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INVESTIGATION OF THE ROLE OF PHYSIOLOGICAL INDICES AS PREDICTORS OF SODIUM LACTATE RESPONSE

by

Patrick Michael Murphy

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1988

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November 4, 1987
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Abstract

INVESTIGATION OF THE ROLE OF PHYSIOLOGICAL INDICES

AS PREDICTORS OF SODIUM LACTATE RESPONSE

by

Patrick Michael Murphy

Adviser: Professor Solomon Steiner

There is a steady increase in the number of investigators who use physiological stimuli to induce an anxiety or panic response. In addition, there has been prolification of criteria set to identify the response. The purpose of the experiments described here was to employ a well standardized method of eliciting a report of panic and to depict a model for interpretation of physiological data as its' predictor. Subjects who report spontaneously occurring attacks reliably report similar response to the infusion of Sodium Lactate. The reliability of this physiological challenge test should allow for greater standardization in the laboratory description of the actual physiological events occurring during the spontaneous attacks.

These experiments attempt to ascertain the pattern of physiological response relative to the dose of lactate received by those who do respond. All subjects included in these experiments reported a response which they rated as significantly similar to their naturally occurring attacks.

The first experiment attempts to correlate individual response systems with the subjects' statement that they are experiencing panic. The peak respiratory rate occured within fifteen seconds of response in all cases. The peak heart rate rise of 20 beats occurs within thirty seconds of response. Minute ventilation rose an average of 2.0 liters within sixty seconds of response.Skin conductance level rose sharply in half the cases and dropped sharply in the other half following lactate onset.

The second experiment is based on the post hoc definition of two subgroups. Those who responded in the first ten minutes and those who responded in the second ten minutes. Time was divided into protocoled ten minute epochs. Within each epoch, group means were used to evaluate the probability that the distributions were significantly different.

Skin conductance level was significantly lower for the early panickers prior to any invasive technique but switched during the second ten minutes. After the second ten minutes, skin conductance level was reduced from baseline for late responders but was increased for early group.

Respiratory frequency was the most significant discriminator between the two groups. With information on the minute ventilation , the results indicated that the early panickers were at their peak levels when they reported panic and the late panickers had passed their peak and had begun to decelerate.

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Jack Gorman, Ray Goetz and the rest of the staff at the Biological Studies Unit made these data possible for me. The quality of their work is evident in this research. The team of the investigators from the Columbia-Presbyterian Anxiety Clinic, especially Dr.Donald Dillon, created these experiments with their expert performance.

I cannot express what I owe my friends and loved ones, they all know what they mean to me.

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1.0 Introduction

1.1 General Introduction

The term psychophysiology has been accepted to define a research orientation within physiological psychology which limits its methods to those which are non-invasive. They are directed at the study of the whole, functioning, physiological system. While facing a reduction in the basic terms in which it may explain biological phenomena, psychophysiology increases the ability of physiology to be heuristic for a wider range of psychological questions. The acceptance of methodological limitations in the physiological investigation of psychological problems is often followed by a dearth of useful answer to questions which are more efficiently addressed with traditional methods. There is a lag time for adequate psychological theories to be formulated as well as reliable biological investigatory techniques to be developed.

In 1884, William James stated that "the bodily changes follow directly the perception of the exciting fact, and that our feeling of these same changes, as they occur, is the emotion." James's use of a concentrically organized perception with the use of the present tense, is somewhat difficult to support with ex post facto techniques. In the 1920's, Walter Cannon initiated a series of experiments which provide the classic model for the testing of the physiological facts in concomitance with James's ideas.

By disconnecting the external sensorium, Cannon essentially turned physiological psychology from an afferent to an efferent model. Although this did not increase theoretical validity, it did maintain equity for physiological determinism and produce functional neurophysiology. Edward Boring and his associates attempted to supply a unifying theory while stressing empirical methodology. The works of these psychologists aimed at putting psychological contracts in terms of hierarchally organized system.

According to activation theory, global unidirectional changes in physiological activity accompany varying states of emotional arousal (Duffy, 1962; Malmo, 1959; Lindsley, 1951). Lacy observed (Lacy, 1967; c.f. Coles, Jennings and Stern, 1984), however, that while some behavioral manipulations such as mental arithmetic produce the classic pattern of physiological arousal (e.g., increases in both HR and electrodermal activity), other manipulations such as those involving perceptual processing produce 'directionally fractionated' response patterns (simultaneous decrease in HR and increase in electrodermal activity). The phenomenon of directional fractionation cannot be adequately explained by arousal theory. Subsequent investigations have demonstrated the directional fractionation of physiological responses both within (e.g. among components of the cardiovascular system) as well as between physiological systems to a variety of psychological stressors.

Lacy (1959) was also one of the first investigators to systematically explore and verify the large individual differences in the patterning of physiological reactivity elicited by stressful conditions. Two basic principles have emerged from this work: Stimulus-Response Specificity and Individual Response Stereotype. The concept of Stimulus - Response Specificity refers to the observation that an individual's pattern of physiological response will vary as a function of the stimulus conditions but will tend to remain stable with repeated replications of the same stimulus configuration. Furthermore, it wgas postulated that the specific pattern of activity in response to a particular stimulus situation would, more or less, be observed in most individuals. The formulation of this hypothesis provided the impetus for much of the early work regarding the differentiation of the emotions based on psychophysiological measures (e.g. Ax, 1953; Engel, 1959, Engel, 1972). The concept of Individual Response Stereotype, on the other hand, refers to the observation that individuals tend to respond in stereotypical, or idiosyncratic, fashion to a wide variety of stimulus situations both in terms of patterning of physiological activity ("Response Stereotype") and in terms of a single response system that responds disproportionally ("response Specificity"). Engel (1960) and Engel and Bickford (1961) demonstrated the coexistence of both Stimulus-Response Specificity and Individual-Response Stereotype intra -

individually. This indicates that observed physiological responses are determined by factors related to both the stimulus conditions and the individual.

1.2 Cardiovascular Psychophysiology

1.21 Cardiac-Somatic coupling

Obrist and his coworkers (Obrist, 1968; Obrist, Webb and Sutterer, 1969; Obrist, Webb, Sutterer and Howard, 1970; Obrist, 1981) have provided strong empirical evidence indicating that under normal, resting conditions, heart rate and somatomotor activity are tightly coupled. Simply stated, an increase in somatomotor activity leads to an increase in heart rate. This serves to supply the additional oxygen and nutrients (i.e. blood flow) required by the working muscles of the active organism. Inhibition of somatomotor activity, on the other hand, reduces metabolic requirements and lead to a reduction in heart rate.

1.22 Heart Rate Levels

White and Gilden (1937) were among the first to observe that anxious patients have higher heart rates than normal subjects. Similarly, Kelly and Walter (1968), found that the resting heart rate of 41 patients with chronic anxiety state to be 97 bpm as compared to 74 bpm for a group of 60 normal subjects. Several other investigators have reported tachycardia associated with anxiety (Lader and Wing,1966 ;Glickstein, 1957).

Liebowitz, et. al. (1984) have recently demonstrated that

patients diagnosed with panic disorder display higher resting levels of heart rate prior to sodium lactate infusion compared to normal controls. Furthermore, patients who go on to have panic attacks during the infusion have higher resting heart levels than those panic disorder patients who do not experience a panic attack during the infusion. Liebowitz et. al. (1984) interpreted this finding as indicating that patients with panic disorder are in a chronic, hyperadrenergic state and that those patients who respond to sodium lactate infusion with a panic attack must be adrenergically 'primed' to panic.

Using 24-hr. ambulatory monitoring of heart rate, Roth (1976) reported positive correlations throughout the day between levels of stress and increased heart rate. In addition, patients in their study with neurocirculatory asthenia, a condition which overlaps various categories of anxiety disorder, were found to experience significantly more tachycardia and cardiac arrhythmias during routine activities and during sleep than did normals.

Freedman, Ianni and Ettedgui (1985) and Taylor (1984) have recently conducted ambulatory monitoring studies of panic disorder and agoraphobia. Both studies demonstrated that panic attacks occurring under conditions of naturalistic stress are associated with significant and "paroxysmal" increases in heart rate.

In the study reported by Freedman, et. al. (1985), panic

disorder patients were compared to controls on measures of heart rate, finger temperature and self-rated anxiety throughout a 24-hr period. During this period, eight spontaneous panic attacks were reported by patients. The results indicated no difference between patients between patients and controls or between patients who experienced a panic attack and those who did not, in respect to tonic levels of physiological activity or self ratings of anxiety throughout the 24-hr. period. However, substantial increases in heart rate and vasomotor activity were observed during panic attacks. The finding that mean heart rate levels for patients and controls did not differ significantly in the natural setting is in direct contradiction to the finding of elevated resting heart rates in laboratory studies of panic disorder patients in comparison to normal controls (Kelly, Michel-Heggs and Sherman, 1971; Freedman, Ianni and Ettedgui, 1984; Liebowitz, et.al.1984). This suggests that differences in resting heart rate levels observed in laboratory studies may result from greater levels of anticipatory anxiety in patients as compared to controls.

