Plasma Cortisol Concentrations Preceding Lactate-Induced Panic

Psychological, Biochemical, and Physiological Correlates

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**Background:** We evaluated the role of plasma cortisol levels in determining sodium lactate–induced panic by reporting psychological, physiological, and biochemical data collected from an extended sample of 214 subjects during the “placebo” infusion (isotonic saline solution) immediately preceding the lactate infusion procedure.

**Methods:** One hundred seventy patients with panic disorder, 101 (59%) of whom were assessed to have panicked (P group), and 69 (41%) who were assessed not to have panicked (NP group) with lactate infusion; and 44 normal healthy volunteer controls (1 of whom panicked with lactate infusion) were studied.

**Results:** Before the lactate infusion, the P group exhibited hypothalamic-pituitary-adrenal (HPA) axis activation (high plasma cortisol levels) and evidence of hyperventilation (low P CO₂ levels) in comparison with NP and control groups. Self-reported fear, dyspnea, and diastolic blood pressure were highest in the P group, intermediate in the NP group, and lowest in the control group. Within the P group, baseline fear scores correlated inversely with P CO₂ levels and positively with cortisol levels while P CO₂ levels correlated negatively with cortisol levels. Significant predictors of lactate-induced panic were prelactate infusion fear and the interaction of high cortisol levels and low P CO₂ levels.

**Conclusion:** Combined data suggest that synchronized elevations of HPA axis activity, self-reported fear, and hyperventilation during the period before lactate infusion predisposes to lactate-induced panic.

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INCREASED ADRENAL secretion of glucocorticoids has been linked to acute stress and various anxiety states involving both clinical and preclinical samples.¹ It is therefore striking that investigators have failed to find any increase in cortisol level during the acute panic attacks experienced by patients with panic disorder when undergoing infusion with sodium lactate, following inhalation of carbon dioxide, or when placed in a phobic situation.²⁻⁴ In an effort to further understand the role of glucocorticoids in lactate-induced panic, we evaluated plasma levels of cortisol during the period immediately preceding lactate-induced panic, presumably reflecting anticipatory anxiety. Data have been collected in our laboratory during the past decade from both patients with panic disorder and healthy volunteers.

During the 30-minute period preceding the lactate infusions, subjects received a slow drip of placebo (either isotonic saline solution or a solution of 1% dextrose in 5 parts water) while biological and rating scale data were collected. We have previously reported that increased subjective fear (as rated by the Acute Panic Inventory [API]), higher heart rate, higher diastolic blood pressure, and indexes of increased respiration (elevated blood pH, reduced P CO₂ level, and reduced phosphate level) during this prelactate infusion period distinguish those patients with panic disorder who will subsequently panic during the lactate infusion (hereafter referred to as the P group) from nonpanicking patients (hereafter referred to as the NP group) and from healthy controls.⁵⁻⁹ These indicators of a state of anticipatory anxiety are hypothesized to prime the patient to panic during the lactate infusion itself.

We wondered whether activation of the hypothalamic-pituitary-adrenal (HPA) axis, reflected by plasma cortisol level elevations, might be associated with anticipatory anxiety, thus clearly distinguishing its biochemical profile from the cortisol level decrease associated with lactate-induced panic.
SUBJECTS AND METHODS

SUBJECTS

The prelactate infusion period, immediately preceding the standard sodium lactate infusion described by Liebowitz et al., was evaluated in patients meeting DSM-III criteria for panic disorder and normal volunteers free of psychiatric illness. Data are reported on biochemical measures (blood cortisol, PCO₂, pH, phosphate, and bicarbonate levels), physiological measures (systolic blood pressure, diastolic blood pressure, and heart rate), and psychological symptoms as assessed by the API. We report on a total of 170 patients with panic disorder and 43 normal controls who were consecutively enrolled into lactate infusion studies. Because of shifts in emphasis during the decade, a full complement of values is not present for all variables; an appreciable reduction of the sample size for certain analyses is observed. Three experimental groups were defined during the prelactate period; normal controls who did not panic with sodium lactate, NP subjects, and P subjects. One hundred one (59%) of the 170 patients with panic disorder were assessed by psychiatric raters to have experienced a panic attack during the lactate infusion. One normal control subject panicked; that subject’s data has been excluded from the current sample. No distinguishing features were evident for this normal control subject at baseline.

