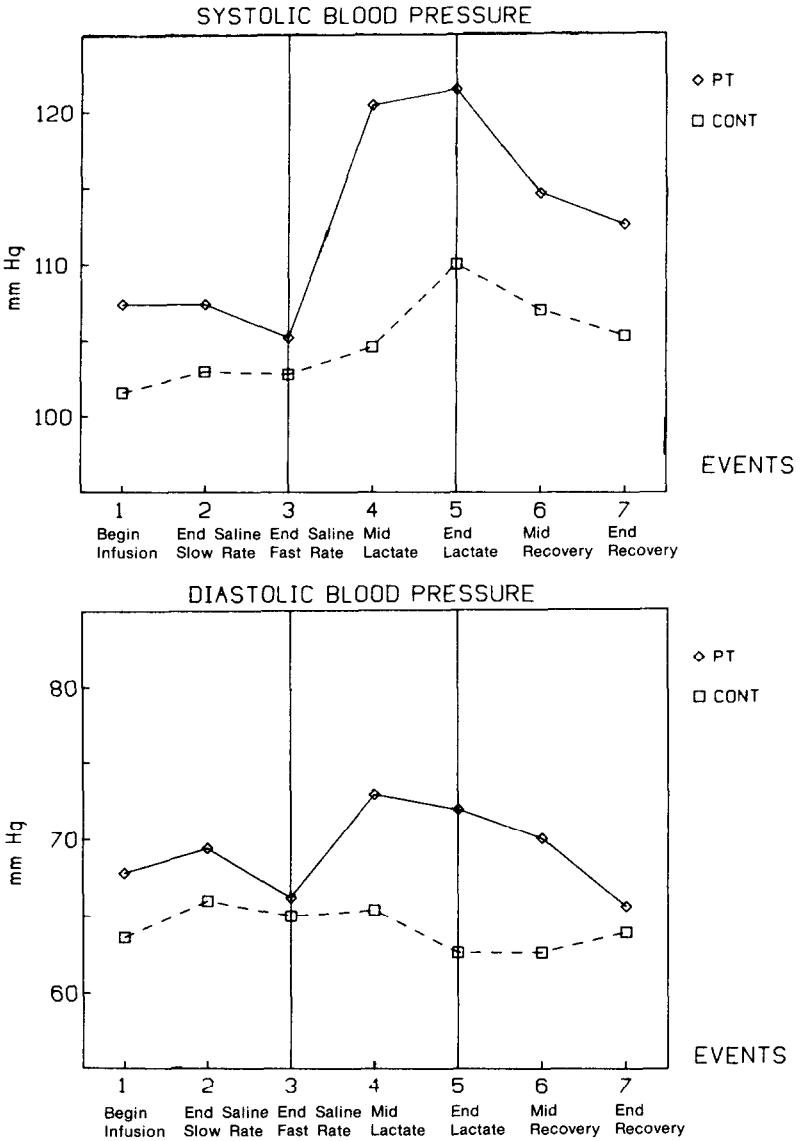
The results for blood pressure are presented in Fig. 4. Blood pressure was the only measure in our experiment which showed a statistically different lactate response for the patient and control groups. Patients had faster and larger increases in systolic blood pressure with lactate. Diastolic blood pressure increased significantly only in patients. This led to significant Time × Group interactions ($p < 0.05$).

These results contrast to those of the pre-infusion laboratory session, during which HR and diastolic blood pressure did not change while systolic blood pressure decreased ($p < 0.05$). During the pre-infusion session, patients' average HR was 8 to 11 bpm higher and systolic blood pressure 8 to 10 mmHg higher than those of controls, both of which differences were almost significant ($p < 0.07$ and $p < 0.06$ for the Group factor, respectively).

Incidence of Lactate-Induced Panic. This incidence is very dependent on the criteria adopted. If we take the demand for stopping the lactate infusion as the criterion, 4 of 10 patients and no controls had panic attacks. This difference is marginally significant ($p < 0.10$; Fisher's exact probability test). However, the request to stop might depend on the subject's tendency to avoid anxiety as well as the actual intensity of the anxiety. Of the four patients who asked to discontinue the infusion, two had a diagnosis of agoraphobia with panic attacks and two a diagnosis of panic disorder with limited avoidance.

Another possible criterion for the occurrence of panic attacks is the number of symptoms reported and the increase in anxiety that accompanied these symptoms. *DSM-III* lists 12 symptoms of panic attacks and requires at least four of these for a diagnosis. In our sample, nine patients and six controls reported four or more of these symptoms on the Symptom Questionnaire. This difference is not significant. If we

Fig. 4. Systolic blood pressure (upper part) and diastolic blood pressure (lower part) (in mmHg) for patients (PT) and controls (CONT) during the lactate infusion session



Note that for 4 of 10 patients the end of lactate occurred before 20 minutes had elapsed.