Tyrer, Lee and Alexander (1980), for example, have reported significant, positive correlations in groups of patients with anxiety neurosis and hypochondriasis between subjective ratings of heart rate and actual heart rate during exposure to anxiety provoking films. Patients with phobic anxiety (agoraphobia accurately perceive variations in their

heart rate. Schandry (1980) found that subjects classified as good perceivers of spontaneous fluctuations in heart activity scored significantly higher on Spielberger's State-Trait anxiety inventory and on a test of emotional ability then did subjects classified as poor perceivers. In view of the putative role of variations in autonomic nervous system activity in the experience of emotion, further research into the perception of autonomically mediated functions in patients with anxiety disorders seems warranted. Recent advances in the development of methods and procedures for assessing visceral perception (e.g. Papillo, Tursky and Friedman, 1981; Katkin, et. al.,1984;Lacroix, 1984) may be usefully employed in the study of clinical anxiety.

Few studies have been reported which explore the possible connection between the anxious patients' frequent complaint of "palpitations" or "skipped beats" and actual dysrhythmia. The experiments of Lown (1979) have shown that stress is capable of inducing ventricular arrhythmias in experimental animals and that manifestation of these disturbances requires intact vagal innervation. Shear et. al. (personal communication) also observed an increase, although not at significant levels in both atrial and ventricular arrhythmias in patients with panic attacks. Previous investigations of lactate induced panic have failed to observe any increase in ventricular or atrial ectopic beats or incidence of serious arrhythmia.

1.23 Heart Rate and Adrenaline

Gorman (1984) has shown that intravenous propranolol in sufficient dose to block beta adrenergic innervation to the heart, not effective in suppressing the surge of heart rate arrhythmia. The normal fluctuation in heart rate that occurs in synchrony with inspiration (HR acceleration) and expiration (deceleration) depends almost entirely on intact vagal tone to the heart.

While there are probably no alpha adrenergic receptors located within the heart, the alpha adrenergic system can have considerable influence over cardiac function. First, beta receptors in the myocardium appear to be far more sensitive to norepinephrine then are other beta adrenergic receptors. Most peripheral norepinephrine is generated from the synapses of alpha adrenergic nerves on the peripheral vessels. Second, the influence of alpha-adrenergic stimulation on the calibre of peripheral vessels effect cardiac function enormously through alteration in arterial pressure and venous return to the right heart.

Finally, cardiac function can be altered through interactions between peripheral and central nervous system influences. Animal studies have demonstrated, for example, that stimulation of certain areas of the brain immediately produces ventricular premature contractions. Patients with severe diabetic peripheral neuropathy lose vagal tone to the

heart and consequently demonstrate drastically reduced respiratory sinus arrhythmia. Stimulation of the pontine noradrenergic center of brain, the Locus Coruleus, increases heart rate in monkeys, but the administration of noradrenalin peripherally increases blood pressure and thus produces a reflexive decrease in heart rate.

Against the backdrop of these theoretical considerations, the repeated findings that anxious individuals have higher heart rates than normals cannot be simply taken to mean that they are more adrenergically stimulated.

Obrist and his colleagues (1986) conducted an experiment that may shed some light on the mechanisms underlying the cardiovascular changes observed in patients with clinical anxiety disorder. Before being exposed to a stressful reaction time task and cold pressure test, subjects in this experiment underwent a graded exercise task to assess the linear relationship between cardiac output (CO) and oxygen consumption (O2). The relationship observed during exercise was then used to evaluate changes observed in the CO-O2 relationship during the stress and cold pressure tasks. During the reaction time tasks, increases in CO in excess of that predicted by the increase in O2 consumption were observed. CO reactions to cold pressure, on the other hand, were found to be consistent with changes in metabolic demand. Blockade of the beta-adrenergic system was more effective in reducing the CO response to the reaction time task than to

cold pressor.

1.24 Peripheral Blood Flow

Several studies have examined the effects of psychological stress on peripheral blood flow through the finger (Abramson and Ferris, 19400; Blair, Glover, Greenfield and Roddie, 1959; Gelder and Mathews, 1968; Bloom, Williams, Bittker, Buchbaum and Wynee, 1972). More recent studies have focused on the reactivity of finger blood flow measures to experimentally induced states of stress and anxiety (Bloom, Houston and Burish, 1976; Bloom and Trautt, 1977; SMith, Houston and Zurawski, 1984; Knight and Borden, 1979; Burish and Horn, 1979).

In a series of experiments, Bloom and his associates (Bloom, Houston, and Burish, 1976; Bloom and Trautt, 1977) observed small but statistically significant correlations between levels of self reported anxiety (Affect Adjective Check List) and reductions in the finger pulse volume amplitude during periods when normal subjects expected to receive a series of electric shocks. Finger pulse volume was more strongly correlated with self rated anxiety than was heart rate (Bloom, Houston and Burish, 1976). These investigators also observed differences in the temporal patterning of finger pulse volume and heart rate responsivity to their anxiety manipulation which could account for the small intercorrelations observed among measures (Bloom and Trautt, 1977). Finger pulse volume reactivity occurred sooner

and recovered earlier following removal of the threat than did heart rate.

Smith, Houston and Zurawski (1984) obtained measures of finger pulse volume amplitude, heart rate and self ratings of anxiety in normal subjects during an experiment designed to compare the physiological and subjective manifestations of anxiety produced by high and low levels of social-evaluative threat (i.e. video-taped interview). During anticipation of the interview, the observed correlation between subjective levels of anxiety and reductions in finger pulse volume amplitude were significant.

Dramatic reductions in finger pulse volume amplitude are consistently observed in response to the cold pressure test (Lovallo, 1975). This maneuver, which involves submerging an extremity into ice water, provokes a generalized peripheral vasoconstriction mediated by alpha adrenergic receptor stimulation. In one experiment, a cold pressure test failed to provoke panic attacks in patients with panic disorder. Furthermore, no difference was observed in the magnitude of the finger pulse volume amplitude response to cold pressor between patients with panic disorder and normals.

A particularly relevant aspect of this research for the study of anxiety disorder concerns the finding that under certain stressful conditions, having both motivational and emotional significance for subjects, an un-coupling of cardiac and somatic activity can be observed. For example, in an

unsignaled reaction time task, where subjects are threatened with shock for slow response times, increases in heart rate have been demonstrated that an excess of metabolic requirements. This arrythmia appears mediated by increased beta-adrenergic tone. In another instances, such as classical aversive conditioning tasks and signalled reaction time tasks, changes in heart rate are proportional to metabolic demand and are mediated by the vagal innervations of the heart.

In view of the complex processes involved in the regulation of heart activity, it is suggested that inquires into the relationship between the heart and clinical anxiety should be designed with the following points in mind.

First, there is virtually no beta adrenergic stimulation to the heart at rest. Theoretically, the administration of beta adrenergic blocking drugs to a subject in a completely non-anxious state, at absolute rest, should have not effect on either the rate of force of cardiac contraction. Vagal stimulation to the heart, on the other hand, remains constant, even at rest.

1.3 Respiratory function

Psychophysiologists routinely measure respiratory function primarily as a means of assessing artifact observed in other physiological response measures (Stern and Anchel, 1968; Shean and Stange, 1971). Rarely have measures of respiratory function served as primary measures in psychophysiological research. Relatively few studies

concerning the psychophysiology of emotion have focused specific attention on the use of respiratory measures for indexing or differentiating among the various emotional states (Dudley, 1968; Feleky, 1916; Finesinger, 1939; Stevenson and Ripley, 1952).

Recent studies have demonstrated the responsivity of the respiratory system to psychological stress (Garssen, 1980; Mavissakalin and Michelson, 1982), the modulating effects of paced respiration on both physiological and psychological components of the stress response (Harris, Katkin, Lick and Habberfield, 1976; Mc Caul, Solomon and Holmes, 1979), and similarities in symptoms produced by stress-induced respiratory changes with those most often reported by anxious subjects (Clark and Helmsley, 1982; Pfeffer, 1978). These have generated strong interest in the psychophysiological assessment of ventilatory function in anxiety disorders.

1.31 Stress Induced Respiratory Response

A number of studies have investigated the relationship between patterns of respiration and specific emotional states. In addition, several studies have focused on the reactivity of the respiratory system to stress in both normal and clinical populations. Recent interest has centered on the role of a specific pattern of respiration, hyperventilation, in the pathogenesis of clinical anxiety disorders.

Several early studies showed characteristic alterations in respiratory patterns to be associated with various

emotional states. For example, Feleky (1916) observed discrete patterns of respiratory activity to six emotions (i.e. pleasure, pain, fear, anger, disgust, wonder) that subjects were required to imagine. Stevenson and Ripley (1952) described specific patterns of respiration occurring in a wide variety of emotional stress elicited during an interview. Two studies (Ancoli and Kamila, 1979; Ancoli, Kamiy and Eckman, 1980) have recently demonstrated a differential pattern of respiratory activity in normal subject during the viewing of a film designed to induce either a positive (i.e. happiness) or a negative (i.e. disgust) affect. It was found that the experience of positive affect was associated with predominately abdominal breathing while the negative effect produced a pattern dominated by thoracic breathing.

1.32 Respiratory Rate and Carbon Dioxide. In the relationship between respiratory parameters and emotional response, several investigators have examined the effects of paced respiration on autonomic nervous system reactivity to a variety of threatening situations (Harris, Katkin, Lick and Habberfield, 1976; Holmes, McCaul and Solomon, 1978; McCaul, Solomon and Homes, 1979; Clark, 1978; Foss, 1975; Sprague, 1977). In a study reported by McCaul, Solomon and Holmes (1979), subjects who were instructed to pace their breathing at a rate of 8 breathes per minute (i.e. half the normal resting rate) were less respondent in skin conductance change and finger pulse

volume levels than were those who were paced at a normal rate. Heart rate was also measured but was not significantly effected by the breathing manipulation.