After a careful explanation from the investigators, all subjects gave written informed consent. Inclusion and exclusion criteria have been reported previously. Only subjects who were drug free for 2 weeks prior to the lactate infusions were studied, with the exception of as-needed benzodiazepines. However, subjects were required to not be receiving benzodiazepines 3 days prior to the challenge procedure and none were assessed to be in a state of benzodiazepine withdrawal during the lactate infusion.

Subjects reported to the Biological Studies Unit, New York State Psychiatric Institute, New York, on the day of the actual infusion. Either a venous catheter (137 patients, 33 control subjects) or an arterial catheter (33 patients, 10 control subjects) was inserted for blood withdrawal. A second venous line was inserted in the right antecubital fossa. To avoid diurnal confounds, all infusions were started between 8:30 AM and 10 AM. A slow 30-minute infusion of an isotonic saline solution preceded the lactate infusion. The first 7 infusions, 4 of which resulted in a panic outcome, used 5% dextrose as the preliminary infusion. After 30 minutes (0 minutes), the isotonic saline infusion was switched to lactate. A panic attack was assessed by nonblinded research psychiatrists (an issue addressed in another report) when the patient experienced a crescendo onset of 4 of the somatic panic symptoms listed in DSM-III plus cognitive symptoms of a fear of dying or losing control, an overwhelming sense of dread or doom, or a strong desire to flee or terminate the experiment. Multiple somatic symptoms did not suffice for a panic determination. Biochemical data are reported from the −30, −15, and 0 minute time points. Phosphate and cortisol levels are reported at only the −15 and 0 minute time points. Blood pressure and pulse rate were assessed at the −15 and 0 minute time points. The 17-item API was administered before the lactate switch (−5 minutes). Each item is rated 0 (none), 1 (mild), 2 (moderate), or 3 (severe).

Blood pressure was measured using an automated blood pressure cuff. Pulse was measured by electrocardiogram. Samples were immediately analyzed on an automated blood-gas analyzer in an adjacent room. Bicarbonate values were determined by the Henderson-Hasselbalch equation and plasma phosphate level by the Fiske and Subbarow techniques. Plasma cortisol level was analyzed by a competitive protein-binding modification of the method described by Murphy. We have combined measures obtained from blood samples drawn at both venous and arterial sites. We have previously reported that venous and arterial blood gas measures, although differing quite substantially in magnitude, are qualitatively comparable in reflecting acid-base differences.

DATA ANALYSIS

To compare prelactate variables between the 3 groups (P, NP, and control subjects), a multivariate analysis of covariance with repeated measures (MANCOVA-RM, 3×3×2) was performed and included all 3 baseline measurements (when available) of each psychological, physiological, or biochemical variable as the repeated measure and sex (male or female) as a factor. Age and the catheter site (arterial or venous) when necessary, were included as a combined covariate. As there were no group × sex interactions, we undertook a second analysis in which catheter site was a factor and sex was dropped altogether. We report results from the second analysis only, as using catheter site as a factor provides the strictest statistical method of handling the arterial and venous catheter site differences. We have not combined sex and catheter site as factors as 12 cells are then generated, leading to low sample sizes in some cells and an expected loss of power. Where indicated by a significant Mauchly sphericity test for time effects, Greenhouse-Geisser corrected probability levels are reported. Of all the API symptoms, 2 items, fearfulfulness and dyspnea, have been reported to predict panic most strongly and were analyzed as separate variables.