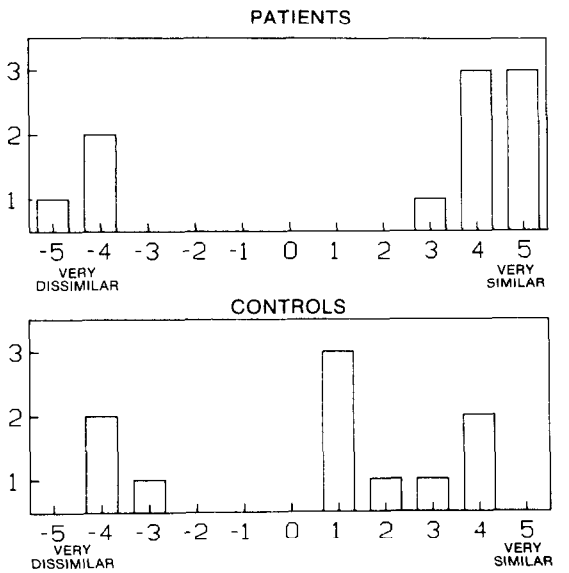
require a 2-point increase on the anxiety scale of the AR as well as four or more *DSM-III* symptoms, eight patients and four controls qualify as having had panic attacks. Again, this difference is not significant. However, these numbers are considerably higher than the number of self-reported panic attacks evoked by the placebo infusions (one patient) or on the first day in the laboratory (one patient) ($p < 0.05$, McNemar test for the significance of changes).

Similarity of Lactate and Ambulatorily Monitored Panic Attacks. During 25 natural panic attacks occurring in the week before the infusion, patients reported an average AR-anxiety level of 4.7, which is somewhat lower than the level reported at the end of the lactate infusion (6.9). The average maximum HR during natural panic attacks was 111.1 bpm. This compares to an average HR of 97.9 bpm at the end of the lactate infusion. Higher HR during natural panic attacks may be due to physical activity since that variable was not controllable outside the laboratory. Furthermore, HR levels during natural panic attacks showed large interindividual and intra-individual variability, and a substantial proportion of panic attacks were not accompanied by HR changes (Taylor et al., in press).

Similarity of Lactate and Retrospectively Described Panic Attacks. Results on four scales are summarized below.

Similarity Rating Scale. Fig. 5 shows histograms of the overall similarity ratings of natural and lactate-induced anxiety for each group. In both groups, seven subjects rated the experiences as similar and three as dissimilar. There was a tendency, especially among the patients, to give extreme ratings.

Fig. 5. Distribution of the Similarity Ratings between lactate effects and usual panic attacks in patients, and between lactate effects and extreme anxiety in controls



Symptom Questionnaire. Table 3 shows the subjects' descriptions of lactate effects and usual panic attacks (patients) or extreme anxiety (controls) on the Symptom Questionnaire. Patients rated lactate as producing equal (PD) or less severe (PA) anxiety symptoms than natural panic attacks. Controls rated lactate as equal to their memories of extreme anxiety on both anxiety symptom scales. Both groups rated lactate as causing equally severe catecholamine and somatic control symptoms, but

more severe hypocalcemia symptoms. Patients gave higher ratings on all scales for both lactate and panic than controls, even on the somatic control symptoms (SC) that were chosen to be irrelevant to lactate or anxiety experiences. There was little overlap in the scores between groups. (Results for the items of the SQ are available from the authors.)

Table 3. Results of the Symptom Questionnaire

	Patients		Controls		ANOVA		
Symptom Scale	Usual panic	Lactate effects	Usual anxiety	Lactate effects	G	E	G × E
Panic-*DSM-III* (PD)	71	57	16	18	$p < 0.001$	NS	NS
Panic-Additional (PA)	64	46	21	18	$p < 0.001$	$p < 0.01$	$p < 0.05$
Catecholamine secretion (CC)	48	44	11	16	$p < 0.001$	NS	NS
Hypocalcemia (HC)	39	58	6	28	$p < 0.001$	$p < 0.01$	NS
Somatic control (SC)	19	14	1	6	$p < 0.01$	NS	NS

Because the scales vary in their number of items, means are presented in % of the maximal possible score for each scale. Event (E) refers to the comparison of usual panic/extreme anxiety with lactate, G refers to group (patients vs. controls), G × E to the interaction of the factors.

POMS and STAI(S). On the POMS patients reported higher levels of tension/anxiety, confusion, depression, and fatigue than did controls, for both natural anxiety and lactate ($p < 0.01$ or $p < 0.001$). Both groups reported less tension/anxiety, depression, and aggression for lactate than for natural anxiety ($p < 0.05$ or $p < 0.01$). On the STAI(S) (Table 2), patients described significantly higher levels of anxiety than controls for both natural panic and lactate ($p < 0.05$). Both groups reported lower levels of anxiety for lactate than for natural anxiety ($p < 0.001$).