Clark (1978) found that subjects who paced their breathing rate at either 16 or 24 breaths per minute reported the highest level of anxiety during the procedure. In addition, significant correlations between anxiety and respiration rate were obtained while no relationship was found between self-reports of anxiety and changes in either cardiac or electrodermal measures. Additional evidence indicating positive correlations between respiratory rate and subjective levels of anxiety has been reported (Lande, Hertz, Korchin, Sabshin and Schwartz, 1962; McCollum, Burch and Roessler,1969).

The results of several studies provide clear evidence indicating a link between psychogenic stress and acute episodes of hyperventilation. Suess, Alexander, Smith, Sweeny and Marion (1980) observed significant reductions in end-tidal CO2 levels accompanied by significant increases in both respiratory rate and scores on the state portion of the State-Trait Inventory, during a task involving threat of electric shock in normal subjects.

1.33 Chronic Hyperventilation

A number of studies show that anxious patients breathe more rapidly and exhibit lower end-tidal CO2 than normal subjects. However, many of these studies have either failed

to control for stress of the laboratory or have made no attempt to differentiate acute from chronic states of hyperventilation in their subjects.

Many investigators hypothesize that at least some patients with anxiety disorder are chronic hyperventilators who when stressed, acutely hyperventilate even more, become alkalotic, and experience the host of physical and emotional symptoms of anxiety.

A particular respiratory pattern, hyperventilation, has been regarded as both a cause and effect of anxiety. By hyperventilating, the organism exhales or 'blows off' more carbon dioxide than is simultaneously produced by cellular aerobic metabolism. This results in a lowered arterial concentration of CO2 (hypocapnia) which, in turn, raises the arterial PH level above normal limits (respiratory alkalosis). This series of events has been shown to produce an almost immediate cerebral vasoconstriction and a concomitant slowing in the frequency of EEG activity. As a consequence, the subject becomes dizzy, lightheaded, nauseated, confused, tremulous and breathless.

An important distinction between chronic and acute states of hyperventilation must be made. Acute hyperventilation is reflected by increased minute volume, decreased end-tidal CO2, decreased carbon dioxide production, decreased arterial CO2 concentration (PCO2), increased pH and decreased serun inorganic phosphate. As hyperventilation is

sustained, however, several compensatory mechanisms intervene. The relative cerebral anoxia caused by vasoconstriction produces a reciprocal vasodilation. The kidney reabsorbs extra titratable acids and excretes excess bicarbonate to return pH to nearly normal level.

Chronic hyperventilators do not appear to be breathing fast despite profound hypocapnia. This because once the hyperventilatory state is established, only a few deep breaths each hour are required to maintain the conditions described above.

Mills (1982) has observed that some anxious patients continue to hyperventilate following a hyperventilation test. Normals, on the other hand, to hypoventilate following the test to bring the PCO2 levels down to normal. This finding provides further evidence suggesting a possibly disregulated respiratory system in anxious patients.

L.C. Lum (1975) has theorized that patients with panic disorder are chronic hyperventilators who have acquired the bad habit of thoracic breathing. By retraining patients to breather diaphragmaticaly, the normal way for adults, he has demonstrated success in blocking future attacks. The results of several studies have demonstrated the clinical efficacy of techniques which involve training in slow and regular breathing for the treatment of hyperventilation syndrome and panic disorder (Rapee, 1973), Grossman, deSwart and Defares, 1985; Clark, Salkovskis and Chalkley, 1985).

In one study (Clark et. al. 1985), psychiatric patients who suffered from recurrent attacks received training in slow breathing and were encouraged to both practice the technique at home and to emply the technique as a coping skill when anxious. During a two week period there were significant reductions in the number of attacks and their severity. In addition, the symptoms continued to decrease during an eleven month period following training and were maintained at 67-month and 2 yr. follow up reports. Additional treatment techniques were implemented following the two week slow breathing training period and therefore the long term effectiveness of the breathing technique per se cannot be isolated.

In a series of recent experiments, Gorman et.al.(1985) have explored the possible role of ventilatory disturbances in patients with panic disorder and found that patients had indices compatible with a state of chronic hyperventilation. During lactate induced panic, there was a significant decrease in PCO2, which indicates acute hyperventilation superimposed on chronic hyperventilation.

Signs of ventilatory disturbance dissipated in patients once the panic attacks had been pharmacologically blunted. There is evidence that training patients not to hyperventilate may attenuate the panic response to sodium lactate infusion in a manner analogous to anti-panic medications. Finally, panic disorder patients who undergo a second lactate infusion

following successful pharmacologic treatment of their anxiety disorder typically complain less of hyperventilation related symptoms as compared to their first infusion.

The evidence reviewed so far suggest that hyperventilation may play a significant role in both the etiology and pathogenesis of panic disorder but does not explain why patients hyperventilate in the first place?

1.4 Electrodermal Activity

1.41 Tonic Conductance Levels

Tonic electrodermal activity has generally been found to be higher in anxious patients than in normal controls (Bond, 1943; Howe, 1958; Conolly, 1979; Lader and Wing, 1964; Fried, Friedman and Welsh, 1967). It has also been found that anxious patients emit a larger number of spontaneous fluctuations in electrodermal activity compared to normal subject (Odegaard, 1932, Solomon and Fentress, 1938; Toone, 1961; Miller and Shmavonian, 1965; Lader, 1967). However, several studies have failed to differentiate between anxious patients and normal subjects on the basis of either tonic or phasic EDA measures.

1.42 Rate of Habituation

Lader and his colleagues (Lader and Wing, 1966; Lader, 1967) have compared the rate of habituation of the SCR in normal subjects and psychiatric patients to a series of auditory stimuli. In one study (Lader and Wing, 1966), 20 anxiety patients and 20 normal controls matched for age and

sex were presented with a series of identical tones (1000 Hz, 100 db) following a 10 minute baseline period. Measures of SCL and number of conductance responses during the baseline period were significantly higher for the anxiety patients the their normal controls. In a second study, Lader (1967) divided 90 patients studies into five diagnostic categories: anxiety with depression, state anxiety, agoraphobia, social phobia, and simple phobia. About two-thirds of the patients across these five groups had experienced weekly panic attacks, although, the percentage within each group was not reported. These 90 patients were compared to 75 normal controls with respect to magnitude, frequency, and rate of habitation of EDA to a series or twenty consecutive tone stimuli (1000 Hz, 100db).

The results indicated no significant differences in SCL either between the patient subgroups or between the patients and the control group. However, patients with anxiety state, anxiety with depression, social phobics and agoraphobia showed a slowed rate of habituation to the stimuli as compared to patients with simple phobia and normal controls. No difference in the rate of habituation was observed between simple phobics and normal controls. An identical pattern of results was also obtained with respect to the number of responses observed during the procedures. On the basis of correlational analysis, it was found that slow habituaters demonstrated more spontaneous fluctuations, experienced higher

levels of general anxiety and experienced more frequent panic attacks than did patients who more rapidly habituated to the stimuli.

1.43 Eccrine Gland to Carbachol

It has been demonstrated that a greater number of eccrine sweat glands are capable of stimulation by intradermal injection of carbachol, a cholinomimetic agent, in anxious patients than normal subjects (Iskander, et. al. 1965; Dobson and Sato, 1972; Maple, Bradshaw and Szabadi, 1982; van den Brock, Bradshaw and Szabadi, 1984). This finding suggests that some anxious patients may have a primary hyperresponsivity to parasympathetic agents.

In a recent study, Buceta, Bradshaw and Szabadi (1985) examined the responsiveness of eccrine sweat glands located on the volar surface of the forearm to intradermal injections of carbachol in both anxiety patients and normal subjects. The technique employed involves coating of the skin of the forearm with a plastic paint which, when dried, was carefully removed and mounted on a slide. When projected on a screen, the actual number of active glands may be visualized and quantified as holes in the dried plastic. The number of active glands was determined under resting conditions and following injecting various concentrations of carbachol.

As had been previously demonstrated by other researchers (cf. Dobson and Sato, 1972) a significant difference in the number of glands during resting conditions was observed

between normal male subjects (x=21.0) and normal female subjects (x=11.3). More importantly, it was observed that in comparison to corresponding groups of normals, a significantly greater number of glands were active for anxious male (x=33.3) and female (x=51.3) patients. Furthermore, in contrast to normals, no significant difference was found for the number of active glands between male and female patients. Following the intradermal injection of carbachol, both male and female patients showed greater responsiveness, in a quantifiable dose-response fashion, than did normal controls.

1.5 Lactate Model

Wamboltz (Wamboltz, W.Z. and Insel, T.R., in press) describes two approaches to the pharmacologic modeling of clinical anxiety. In the "complete" model, proposed anxiogenic agents are administered to normal, healthy subjects with their resulting effects evaluated for anxiomimetic properties. In the "provocative challenge model", the proported anxiogenic agents are applied to a prescreened, vulnerable population and the effects are compared to reports of naturally occurring symptomology. The sodium lactate infusion has been most widely employed as a provocative test in which it has been shown to be selectively more active in volunteers from the clinical panic disorder population than in their normal controls. Wamboltz and Insel point out sodium lactate infusion is heuristic for research differentiation of the anxiety population independent of speculation about its

implications for mechanism. This research would strongly increase the internal validity of lactate infusion as a psychological model and more specifically, as an appropriate baseline for further scientific exploration of these phenomenon.