Our second investigation examined the associations between HPA axis activity and other variables within each group. Correlations between cortisol and phosphate levels used means of the −15 and 0 minute time points. For the remaining biochemical variables (pH, PCO₂, and bicarbonate), the means for the partial correlational analysis were determined from data for the 0, −15, and −30 minute time points. For partial correlations between biochemical, psychological, and physiological variables, only data obtained from the 0 minute time point were used. The data from each of the groups were entered into separate partial correlation analyses with catheter site (arterial vs venous) as a control variable whenever appropriate. Significant correlations in the P group were compared with the equivalent correlations from the NP and control groups using the Fisher r-to-z transformation.

For the third aim, the identification of cortisol level elevation as a predictive baseline variable of lactate-induced panic, logistic regression used panic or no panic as an outcome variable. At the first step, sex and age were entered into the equation as control variables; followed at the second step (forward stepping procedure) by the z scores for pH, PCO₂, cortisol, bicarbonate, and phosphate levels, as well as the interaction terms for cortisol with the 4 other biochemical variables. Separate z score conversions were performed on data from subjects grouped by arterial vs venous blood draw sites. Logistic regression analyses were first applied to all subjects and then only to patients with panic disorder. When the phosphate level was included in the analysis, the sample size was substantially reduced because phosphate was the least consistently measured variable. We therefore report predictor analyses with and without phosphate. Significance was fixed at an α level of less than .05, 2 tailed.
Table 1. Means, Standard Deviations, and Number of Subjects for Biochemical Variables*

<table>
<thead>
<tr>
<th>Variable, Time Point Before Sodium Lactate, min</th>
<th>Mean (SD)</th>
<th>Group Effects</th>
<th>Catheter Site Effects</th>
<th>Time Effects</th>
<th>Pairwise Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Controls</td>
<td>NP Group§</td>
<td>P Group§</td>
<td>F</td>
<td>df</td>
</tr>
<tr>
<td>pH −30</td>
<td>7.37 (0.032)</td>
<td>7.37 (0.045)</td>
<td>7.39 (0.043)</td>
<td>4.36</td>
<td>2,182</td>
</tr>
<tr>
<td></td>
<td>−15</td>
<td>7.38 (0.026)</td>
<td>7.38 (0.040)</td>
<td>7.40 (0.045)</td>
<td>5.26</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>7.38 (0.022)</td>
<td>7.39 (0.041)</td>
<td>7.41 (0.048)</td>
<td>3.71</td>
</tr>
<tr>
<td>PCO2 level, mm/Hg −30</td>
<td>43.6 (8.0)</td>
<td>43.1 (6.5)</td>
<td>41.8 (6.3)</td>
<td>24.6 (2.2)</td>
<td>24.1 (2.8)</td>
</tr>
<tr>
<td></td>
<td>−15</td>
<td>42.3 (4.9)</td>
<td>41.5 (6.5)</td>
<td>39.6 (6.1)</td>
<td>24.3 (2.0)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>41.4 (8.6)</td>
<td>40.9 (6.4)</td>
<td>38.9 (6.7)</td>
<td>24.3 (1.9)</td>
</tr>
<tr>
<td>Bicarbonate level, mmol/L −30</td>
<td>11.8 (4.4)</td>
<td>11.2 (5.0)</td>
<td>13.2 (5.8)</td>
<td>11.4 (4.5)</td>
<td>11.3 (5.8)</td>
</tr>
<tr>
<td></td>
<td>−15</td>
<td>3.12 (0.50)</td>
<td>2.88 (0.49)</td>
<td>2.72 (0.71)</td>
<td>3.09 (0.57)</td>
</tr>
</tbody>
</table>

* NP group indicates patients with panic disorder who did not panic with sodium lactate infusion; P group, patients with panic disorder who panicked with sodium lactate infusion. No significant interactions were observed for group × blood average or group × time. Greenhouse-Geisser correction performed for time effects (except for phosphate). All data covaried for age.
† For pH, PCO2, and bicarbonate level measurements, n=90; for cortisol level measurement, n=73; and for phosphate level measurement, n=86.
‡ For pH, PCO2, and bicarbonate level measurements, n=65; for cortisol level measurement, n=51; and for phosphate level measurement, n=44.
§ For pH, PCO2, and bicarbonate level measurements, n=34; for cortisol level measurement, n=33; and for phosphate level measurement, n=23.
| See post hoc analysis for phosphate in “Results” section (P<NP, P>controls, NP<controls).