Discussion

Our results demonstrate that sodium lactate infusions increase anxiety and cardiovascular arousal in both patients prone to panic attacks and controls. These changes appear specific to lactate since they did not occur during saline infusion or on a previous day when subjects remained in the recording booth for the same length of time. Anxiety was specifically increased by lactate in contrast to other moods such as depression. Measures of subjective anxiety and HR showed a very close degree of covariation for the whole experimental session.

The most prominent difference between patients and controls was constantly elevated anxiety and HR in panic patients, beginning in the baseline (before lactate) period and continuing throughout the session. These differences were present even on the previous laboratory day. Baseline differences between patients and controls have largely been neglected in the interpretation of lactate infusion studies (cf. Margraf et al., 1986), although they have been reported by Kelly et al. (1971), Freedman et al. (1984), and Liebowitz et al. (1984, 1985).

Our findings for anxiety and HR do not support previous reports that most patients prone to panic attacks are more reactive to lactate than controls. This cannot be because our patients were made less anxious by lactate or had lower HR, since their

STAI(S) and HR levels were as high as reported by other groups. Furthermore, the absence of differences between patients and controls could not be a ceiling effect, since our patients' anxiety scores were seldom maximal and only two patients reached HR $\geqslant 130$. Furthermore, it is unlikely that our small sample size was responsible for the results. Time and Group effects were highly significant, and the F ratios for the interactions with the Group factor would have had probabilities larger than 0.05 even with an infinite sample size. Our results are in line with those of Freedman et al. (1984), who also failed to observe greater HR reactivity in patients.

While patients and controls as diagnostic groups did not differ in reactivity, subgroups of more reactive patients may exist. Four of our patients for whom lactate was stopped early showed more rapid HR increases and decreases than other patients or controls. Thus, some patients may differ in the speed of HR reactivity if not in degree. Interestingly, these patients showed higher baseline anxiety than other patients and controls. Since there were only four patients in this group, statistical comparisons would not have been meaningful.

Patients reported much more severe lactate-induced symptoms than controls on the Symptom Questionnaire. However, without further evidence, this cannot be taken as proof that patients were more reactive to lactate. The greater severity of lactate-induced symptoms in our patients may reflect only a tendency for them to endorse items indiscriminately, since patients also had high scores on our Somatic Control Scale, which comprised items irrelevant to anxiety or lactate infusion.

Systolic and diastolic blood pressure were more reactive to lactate in patients than controls. In Liebowitz et al. (1985), this difference in blood pressure reactivity was significant only for diastolic blood pressure. Consistent with their findings, we found no baseline blood pressure differences between groups. Thus, certain physiological variables may register differential reactivity in the absence of differential psychological reactivity. Only further replications can rule out the possibility that these variables emerged from larger sets by chance.

Patients usually describe their panic attacks as having an abrupt onset, so an abrupt surge in anxiety and its physiological concomitants might be expected. This was the case in only two patients and only one variable, namely heart rate. At first glance, lactate-induced anxiety also seems less intense than natural panic attacks. Our subjects did not report their lactate anxiety as being any more intense than the anxiety they felt when they first entered the laboratory. Their average HR increase of 20 bpm is much less than that sometimes recorded during natural panic attacks (Lader and Mathews, 1970; Taylor et al., 1983, in press; Cohen et al., 1985), or in inexperienced healthy parachutists before jumping (Fenz and Epstein, 1967), but is more on a par with the increases found in normal students before examinations (19 bpm; Hickam et al., 1948). Other investigators have found the same moderate anxiety levels and HR increases after lactate that we have (cf. Margraf et al., 1986).

However, a direct comparison in our patient sample of heart rates and anxiety ratings during lactate and during ambulatorily monitored natural panic attacks showed that lactate effects were of comparable magnitude to those of naturally occurring panic attacks. Not all natural panic attacks lead to extreme anxiety or large HR increases. Furthermore, symptom patterns that subjects experienced with lactate were quite similar to those that they described for natural anxiety, except that

symptoms of hypocalcemia were more predominant as Liebowitz et al. (1984) had found. The fact that the majority of our subjects rated lactate effects as globally similar to natural anxiety is consistent with a similarity in symptom patterns.

In conclusion, lactate was shown to induce a subjective and physiological state that has features of panic attacks. However, our data show that controls as well as patients react to lactate infusions with substantial anxiety, and HR increases. Our study found clear-cut differences between the groups only for blood pressure and the request to stop the infusion. The latter is an arbitrary measure, reflecting many psychological factors in addition to anxiety. For anxiety and HR, differences present before the lactate infusion are sufficient to explain the different levels occurring during lactate. Thus, our data do not support the hypothesis that response to lactate is a biological marker of a person's proneness to panic attacks.

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