In a recent critic' of current research into the phenomena associated with a lactate model of anxiety, Margraf and his colleagues (Margraf, et al., 1986) state that "...the assessment of dependent variables, especially psychophysiologic variables, are rarely described in sufficient detail. Furthermore, the results are often reported incompletely and only qualitatively".

1.51 Effect on Heart Rate

The rather sudden and dramatic increase in heart rate observed during a spontaneous panic attack has been documented by Liebowitz, et. al. (1984) using lactate infusion induction of panic in the laboratory. Research such as this points to the heuristic value of combining modern psychological methods in relating the significance of subjectively and objectively rated "panic" with noninvasive psychophysiology to depict a psychopathophysiology of the "panic" response.

Liebowitz, et. al., (1984) have recently demonstrated that patients diagnosed as having panic disorder display higher resting levels of heart rate prior to sodium lactate infusion as compared to normal controls. Furthermore, patients who go on to have panic attacks during the infusion

have higher resting heart rate levels than those panic disorder patients who do not experience a panic attack during infusion. Liebowitz et al. (1984) interpreted this finding as indicating that patients with panic disorder are in a chronic, hyperadrenergic state and that those patients who respond to sodium lactate infusion with a panic attack must be adrenergically 'primed' to panic. Although, based on the results of the glucose and saline placebo infusions conducted by Pitts and McClure (1967), Wamboldt and Insel (in press) come to the conclusion that "It is clear that increased baseline arousal alone is not sufficient, in and of itself, to precipitate a panic attack, the trigger is also specific" (i.e. to sodium lactate).

The consistent finding of increased heart rate during lactate induced panic has recently generated some controversy regarding its interpretability as a differential discriminator between patients and controls. Lactate infusion increases heart rate steadily in all subjects so that some have questioned whether the increase seen in patients who actually panic during the infusion is not merely a continuation of baseline difference. However, the application of statistical procedures designed to correct for these baseline differences and for the ubiquitous increase in heart rate provoked by the infusion has shown that lactate induced panic is indeed associated with a "precipitous" rise in heart rate. The nature of a clinically relevant "precipitousness"

is indicative of the type of research necessary to increase the viability of this procedure in a psychologically functional model.

1.52 Effect on Blood Pressure

Liebowitz et al., (1985), reported changes in systolic pressure, diastolic pressure and heart rate at 5 minute intervals and at point of panic during sodium lactate infusion for controls, panickers and non-panickers. The results indicated that heart rate and systolic pressure increased significantly across the time periods and that the heart rates of non-panickers increased significantly greater than those of the controls. For the point of panic measures, broken down into 5 minute groups, those who panicked in the first 5 minutes had heart rates significantly greater then the non-panickers as did the those who panicked at the 15 minute period. The diastolic blood pressure of those who panicked at the 15 and 20 minute interval were significantly greater then the non-panickers.

1.53 Multivariate Analysis

The research cited above is exemplary of the directions taken to better define the hemodynamic events occurring during the lactate infusion protocol. It is necessary to look at studies which report the independent function of multiple systems to see the "next step" taken to extrapolate the psychophysiological utility of the lactate model.

In a recent study, Freedmen, Ianni, Ettedgui, Pohl and

Rainey (1984) measured heart rate, respiration rate, skin temperature, muscle tension and skin conductance level during sodium lactate, isoproterenol and placebo infusions. Each subject received one of each infusion substance and the results were collapsed across groups. Minute by minute data was averaged within 5 minute periods which reflected the baseline 1, saline 1, infusion, saline 2 and baseline 2 course of the protocol and three way repeated analysis of variance (group X period X drug) were done for each period. Finger temperature showed significant group by period interaction with patients having lower finger temperature then controls during saline 1 and drug infusion. This result was seen for both right and left hands. Significant increase in skin conductance level was found across periods for all groups with a significant response as well as the interdependent nature of physiological systems in statistical models (Kerlinger and Pedhazure, 1973). Thus, reducing the amount of total systematic variance which may be accounted for by the use of physiologically relevant time intervals (Papillo, J.,personal communication) and a multivariate statistical model (Gottman, 1984; Kerlinger, 1978 Karas, S., personal communication).

2.0 Statement of the Problem.

I intend to peripherally measure four of the many possible physiological response modalities during the lactate infusion of individuals who meet DSM-III and Research Diagnostic Criterian for panic disorder with agoraphobia. Changes in

heart rate, total tidal volume, finger pulse amplitude and skin conductance level will be measured continuously and averaged across 15 second intervals to predict the temporal occurrence of subjectively reported and objectively rated "panic attacks" in patients with diagnosed panic disorder and agoraphobia.

The same measures, evaluated together may used to partial the relative contributions of each response system to the variances at circumscribed time samples during the lactate protocol. These results should provide statistical discriminatory power between the physiological response patterns demonstrated by those volunteers from the clinical sample who report "panic" at low dose and those at high dose during the lactate protocol.

3.0 General Methods

Subject selection and infusion procedures used are a refined version of those that were developed from research cited in Liebowitz et. al (1984) and Liebowitz et. al (1985). Their techniques, with subsequent changes as are particular to the methods used in this study are reported with permission of the authors. Treatment of Acute Panic Inventory responses, physiological data collection techniques and resulting psychophysiological analysis are unique to this study and are therefor more completely detailed. The subjects used in this study are a subset of patient volunteers from the Anxiety Disorder Clinic located at the New York State Psychiatric

Institute. The diagnostic sample from which patients have been drawn is documented across a multiplicity of efforts carried out by the research team directed by Drs. Klein, Gorman, Liebowitz and Fyer and associates from the Dept. of Psychiatry, Columbia University. Subject selection procedures which are beyond those cited below can best be described as in Liebowitz and Klein (1981)

3.1 Subject Selection

All patient subjects met DSM-III (APA 1985) criteria for panic disorder or agoraphobia with panic attack. They were all outpatients between the ages of 18 and 60. Exclusion criteria included concurrent depressive episode, inability to discontinue psychotropic medication for at least two weeks (excluding low doses of benzodiazepines, which were discontinued for at least three days prior to lactate infusion), current alcohol or psychoactive drug abuse, or any medical condition or current medication that increased risk in participation.

Subjects were recruited through media presentations, advertisements, medical referrals and word of mouth. Written consent was obtained from each subject after full explanation of study procedures.

3.2 Baseline Procedures

Subjects enter the hospital for their first lactate infusion after abstaining from caffeine, other stimulants, alcohol and cigarettes for at least 12 hours and ingesting

only a light breakfast. Patients were informed that they would receive both a control substance and lactate but did not know their respective timing. Several staff members of the Anxiety Clinic and Biological Studies Unit were in constant attendance and were not blind to the procedure.

3.21 Calculation of Lactate Dose

Upon entering the Biological Studies Unit, patients are initially weighed for calculation of the volume of lactate solution necessary to provide a total possible dose of 10 ml/kg body weight of 0.5M sodium racemic lactate when administered across a twenty minute infusion.

3.22 Ratings of Spontaneous Attacks

They are then asked to provide a urine sample and reduce bladder load. Patients are then assessed by the project psychologist for their current anxiety state as well asked to rate there severity of their worst panic attack on a scale of 1 to 10. Patients are then asked to respond to the Acute Panic Inventory (API). The items of this scale were developed by the staff of the anxiety clinic and are included in appendix 2. The responses by the patients are limited to a rating of present sensations from nothing, mild, moderate to severe.

3.23 Electrode Placement

Following this interview, two sets of three cardiac monitoring electrodes (right clavicle, left rib cage and right hip) are applied and tested for impedance. This is followed

by the fitting and adjusting of strain gauges (Respitrace Inc.) around the thoracic and lower abdominal areas of the torso. Two silver-silver chloride electrodes are then applied to the index and middle fingers of the right hand. In addition to the physiological indices reported on in this study, EEG recording electrodes are applied at left central and occipital regions. After the attachment of these recording devices, the patient is instructed to breathe into a 800 cc respiratory bag, for calibration purposes, three times in an upright position and then three times in a supine position, the former being the position in which the infusion will take place. At this time a finger pulse monitor is fixed on the middle finger of the right hand and the hand is placed in a black box to avoid light interference.

3.24 Resting, Eyes Closed and A.P.I.

After the attachment of electrodes, the patient is asked by the psychologist to remain in a supine position with their eyes closed for five minutes while he waits outside. The psychologist then re-enters the room, makes a loud clap with his hands and asks the patient to count form one to five three times. the patient is then asked the times form the API in the supine position.

3.3 Infusion Procedures

3.31 Needle Insertion

The attending psychiatrist then inserts a needle into the vein of the right arm through which the infusion will take

place. A consulting anaestheologist then inserts a flexible plastic catheter into an artery in the left wrist from which blood samples are drawn every five minutes or at point of panic by a staff technician. A blood pressure cuff is then wrapped around the biceps of the left arm, with pressure sampled every five minutes (and/or at point of panic) throughout the procedure. With the needles inserted, a slow I.V. drip of 5% dextrose in water is opened and is run for the next twenty minutes.

3.32 Rating, A.P.I. and Eyes Closed

Ten minutes later, the patient is again asked to respond to the items and instructed to remain quiet with their eyes closed for the next five minutes. When the eyes closed period is over the patient is asked by the psychiatrist to spontaneously report on how they feel both emotionally and physically for the rest of the procedure.