To increase overall sample size, we added additional subjects and also pooled arterial and venous prelactate data, allowing an amalgamation of all previous studies. A varying number of the subjects have been included in previous reports.5-9 We wished to address the following questions: (1) Are serum cortisol levels elevated during the prelactate period in the P group? (2) Do elevated cortisol levels in the P group during the prelactate period correlate significantly with any of our previously described measures that distinguish the P from the NP or control groups? and (3) Using logistic regression analysis, is cortisol level a factor we can identify as a predictor that distinguishes those who will panic with lactate infusion from those who will not?

RESULTS

AGE, SEX, AND CATHETER PLACEMENT SITE

Mean (±SD) ages were as follows: control group, 29.8±7.2 years; NP group, 33.2±8.0 years; and P group, 33.1±7.6 years and were significantly different (F=3.29, df=2,210, P<.04). Sex distribution in the 3 groups was significantly different (χ²=11.84, df=2, P<.003); only 30% of the control group was female, while 58% of the NP group and 60% of the P group were female. Age and sex are therefore used as covariates.

The proportion of normal control subjects vs patients with panic disorder having arterial catheter placements did not differ (control group=23%, NP group=26%, P group=15%). The panic response among patients did not differ significantly by catheter placement; 45% of the patients with arterial placement and 63% of the patients with venous placements panicked.

RESPONSE TO INVESTIGATORY QUESTIONS

Question 1: Are serum cortisol levels elevated during the prelactate period in P group patients? Cortisol levels (Table 1) showed a significant pattern (P<.03) of group differences, with elevated cortisol levels observed in the P vs NP groups (effect size=.39 for both the 0 and the −15 minute time points) and in the P vs control groups (effect size=.43 and .35 for the 0 and −15 minute time points, respectively). These are medium effect sizes. The NP and control group were indistinguishable. For PCO2 (Table 1), lower levels were observed in the P group in comparison with both the NP group and control group, who were indistinguishable. For pH (Table 1), the P group showed significantly more alkalosis than the control group and was marginally alkalotic in comparison with the NP group. An overall group effect for bicarbonate level reductions in both patient groups indicates marginal renal compensation for respiratory alkalosis (Table 1).
The API total score (Table 2), the fear item of the API, the dyspnea item of the API, and diastolic blood pressure were highest in the P group, followed by the NP group, who in turn had significantly higher measurements than the control group (diastolic blood pressure in the NP group was only marginally higher than in the control group; overall group effect, age and sex covaried, \( F = 6.74, df = 2,183, P = .002 \)).

For phosphate levels, no significant group effects were observed using the MANCOVA-RM. Using a cutoff approach, Gorman et al\(^5\) reported that a plasma phosphate level of 2.25 mg/dL or less at 0 minutes virtually assured the occurrence of a panic attack. Two (6%) of 31 controls, 7 (12%) of 65 NP subjects, and 27 (29%) of 92 P subjects fell below this cutoff point (\( \chi^2 = 10.37, P < .006 \)). The extended sample results are virtually identical to the original subsample. The P group exhibited a greater ratio of subjects below the cutoff than the NP group (\( \chi^2 = 7.75, P < .005 \)), whereas the NP group did not differ from the control group.

Both groups with panic disorder exhibited higher heart rates than control subjects (group effect, controlled for age and sex; \( F = 6.17, df = 2,180, P < .003 \)). No group effects were noted for systolic blood pressure. Additional physiological statistics not reported in the tables or text are available on request.