3.33 A.P.I., Eyes Closed and Lactate On

After five minutes the psychologist again asks the items of the API and instructs the patient to close their eyes for five minutes. During the first two minutes of the eyes closed period, the psychiatrist speeds up the dextrose in water drip and then two minutes later turns a stopcock which switches infusion supply to lactate.

3.34 Response Report

The sodium lactate infusion continues from this point for ten minutes or until patient reports a panic attack. At

ten minutes following lactate onset the psychologist is scheduled to again ask items from the API or at the point at which the patient reports the panic attack. When and if the patient reports a panic attack the lactate drip is closed and the infusion is again switched to the 5% dextrose in water solution. If no panic is reported there is another series of API items with subsequent five minute eyes closed period while the lactate is run for twenty minutes.

3.4 Signal Detection

3.41 E.K.G. Signal and Cardiotachometer

The recording of cardiac performance is achieved by passing the combined potentials of the clavicle and rib cage electrodes into one side of a Grass differential amplifier and the potential of the contralateral hip electrode into the other side. This produces an E.K.G. signal biased to exaggerate the R-wave formation. the resulting signal is feed into a Grass cardiotachometer. The circuitry of the cardiotachometer, in response to detection of R-waves on the E.K.G. signal, electronically calculates the reciprocal of the time interval between successive heart cycles. The voltage output of the tachometer is calibrated in terms of beats per minute (bpm). Both the E.K.G. signal and the stepped line tracing of the tachometer are displayed on a polygraph.

3.42 Abdominal and Thoracic Breathing

Respiratory function is recorded by measuring change in resistance of two strain gauges banded around the chest and

abdomen. The output of the bands are feed directly into a Respitrace Inc. amplification system. This system allows for the equating of the difference in the relative analog signals of the two bands as well as computing an analog sum of the two channels. These three signals are then feed into independent Grass integrated amplifiers and graphed on a polygraph.

3.43 Skin Conductance Level

A Grass Instruments Model 79 polygraph, equipped with two low-level DC preamplifiers, recorded skin resistance. The amplifiers output eight uA to the skin through Grass Instruments Ag/AgCl electrodes with a .05 molar NaCl paste electrolyte.

3.44 Finger Pulse Volume

The measure of the finger pulse volume is the output of a photo electric cell which is being charged by an infrared light passed through the middle finger of the patients' right hand. This output is fed into a Grass low pass amplifier set at .01 to .05 microvolts sensitivity with a short time constant. The amount of blood in the radiating pulse is inversely reflected in the voltage output of the photo-electric cell. The relationship is represented by the positive amplitude of the resulting signal.

3.5 Data Collection

3.51 Analog to Digital Conversion

The voltage output of each amplifier is read by an analog/digital converter triggered every .02 secs. by the

internal clock of a DEC MNC/LAB computer. The resulting data set is interpreted by the waveform analysis routines of the Psychophysiological analysis System (Tursky, B., Papillo, J. and Pijacki, R., in press). The physiological data (heart rate (HR), amplitude of the finger pulse (FPV), skin conductance level (SCL), number of skin conductance responses (SCR) and respiratory tidal volume (TV)) collected during the fifty minutes of the Lactate protocol are initially averaged into the means of fifteen second intervals according to the clock variable (TIME) for each subject. The standard deviation for each fifteen second interval is also calculated at this point, missing data is excluded by case.

3.52 Sampling of H.R., F.P.V. and S.C.L.

The output of this program includes the rate of the heart on a beat by beat basis as produced by the tachometer. In addition, the heart rate is expressed in absolute frequency by the count of R-Wave occurrences. The values for the finger pulse volume and the skin conductance level are sampled from the originally continuous data set at a rate equivalent with the heart rate.

3.53 Minute Ventilation

The abdominal and thoracic respiratory, as well as the skin conductance response signals are preliminarily treated according to the format of the DEC enveloping routines. These produce the times and absolute value of the signals in a peak and trough detection scheme. The time of return from peak to

fifty percent of the baseline value is also output. In addition, the absolute value of the distance from trough to peak in the respiratory data is compared to the calibration values achieved on a 800 cc rebreathing bag.

4.0 Experiment 1

4.1 Introduction:

Experiment one attempts to correlate the time of panic with significant physiological responses. The correlation between the times of major physiological responses and the time of report should act to describe the degree to which they occur together. This would allow further understanding of the action by each physiological response system at an anxiogenic dose of lactate.

4.2 Procedures

There are 12 subjects in the sample,N=12. They are matched for panic reports at three minute intervals in the twenty minutes following the onset of lactate. There are two subjects' scores represented at each of six points in the data set. The criterion for each of the physiological indices are the times at: a) peak heart rate, b)peak respiratory rate,c) highest level of skin conductance and d)the lowest finger pulse volume. The scores are averages of 15 second periods.

Because of initial assumptions (criterion) about the direction of the scores, one tailed T-tests for comparison of individual scores are used for each correlation. There are four correlations performed that use the times of each

criterion by the panic times. Two tailed T-tests are performed to determine the correlation of each criterion occurrence with those of the others. The probability of each correlation is evaluated for occurrence in a standardized normal distribution.

4.3 Results

4.31 Heart Rate

The correlation between time of panic and time of peak heart rate was .95. When this is interpolated into time, the time of subjective response occurred within thirty seconds of the peak heart rate with a probability less then 05. error. The correlation of peak heart rate with the time of peak respiratory rate is identical. Heart rates' correlation with the time of the lowest finger pulse volume and the greatest skin conductance was below .65. ($p<.50$). The Finger Pulse Volume response and the skin conduction level response could have occurred plus or minus five minutes of the heart rate increase.

4.32 Respiratory Rate

Time of panic and time of peak respiratory rate were correlated at .99. In time, this would mean that the peak respiratory response occurred within 15 seconds of the report for all subjects. The probability of this correlation is less then .01. Correlation with time of the finger pulse response was .65. It was .45 with time of the greatest increase in the skin conductance level. These scores are not significant

beyond .05 probability.

4.33 Finger Pulse Volume

Time of panic and time of the lowest level of the finger pulse were correlated at .57. This would indicate that either half the subjects had the greatest decrease in F.P.V. at time of report or that all the subjects had lowest F.P.V. plus or minus about five minutes from time of report. The lowest finger pulse level correlated .51 .58 and .32 with H.R., S.C.L. and R.R. respectively.

4.34 Skin Conductance Level

Time of panic and time of peak skin conductance level were correlated at .34. This would indicate that the greatest level of skin conductance could have occurred approximated 9.5 minutes away from the time of panic. The correlations with the criterion of the Finger Pulse Volume, Respiratory rate and the Heart Rate were .55,.54 and .50 respectively.

4.4 Discussion

The results from experiment one point to two levels of predictability from the variables measured. The occurrence of the heart and respiratory rate criterion closely parallel the time of panic but the time of the lowest finger pulse volume and the highest skin conductance levels do not.

The close temporal relationship between heart rate increase and the time of panic supports the findings of almost all research which uses the word "panic" to describe its' independent variable. The exact timing of the peak heart rate

in this study makes the observation more reliable then those reported Leibowitz et al. (1984), Freeman et al (1985) or Margraf et.al (1985).

The high degree of correlation between the time of the heart rate and respiratory criterion was previously approximated by Freidman et.al who were only able to place the increases within five minutes of each other. The results here indicate a much closer occurrence. The works by Clark (1978), Solomon and Holmes,(1979) and Suess, Alexander, Smith and Sweeney (1980) all placed the increase in respiratory rate at the time of greatest reported anxiety but were not able to place this within 15 seconds of the verbal report.

The relationship,or the lack of one, between the time of panic and that of the finger pulse could not have been predicted by the works of Bloom et.al(1976),Bloom and Trautt(1977) or even by Lovallo's use of the cold pressor test. The results would indicate that the effect of the Lactate infusion differs in the rate at which vascular action occurs relative to the subjective report of panic. The procedures in this experiment do not accurately discriminate the role of the magnitude of the response relative to those produced by techniques such as cold pressor.

The highly accurate studies of Lader et.al, which exposed panic disorder subjects to high decibel tones and the detailed work of Dobson and Sato,(1972)with carbachol, clearly point to a defined eccrine gland response to anxiety. From the

results of this experiment it is unclear as to temporal the patterning of this response with lactate infusion. It seems safe to say that the skin conductance response to lactate induced panic does not occur within the same time frame as the heart rate or respiratory rate increases.

In summary, the respiratory and heart rates are significantly correlated with the subjective report of panic to lactate stimulation. This appears to be a time dependent,unidimensional relationship. The finger pulse volume and skin conductance level criterion do not discriminate the panic time from the rest of protocoled time and require further analysis to depict the precise nature of their relationship both to the time of panic and to the heart and respiratory criterion. It may be possible to test this data to uncover the relationship of the F.P.V. and S.C.L. to the time of panic, the H.R. and R.R.. A test for this hypothesis could be carried out by imposing a different distribution on the scores based on the time of panic. Analysis of group differences could then be used to test for the degree to which the times of the criterion occurrence predicts group inclusiveness.

5.0 Experiment 2

5.1 Introduction

This experiment is based on the definition of two subgroups from within a sample of subjects who reported panic to the infusion of Sodium lactate. The groups are based on the

subjects' latency to respond from the time of lactate onset. In addition, the time course is broken down by the events on the experimental protocol. The purpose of this experiment is two fold. In the first instance, it is purely descriptive. It attempts to use accurate physiological monitoring techniques to describe the responses of multiple systems in the laboratory induction of panic. In the second place, this experiment attempts to clarify the temporal relationship of criterion in the finger pulse and skin conductance level to the subjective report of panic.