### SEX AND TIME EFFECTS

The absence of a sex \( \times \) group interaction for any of the psychological, physiological, or biochemical variables in the first MANCOVA-RM, in which sex was used as a factor, indicates that the group effects observed were not carried by a disproportionate contribution from either sex. Nevertheless, women in general have lower PCO\(_2\) (\( F = 23.79, df = 1,181, P < .001 \)) and bicarbonate levels (\( F = 33.08, df = 1,181, P < .001 \)) and higher phosphate levels (\( F = 4.11, df = 1,127, P < .04 \)). There was no time or group \( \times \) time effect for plasma cortisol levels, suggesting that catheter insertion effects were not discernible at the −15 minute and 0 minute time points. Time effects, evidenced by progressive increases in pH and reductions in PCO\(_2\) and phosphate levels, occurred during the prelactate period (Table 1). The time effects noted above must be assumed to be equivalent for each of the groups and each sex, as no group \( \times \) time, sex \( \times \) time, or group \( \times \) sex \( \times \) time interactions were observed.

**Question 2:** Do elevated cortisol levels in the P group during the prelactate period correlate significantly with any of our previously described measures that distinguish the P group from the NP or control groups? Patients with panic disorder in general showed higher variances than normal volunteers for all biochemical measures. However, phosphate was the only variable for which the P group exhibited a significantly greater variance than the NP group (data available on request). Consistent with general acid-base physiology, PCO\(_2\) was robustly negatively correlated with pH in all 3 groups. The Henderson-Hasselbalch equation was used to determine bicarbonate levels, which therefore were positively correlated with carbon dioxide.

Within the P group (Table 3), cortisol levels were inversely correlated with PCO\(_2\) levels and positively with pH. Also within the P group, phosphate levels correlated positively with PCO\(_2\) and bicarbonate levels and inversely with pH. The phosphate and PCO\(_2\) correlation in the P group was greater in magnitude than that observed in the NP and control groups, whereas the phosphate and pH correlation was greater in magnitude than that observed in the NP group (Table 3). Thus, significant correlations in the P group indicate a positively linked relationship between respiratory alkalosis and adrenal cortisol secretion during the prelactate period.

Within the P group (Table 4), fearfulness (as measured by the API) was significantly correlated with low PCO\(_2\) and high cortisol levels. Although not significant in the control or NP groups, the same correlations were not distinguishable from the P group. Also within the P group, increases in API scores were significantly associated with high pH and low PCO\(_2\) levels, and marginally with lower phosphate levels. No significant correlations with API scores were observed in the NP group but no subjects were distinguishable from the P group.

### Table 2. Means, Standard Deviations, and Number of Subjects for Psychological Variables at 0 Minutes Before Sodium Lactate Infusion*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>N</th>
<th>F</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>API total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>1.40 (2.30)</td>
<td>40</td>
<td>25.60</td>
<td>2,202</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NP group</td>
<td>4.98 (5.10)</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P group</td>
<td>7.49 (4.94)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear item score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>0.22 (0.48)</td>
<td>40</td>
<td>24.93</td>
<td>2,202</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NP group</td>
<td>0.78 (0.93)</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P group</td>
<td>1.29 (0.86)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea item score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>0.0 (0.0)</td>
<td>40</td>
<td>8.58</td>
<td>2,202</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NP group</td>
<td>0.34 (0.69)</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P group</td>
<td>0.48 (0.69)</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*API indicates Acute Panic Inventory; NP group, patients with panic disorder who did not panic with lactate infusion; and P group, patients with panic disorder who panicked with lactate infusion. All comparisons have been controlled for age. For pairwise comparisons, all 3 of the above measures were highest in the P group, followed by the NP group, who in turn had significantly higher measurements than the control group.

†Bartlett-Box for variance difference is significant.
ever, in the control group, an increase in total API and fearfulness scores was associated with lower phosphate levels (respectively: \( r = -0.58, \text{df}=24, P=.001 \); \( r = -0.47, \text{df}=24, P=.02 \)).

Cardiovascular variables did not shed additional light on the correlational analysis (data available on request).