5.2 Procedures

5.21 Criteria for Groups

Twelve subjects are included in this sample, (N=12). They were selected for latency to panic times which occurred at three minute intervals within twenty minutes of lactate onset. There are two subject scores at each of the six data points.

Those subjects who panicked within the first ten minutes comprise the EARLY response group, (n=6). The actual distribution of scores in this group were two subjects each at three, five and eight minutes.

Those subjects who panicked between ten and twenty minutes following lactate onset comprise the LATE response group, (n=6). The actual distribution of scores in this group were two subjects each at twelve, fifteen and eighteen minutes.

5.22 Breakdown of Time

Time is divided into five epochs which are ten minutes in duration. They comprise the major events of the experimental protocol (see Appendix). The epochs are extensively described in the General Methods section of section 3.0 in the body of the text but to reiterate briefly,they are as follows. Epoch one is the baseline time. This time occurs before any invasive procedure occurs. Epoch two follows the needle insertion and during the slow drip of the saline solution. Epoch Three is a continuation of epoch two but in the last three minutes the I.V. drip is speeded up from three drips per second to five drips per second. Epoch four begins the infusion of lactate, the early group reported response during this time. Epoch five is a continuation of epoch four, the late group reported response in this time.

5.3 Results

The numbers reported in this experiment are the averages of the six subject's scores in each of the epochs for each group. The units of measure are beats per minute for heart rate, liters of air for minute ventilation and umhos for skin conductance levels. The finger pulse volume is essentially an uncalibrated signal, the method used in Bloom and Trautt (1977) was adopted in deciphering the unit of measure in which to report the results. Bloom and Trautt reported the results of finger pulse in millimeters of pen deflection from diastolic trough to the systolic peak. They note that the

should be randomly distributed throughout the population. Because this uses tonic levels and changes to make comparisons between groups , their methods will be assumed.

5.31 Mean Heart Rate of Group by Time (table one)

Mean Heart rate during Epochs Four and Five are significantly higher then in Epochs One,Two and Three for both groups. There is a nineteen beat per minute jump in epoch Four by the EARLY group compared to only a six beat increase for the LATE group. This trend is continued upward (2.3 b.p.m.) for Epoch Five at the end of which the early group ends the experiment with a heart rate over twenty beats above baseline. Heart rate increases at a rate of 2.0 to 4.0 beats per minute across the first four epochs for the late group. There is a five beat increase in Epoch Four with a continued trend upward until the rate is approximately fifteen (15) beats per minute faster in Epoch Five. The difference in heart rate between the groups was greatest in Epoch Four. The rate for the EARLY group was seven b.p.m higher for the LATE group.

The standard deviation in the heart rate scores is significantly different between the groups. The s.d. for the early panickers is four to five times higher then that of the late panickers through the first four epochs. In the fifth epoch the s.d. for the early panickers doubles in size where as the late panickers decreases two beats.

5.32 Mean Finger Pulse Volume by Group by Time (Table 2)

The finger pulse volume fluctuated significantly

between Epochs One and Two for the early group. There was an average decrease of 9.1 mm. There is a subsequent 7.1 mm. increase from Epoch Two to Epoch Three for the early panickers. This is followed by a 10.0 mm. decrease into Epoch Four. This decrease is followed by a 4.8 mm. increase into Epoch Five.

The levels of volume decreased 8.5 mm. between Epoch One and Epoch Two for the late panickers.There is a subsequent 9.2 mm. increase from Epoch Two to Epoch Three. There is a 8.2 mm. decrease in Epoch Four from Epoch Three. This is followed by an 8.7 mm. increase from Epoch Four to Epoch Five.

The volume level scores for the LATE panickers are significantly correlated with those of the EARLY group. Both groups' scores drop from epoch one into two then rise again in epoch three, fall again in epoch four then climb in epoch five. The values are 5.0 to 8.5 mm. higher for the late panickers then for the early panickers across all epochs.

The s.d.in the f.p.v. scores ranged from 2.7 to 4.9 mm. for the early panickers.The s.d. of the early panickers'scores increased and decreased proportionally to changes in the absolute volume. The s.d. for the early panickers was lowest in epoch four and highest in epoch five.

The s.d. for the late group does not flucuate as closely with the absolute volume changes as that of the early group. During epochs one and two the f.p.v. essentially sits within a 0.1 mm. margin. This is followed by a slight decrease in

variation in epoch four and a return in epoch five.

The s.d.of the F.P.V. is significantly higher (@ 25 mm.) for the late panickers when compared to those of the early group across all Epochs. The 14 mm. drop in epoch four by the early group is the most distinct event.

5.33 Skin Conductance Level by Group by Time (Table 3)

The skin conductance level of the early panickers is significantly higher in Epoch One then the rest of the Epochs. There is a forty umhos drop from Epoch One into two, from 120.6 umhos to 84.6 umhos. This level then remains within a 0.5 umhos margin throughout.

For the late panickers, skin conductance level starts low (53.7 umhos) in epochs one and two. The S.C.L. then rises sharply during epoch three (133.5 umhos). There is a sixty one point increase from Epoch Two to Epoch Three, a 10.0 umhos decrease into Epoch Four and a final increase of 80.0 umhos into Epoch Five. The average S.C.L. was higher for the LATE group then the EARLY group. Except for the sudden drop after baseline, the EARLY groups' scores do not vary greatly from their mean of 88.5 umhos. The LATE group has a practically strait line, rising from 53.7 umhos at Epoch One to 202.0 in Epoch Five.

The is a relatively low level of standard deviation in the epoch means. The s.d. of the late panickers is consistently higher then that of the earlier panickers but not significantly so, approximately 0.7 umhos. Even when the level

scores are well over 100 umhos apart, there is only 0.6 umhos difference in variability.

5.34 Mean Minute Ventilation by Group by Time (Table 4)

The average minute ventilation was 7.3 liters across all Epochs for the early panickers. This level remained within a 1.0 liter range for Epochs One,Two and Three. There is an increase of 1.5 liters from Epoch Three to Epoch Four which is the greatest increase for both groups. The early panickers decrease 0.5 liters again, from Epoch Four to Epoch Five. The early group is 2.0-3.0 liters above their baseline minute ventilation during panic.

The average M.V. for the late panickers is 6.8. There is a 1.0 liter increase between each Epoch until epoch five. The M.V. level rises from 5.1 to 8.4 liters from Epoch One to Epoch Four. There is a subsequent decrease of 1.0 liter from Epoch Four to Epoch Five.

The M.V. scores between groups are highly correlated. The two groups' scores parallel each other across Epochs. The levels of the EARLY group is always 0.5 to 0.9 liters higher then those of the LATE group.

The average S.D. across Epochs is 0.6 liters. There is no significant difference in change scores between Epochs. The S.D. scores are not highly correlated with the variation of the M.V. levels. The highest level, 1.1 liters, is during Epoch four for the early panickers and the lowest,0.1 liters,is during Epoch Five for the late panickers.

Respiratory rate was significantly different for the early panickers then the late group. From epoch three on, the early panickers had by far ($p.<.004$), higher rates of breathing across the entire ten minute epochs. Both groups had their highest scores in epoch four, at lactate onset although the early panickers had a 1.3 breath per minute increase where as the late panickers had only a 0.3. The relative lack of the respiratory frequency to discriminate the fifth epoch from the other epoch for the late panickers is clearly an indication that there is a more complex answer to the pulmonary response during panic rather than simply frequency.

5.35 Multivariate Analysis of Variance

A multivariate analysis of variance (MANOVA) with repeated measures, is used to evaluate the individual F scores in a single equation O'Brian and Kaiser (1985) point out the MANOVA'S multivariate normality can be violated to a significant degree without seriously affecting the validity of the p values or the power of the test. The lack of a normality or sphericity in the data is very important in this study because each subsequent score is highly dependent on its' prior value. The physiological variables are treated as within subjects factors, the five time samples are the between subject factor.

The group of all responders are included in a multivariate repeated measures design across time as divided into epochs. In the first MANOVA, the means of each physiological measures

are included,across epochs,for the entire sample.(Table Five) This demonstrates the contribution of each scores variance to the total irrespective of time of panic.

A second,independent MANOVA equation is computed with the means of the late responders having been subtracted out. This proportions the contribution by each variable to the total variance for the low dose responders, (table six). Finally, another independent MANOVA is completed in for the scores of the late responders (Table seven). The Fishers' Exact F scores and their corresponding probabilities are rank ordered within each table.

When the overall mean is used, the variance of the heart rate, minute ventilation and tidal volume are least probable ($p<.01$, see Table 5). They are followed in order by respiratory frequency, skin conductance level and finger pulse volume. When the means for the high dose responders are taken alone, only the heart rate is significant beyond .01 (see Table 7). Tidal volume, minute ventilation and skin conductance made up the next three lowest probable variations followed by respiratory frequency and then by finger pulse volume.

The rank of the least probability for the total group variance indicate that heart rate is the greatest contributor of variance. The 3.31 point difference in F-scores between the early and late panickers show that the two groups add similarly to the total group variance.

The indices of pulmonary performances were highly variant between the groups. For the combined groups, minute ventilation varied most, followed by respiratory frequency then , tidal volume. Between the early and late groups, there is a distinct juxtaposition for frequency and tidal volume. Respiratory frequency clearly contributes more to variance in pulmonary variables for the early group then does tidal volume. For the late panickers, tidal volume and minute ventilation contribute significantly more then does respiratory frequency.