Question 3: Using logistic regression analysis, is cortisol level a factor we can identify as a predictor that distinguishes those who will panic with lactate infusion from those who will not? As a predictor of panic outcome, the individual API item of fear, which was largely equivalent to the API total score but more specific to anticipatory anxiety, was used (API data available on request). Including variables from all 3 groups (including phosphate levels), the API fear item score and the interaction of high cortisol and low PCO2 levels significantly predicted a panic outcome (Table 5). Repeating the logistic regression analysis model including just patients with panic disorder (including phosphate levels), both the high cortisol and low PCO2 level interaction and the API fear item score predicted panic significantly.

Excluding phosphate levels as a requirement for inclusion in the analyses led to a substantial increase in the sample size but did not significantly alter the results.

In an additional analysis (data available on request), we excluded the API fear item score to elucidate other possible predictive variables that may be subserved under the fear response. Among the patients with

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### Table 3. Partial Correlations of Baseline Biochemistry Within Study Groups (Controlling for Arterial or Venous Catheter Site)*

<table>
<thead>
<tr>
<th>Correlation</th>
<th>P Group (df)</th>
<th>NP Group (df)</th>
<th>All Patients (df)</th>
<th>Control Group (df)</th>
<th>Correlation Comparison§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol/PCO2</td>
<td>-0.36 (60)†</td>
<td>0.08 (44)</td>
<td>-0.20 (107)†</td>
<td>-0.27 (22)</td>
<td></td>
</tr>
<tr>
<td>Cortisol/pH</td>
<td>0.26 (61)†</td>
<td>0.1 (45)</td>
<td>0.22 (109)†</td>
<td>0.14 (24)</td>
<td></td>
</tr>
<tr>
<td>Phosphate/pH</td>
<td>-0.54 (65)†</td>
<td>-0.06 (41)</td>
<td>-0.05 (107)</td>
<td>-0.21 (19)</td>
<td>P-&gt;NP</td>
</tr>
<tr>
<td>Phosphate/PCO2</td>
<td>0.53 (65)†</td>
<td>0.06 (41)</td>
<td>-0.43 (109)†</td>
<td>0.21 (19)</td>
<td>P-&gt;NP</td>
</tr>
<tr>
<td>Phosphate/bicarbonate</td>
<td>0.39 (65)†</td>
<td>0.07 (41)</td>
<td>0.26 (109)†</td>
<td>0.18 (19)</td>
<td></td>
</tr>
</tbody>
</table>

*P group indicates patients with panic disorder who panicked with sodium lactate infusion; NP group, patients with panic disorder who did not panic with lactate infusion. Ellipses indicate not applicable. The baseline means for pH, PCO2, and bicarbonate levels were derived from the −30, −15, and 0 minute time points. For the partial correlation (phosphate and cortisol levels), both the high cortisol and low PCO2 levels significantly predicted a panic outcome. Repeating the logistic regression analysis model including just patients with panic disorder (including phosphate levels), both the high cortisol and low PCO2 level interaction and the API fear item score predicted panic significantly.

Excluding phosphate levels as a requirement for inclusion in the analyses led to a substantial increase in the sample size but did not significantly alter the results.

In an additional analysis (data available on request), we excluded the API fear item score to elucidate other possible predictive variables that may be subserved under the fear response. Among the patients with
panic disorder only, the API dyspnea item score emerged as a significant predictor of panic outcome.

In summary, the logistic regression analyses, irrespective of model of inclusion, indicated that the most consistent baseline predictors of panic were fear (and dyspnea subsumed under fear) and the combination of high cortisol and low PCO₂ levels.

By analyzing data on this expanded sample of 214 subjects undergoing lactate infusion, we now show that cortisol levels are elevated during the 30-minute period prior to lactate infusion in the P group vs the NP group. This provides confirmation for the idea that activation of the HPA axis may be specific to anticipatory anxiety states, rather than to acute panic itself.²⁻⁴ Hollander et al previously reported that baseline cortisol levels were elevated specifically in late panickers (defined as panic during minutes 15-22 of the infusion) vs early panickers (panic during minutes 0-15 of the infusion). In the current study, with a larger sample, we indicate that cortisol level elevations can be generalized to all lactate panickers. In fact, on reanalysis of the Hollander et al subsample, it was evident even at that point of data collection that significantly elevated baseline cortisol levels were already statistically detectable in the P group as a whole.