In these equations, skin conductance and finger pulse are the least contributors to total variance. Skin conductance variance is significantly higher then that of the finger pulse.

5.44 Discussion

In summary, the second experiments is based on the post hoc definition of two subgroups, early and late responders. Those who responded in the first ten minutes comprise the early group and those who responded in the second ten minutes make up the late group. The epoch means and standard deviations for each of the physiological measures were evaluated for the probability that the distributions were significantly different.

The first purpose of this experiment was to more clearly describe physiological action of the measured systems at an anxiogenic dose of lactate. By defining two subgroups it

is clearly seen that there are different patterns of response dependent upon critical dose of lactate tolerated.

The peak heart rate levels can be seen to have some divergence from the epoch in which the subject reported panic. When the scores are averaged across the entire epoch, the early group had its' highest level in epoch five, after they had reported panic. Although this is a less precise manner of looking at the data then in the first experiment, it is probable that this is the reason that peak heart rate predicted panic within thirty seconds rather than fifteen.

Again, this data is in agreement with the body of literature which employs heart rate as a measure of panic. As an extrapolation of the findings that panic disorder subjects did not have higher resting heart rates then normal controls in laboratory procedures,(Kelly,Michel-Heggs and Sherman(1971), Ianni and Ettedgui,1984, and Liebowitz et.al,1984), these results did not find greater resting heart rate levels in early panickers then late panickers.

The finding that the standard deviation of the heart rate is multiplicatively higher in the early panickers is in agreement with what the literature predicts. The reports of Liebowitz et.al (1984), Gorman et.al,(1984), Lown,(1979), Tyler, Lee and Alexander,(1980) have all described a "precipitous" rise in heart rate as the sin quo non of panic. The combination a significantly raised heart rate across more then a ten minute average and a standard deviation greater

then twice the level of matched panicking controls should provide evidence in support of such a statement.

The use of minute ventilation, in addition to respiratory frequency, is a more stringent test of pulmonary function in this experiment then in experiment one. The minute ventilation certainly increases following the onset of lactate, it does increase at a rate of approximately one liter of air greater for the earlier panickers then the late. Considering the hyperventilation studies reported by Gorman (1984) and his comments in Papillo, Murphy and Gorman (in press), the likelihood that this one liter of air is significant is highly probable when a state of chronic hyperventilation can be maintained by a single extra breathe every few minutes.

When the time of the subjective report is the criterion for group inclusion, as in experiment two, the early panickers are at peak minute and greatest respiratory rate in the epoch that they report panic, the late panickers parallel the early group and therefore panic after having reached peak levels.

This finding would seem to coincide with the results of Mills (1982) if one agree that the late panickers are more like normals then are the earlier panickers. Mills found that anxious subjects tended to continue to hyperventilate following hyperventilation test where as normals would begin to hypoventilate to bring PCO2 back to normal. I think this is an important contribution from this study and warrants further

study. This study does not adequately measure the many possible parameters of pulmonary function and therefore cannot predict to studies which employ gas analysis, metabolic end product study or even the breathing component analysis of Lum (1975), Grossman et.al (1985)and Clark et al.(1985).

The performance of the finger pulse in this experiment is again counter to the literature, as it was in experiment one. The finding of Bloom, Houston and Burish (1976) that reduction of the finger pulse is more closely correlated with stated anxiety then heart rate is not supported here. The fact that the finger pulse decreased for all subjects immediately after the insertion of the blood sampling needle and immediately after to increase of the saline flow from three to five drops per second would more highly implicate vascular manipulation rather then subjective anxiety in predicting finger pulse volume in this study.

The definition of the two subgroups based on time of panic clearly demonstrates a significant difference in the skin conductance response. The baseline difference,a total of almost 80 umhos, is highly predictive of time of panic. The early panic appear to enter the laboratory situation rather well but immediately "let go" at the onset of the invasive procedures. The late panickers enter the situation with higher conductance but gradually become less and less as they go along. From this data it would appear that there are two distinct groups based on the skin conductance level.

It is difficult to compare the skin conductance response of this experiment to the work of Lader et.al or to the work of Buceta et.al and Dobson et. al. There may simply be an order of magnitude difference between the panic patients infused with lactate and the anxious patients exposed to noxious tones or intradermal injections of carbachol. If the extreme level of conductance by the early panickers is viewed as the inability to habituate the eccrine gland response then, the studies are in complete agreement. In this study, the skin conductance response is the best single predictor of early or late panic to sodium lactate infusion.

6.0 Summary

The literature cited above point to generally defined cardio-pulmonary responses in lactate induced panic. The two experiments performed in this study precisely depict the heart rate and respiratory rate levels relative to the point of subjective panic.

Experiment one provides strong evidence that these physiological data are reliable predictors to the subjective report of a lactate response. Strong correlates such as peak respiratory frequency and heart rate increase prediction as to when the subject will request the stopping of the lactate. The finger pulse volume and peak skin conductance level failed to provide specifically discriminating factors to the point of panic.

9.0 Tables and Figures

Table 1.

Heart Rate by Group by Time

Epoch	Early	Late	F	prob.
Epoch 1	67.3	70.7	.24	.63
Epoch 2	70.0	70.4	.003	.95
Epoch 3	67.4	74.0	.34	.57
Epoch 4	85.3	78.4	1.15	.30
Epoch 5	88.8	86.8	.04	.82

Heart Rate s.d. by Group by Time

Epoch	Early	Late	F	Prob.
Epoch 1	20.2	3.4	3.46	.09
Epoch 2	24.0	3.9	6.55	.02 *
Epoch 3	11.6	3.4	1.40	.26
Epoch 4	21.2	5.4	4.30	.06
Epoch 5	19.2	11.4	0.81	.38

Table 2.

Finger Pulse Volume by Group by Time

Epoch	Early	Late	F	Prob.
Epoch 1	423.4	496.2	.30	.59
Epoch 2	355.1	409.7	.44	.51
Epoch 3	419.7	501.0	.65	.31
Epoch 4	324.1	417.3	1.12	.31
Epoch 5	367.1	534.3	1.52	.24

Finger Pulse Volume s.d. by Group by Time

Epoch	Early	Late	F	Prob.
Epoch 1	65.6	42.8	1.86	.11
Epoch 2	65.2	42.6	2.90	.11
Epoch 3	59.9	41.5	1.76	.21
Epoch 4	52.4	27.0	3.38	.09
Epoch 5	57.8	49.4	0.27	.60

Table 3.

Skin Conductance Level by Group by Time

Epoch	Early	Late	F	Prob.
Epoch 1	120.6	53.7	2.01	.18
Epoch 2	84.6	62.0	1.74	.2
Epoch 3	84.6	133.5	.58	.46
Epoch 4	85.2	123.0	.41	.53
Epoch 5	84.7	202.0	1.83	.20

Skin Conductance Level s.d. by Group by Time

Epoch	Early	Late	F	Prob.
Epoch 1	.10	.26	1.68	.22
Epoch 2	.14	.17	.08	.77
Epoch 3	.10	.19	1.34	.27
Epoch 4	.14	.24	.65	.23
Epoch 5	.09	.15	.70	.41

Table 4.

Minute Ventilation by Group by Time

Epoch	Early	Late	F	Prob.
Epoch 1	6.2	5.1	.53	.48
Epoch 2	7.1	6.1	.42	.52
Epoch 3	7.5	7.2	.03	.85
Epoch 4	9.0	8.3	.10	.74
Epoch 5	8.6	7.3	.27	.60

Respiratory Rate s.d. by Group by Time

Epoch	Early	Late	F	Prob.
Epoch 1	4.7	4.0	2.56	.14
Epoch 2	4.7	4.0	2.56	.14
Epoch 3	4.5	3.8	4.66	.05 *
Epoch 4	5.8	4.1	13.59	.004**
Epoch 5	5.6	3.7	13.26	.004**

Table 5.

Repeated Measures MANOVA

All Responders by Time

Source of Variation	F	Prob.
Heart Rate	17.05	p.< .000
Minute Ventilation	6.42	p.< .000
Respiratory Frequency	4.10	p.< .070
Tidal Volume	3.34	p.< .019
Skin Conductance Level	1.05	p.< .385
Finger Pulse Volume	.83	p.< .514

Table 6

Repeated Measures MANOVA

Early Responders by Time

Source of Variation	F	Prob
Heart Rate	10.76	p.< .000
Respiratory Frequency	6.00	p.< .007
Minute Ventillation	4.01	p.< .002
Tidal Volume	2.14	p.< .119
Skin Conductance Level	1.05	p.< .500
Finger Pulse Volume	.43	p.< .784

Table 7.

Repeated Measures MANOVA

Late Responders by Time

Source of Variation	F	Prob
Heart Rate	7.45	p.< .001
Tidal Volume	1.93	p.< .155
Minute Ventillation	1.92	p.< .156
Skin Conductance Level	1.70	p.< .190
Respiratory Frequency	.91	p.< .477
Finger Pulse Volume	.70	p.< .601

8.0 Bibliography

Ancoli, S., Kamiya, J., Ekman, P. (1980) Psychophysiological differentation of positive and negative affects, Biofeedback and Self Regulation, 5, 356-357.

Ax, A.F. (1953). The Physiological Differentation between Fear and Anger, Psychosomatic Medicine, 15(5), 533-442.