We further show that within the P group, a triad of associated findings occurs during the prelactate period: elevated cortisol levels, hyperventilation, and fear. This raises the possibility that a particular biological and emotional state sets the stage for the occurrence of a panic attack. The patient about to panic manifests, in a correlated fashion, increased fear, hyperventilation, and a HPA axis stimulation.

These findings must be confirmed prospectively. It is possible that they apply only to the laboratory setting or to the lactate infusion paradigm. Furthermore, a number of factors in addition to the post hoc nature of these analyses encourage caution in interpreting our findings. The study pooled both venous and arterial blood samples by using a factor analysis. In general, a lack of consistency of variables between arterial vs venous catheter sites would have increased variance and worked against significant group differences. The group comparisons comparing correlations are performed on fluctuating and often small sample sizes, making interpretation difficult. As the test for correlational differences between groups depends strongly on sample size, great caution needs to be taken in drawing any inferences when significant differences are lacking. Finally, because of the lack of correction for multiple comparisons, interpretations should be regarded with circumspection. Nevertheless, analysis of data from this expanded sample of subjects largely confirms our earlier reports.⁵⁻⁸⁻¹⁰⁻¹³

Sex effects in this extended sample, when analyzed as a factor, did not contribute any further information regarding prediction of lactate-induced panic. However, the number of female control subjects was relatively low, and this may have increased the likelihood of a type II error for interactive effects with sex by reducing power in that cell. Evidence for progressive autonomic activation was evident in all subjects but not specific to any group. Thus, the prelactate period is not an acclimated, stable baseline period, but rather a period of apprehension toward the impending lactate infusion.

Identification of putative neural substrates that may underlie anticipatory anxiety have been facilitated by extensive documentation of fear mechanisms in animals.¹⁶⁻¹⁸ A candidate neural system for the anticipatory anxiety preceding lactate-induced panic described in this article focuses on the central nucleus of the amygdala and its caudal efferents, termed the ventral amygdalofugal pathways. Direct electrical stimulation of portions of the amygdala in humans and animals produces fear and escape responses, via well-delineated pathways that activate the periaqueductal gray matter and hypothalamus.¹⁰ Neurons of the central nucleus of the amygdala project to the paraventricular neurons of the hypothalamus,¹⁹ possibly accounting for the HPA axis activation observed in the P group. Central amygdaloid projections also project to the pontine nucleus parabrachialis, implicated in fear-driven hyperventilation.¹⁰ Moreover, amygdaloid neurons are synchronized with the respiratory cycle through connections to brainstem respiratory centers.²² Progressive activation of ventral amygdalofugal pathways may ultimately trigger firing of the periaqueductal gray matter neurons, at which point panic and escape responses may be observed.²²

Of note, activation of the central nucleus of the amygdala follows stimulation by the basolateral nucleus of the amygdala, which receives afferent projections from information-processing structures such as prefrontal cortex, parahippocampal areas, and the hippocampus itself. In one study, abnormally asymmetric (right greater than left) parahippocampal gyrus metabolism, as measured by positron emission tomography, was implicated in predicting lactate-induced panic.²¹ Although the site of activation during lactate-induced panic was thought to be temporopolar, it was confounded with masticatory muscle activity and the findings were retracted.²¹²² The prelactate parahippocampal findings were not retracted, however, and suggest abnormal paralimbic metabolic activity in anticipatory anxiety.

In conclusion, the current study provides evidence that the triad of fear, hyperventilation, and HPA axis activation are significant predictors of lactate-induced panic. Further, we have demonstrated that the individual components of the triad seem to move in synchrony with each other only within the P group, suggesting activation of a putative common neural substrate. Further investigations of the relationship of this panic-facilitating neural substrate to the suffocation alarm mechanism proposed by Klein²³ are suggested.

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REFERENCES


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