Askelrod, S.D., Gordon, D., Ubel, F.A., Shannon, D.C., Barger, D.C., Cohen, R.J., (1981). Power Spectrum Analysis of Heart Rate fluxuations, a quantative probe of beat to beat cardiovascular control, Science, 2183, 220-222

Barr, T.C., Telch, M.J., Havvik, D. (1982). Ambulatory Heart Rate Changes during Panic Attacks. J. Psychiatric Res., 17(3), 261-266.

Bellack, A.S., Lombardo, T.W., (1985). Measurement of Anxiety. In S.M. Turner (Ed) Behavior Theories and Treatment of Anxiety New York, PLenum.

Benjamin, L.S. (1967). Facts and Artifacts in using analysis of Covariance to undo the law of initial values. Psychophysiology, 4, 187-206

Bernstein, D.A. & Nietzel, M.T. (1974). Behavioral avoidance tests: The effects of demand characteristics and repeated measures of two types of subjects. Behavior Therapy, 5, 183-192.

Blair, D.A., Glover, W.E., Greenfield, A.D.M. & Roddie, I.C. (1959) Excitation of Cholinergic vasodilatory nerves to human skelatal muscles during emotional states. J. of Physiology, 148, 633-647.

Bloom, L.J., Houston, B.K., Burish, J.G. (1976). A Evaluation of Finger Pulse Volume as a measure of Anxiety. Psychophysiology, 13, 40-42.

Bloom, L.J., Trautt, G.M. (1977) Finger pulse volume as a measure of anxiety: Further evaluation. Psychophysiology, 14, 541-544.

Bohrer, R.E. & Porges, S.W. (1982). The application of time series statistics to psychological research, An Introduction. In G. Keren (Ed.) Statitical and Methodological issues in psychology and social science research. Hillsdalem N.J., Lawrence Erlbaum & associates.

Bond, D.D. (1943). Sympathetic and vagal interaction in Emotional responses of the Heart. American J. of Physiology, 138, 468-478.

Bond, A. J., James, D.C., Lader, M.H. (1974). Physiological and Psychological measures in Anxious Patients. Psychological Medicine, 4, 364-373.

Bogdonoff, M.D., Combs, J.J., Bryant, G.D., and Warren, J. (1959). Cardiovascular Responses in Experimentally induced alterations of Affect. Circulation, 20, 353-359.

Borkovic, T.D., Weerts, T.C., Bernstein, D.A., (1977) Assessment of Anxiety. In A.R. Ciminero, K.S. Calhoun and H.E. Adams (Eds) Handbook of Behavioral Assessment New York, Wiley

Brener, J.M. (1980). The measurement of Heart Rate. In P.H. Venerables & I. Martin (Eds.), Techniques in Psychophysiology. London, Wiley.

Brener, J.M., Phillips, K.C., and Connally, S.R. (1977). Oxygen Consumption and Ambulation during operant conditioning of Heart Rate increases and decreases in Rats., Psychophysiology, 14, 483-491.

Brown, C.C. (1967) A Proposed Standard Nomenclature for Psychophysiological Measures, Psychophysiology, 4, 260-264.

Brown, O.R., Kloster, F.E., Demots, H. (1975). Incidence of Mitral Valve Prolapse in the Asymptomatic Normal. Circulation, Suppl II, 77.

Buell, J.C. (1984). Impedance Cardiography and Plethismography. In, Cardiovascular Instrumentation: Application of New Technology to Biobehavioral Research. (Eds) J.A. Herd, A.M. Gotto, P.G. Kaufaman, S.W. Weiss, N.I.H. Publication #84-1654

Burish, T.G., Horn, P.W. (1979) A evaluation of frontal EMG as an index of general arousal, Behavior Therapy, 10, 137-147.

Channey, D.S., Heninger, G.R., Jalow, P.I. (1985). Increased anxiogenic effects of caffine in panic disorders. Arch of Gen. Psychiatry. 42, 233-243.

Chattopadhyay, B., Cooke, E., Toone, B. & Lader, N.H. (1980). Habitation of Physiological Responses in Anxiety. Biological Psychiatry, 15, 711-721.

Chesney, M.A. (1984). Non-invasive Amebulatory Blood Pressure Monitoring. In Cardiovascular Instrumentation: Application of New Technology to Biobehavicral Research. (Eds) J.A. Herd, A.M. Gotto, P.G. Kaufman, S.W. Weiss, N.I.H. Publication #84-1654

Chronbach, L.J. & Furby, L. (1970). How should we measure change or should we. Psychological Bulletin, 74, 68-80.

Clark, M.E. (1978) Therapeutic applications of physiological control: The effectiveness of respiratory pacing in reducing autonomic and subjective distress. Unpublished Doctoral Dissertation, Kentucky State University

Clark, D.M. & Hemsley, D.R. (1982) Effects of Hyperventilation: individual variability and its relation to personality. J. Behavior Therapy and Experimental Psychiatry., 13, 41-47.

Cohen, H., Goodenough, D., Witkin, H. (1975). The Effects of Stress on Components of the Respiratory Cycle. Psychophysiology, 12, 377-380.

Cohen. M.E. & White. P.D. (1972). Neurocirculatory Asthenia. Mil. Med., 137, 142-144.

Cohen, D.H., Macdonald, R.L. (1974). A selective review of central neural pathways involved in cardiac control. In Cardiovascular Psychophysiology, Current Issues in Response Mechanism, Biofeedback and Methadology. P.A. Obrist, A.H. Black, J. Brenner, L.V. DiCara. (Eds). Chicago, Aldine.

Comroe, J.H. (1974) Physiology of Respiration (2nd ed). Chicago, Yearbook Medical Book Publishers Inc.

Connally, J.F. (1979). Tonic Physiological Responses to Repeated Presentations of Phobic Stimuli, Behav, Res, Ther, 17, 189-196.

Cook, M.R. (1974). Psychophysiology of peripheral vascular changes. In Obrist, P.A., Black, A.H., Brener, J., DiCara, L. V. (Eds.) Cardiovascular Psychophysiology: Current Issues in response mechanism, biofeedback and Methodology. Chicago, Aldine, p.6084-6102.

Coryell, W., Noyes, R., Clancy, J. (1982). Excess Moratlity in Panic Disorder, Arch. of General Psychiatry, 39, 701-703.

Dawson, M.E., Shell, A.M. & Canntina, J. (1977) Autonomic Activity in depressive illness. Psychophysiology, 14, 226.

Dudley, D.L. (1969) Psychophysiology of respiration in health and disease. New York, Appleton-Century-Croft.

Duffy, E. (1962). Activation and Behavior, New York,Wiley

Eckberg, D.L., Cavanaugh, M.S., Mark, A.L., Aboud, F.M. (1975). A Simplified Neck suction Device for Activation of Carotid Baroreceptors. Circulation, 85, 167-173.

Edelberg, R. (1972). Electrodermal Recovery Rate, Goal-Orientation and Aversion. Psychophysiology, 5, 512.

Ehlers, A., Margraf, J. Roth, W.T. (1986) Experimental induction of panic attacks. In I. Hand and H. Wittchen, (Eds), Panic and Phobias, Empirical evidence of theoretical models and long term effects of behavioral treatments. Berlin, Springer-Verlog.

Engel, B.T. (1960). Stimulus-Response and Individual Response Specificity. Arch. of Gen. Psychiatry, 2, 305-313.

Engel, B.T. (1972). Operant Conditioning of Cardiac Function. A status Report. Psychophysiology, 9, 161-177.

Engel, B.T. & Chism, R.A. (1967). Effect of Increases and Decreases in Breathing rate on Heart Rate and Finger Pulse Volume. Psychophysiology, 4, 83-89.

Engel, B.T. & Bickford A.F. (1961) Stimulus-Response and Individual-response specificity in essential hypertensive. Arch. of General Psychiatry, 5, 478-489.

Feleky, A. (1916) The Influence of emotions on respiration. J. of Experimental Psychology, 1, 218-222

Finesinger, J.E. (1944) The effect of pleasant and unpleasant Ideas on the respiratory pattern. American J. of Psychiatry, 100, 649-667.

Foss, T.P. (1975) Effectiveness of breathing therapy treatment program on the reduction and management of anxiety. Unpublished Doctoral Dissertation, University of Maryland.

Fouad, P.G., Taruzi, R.C., Ferrerio, C.M., Fighaly, S., Alicandri, C. (1984). Assessment of Parasympathetic Control of Heart Rate by a Noninvasive Method. Amer. J. of Physiology, 246, H838 - H842.

Fowles, D.C., Christie, M.J., Edelberg, R., Gringe, W.W., Lykken, D.T., Venerables, P.H. (1981) Publication recommendations for electrodermal measurements. Psychophysiology, 18, 3.

Fredrikson, M. (1981) Orienting and Defensive responses to phobic and conditioned stimuli in phobics and normals. Psychophysiology, 18, 456-465.

Freedman, R.R., Ianni, P., Ettdgui, E., Pohl, R., Rainey, J.M., (1984). Psychophysiological Factors in Panic Disorder, Arch. of Psychiatry ,17, 66-73.

Frolich, E., Tarazzi, R., Dristan, H. (1969). Hyperdynamic B-Adrenergic Circulatory State. Arch Int. Medicine, 123, 1-7.

Furedy, J.J. & Heslegrave, R.J. (1983) A consideration of recent criticism of T-wave amplitude index of myocardial sympathetic function. Psychophysiology, 20, 204.

Garssen, B. (1980) Role of stress in the development of the hyperventilation syndrome, Psychotherapy and Psychosomatics, 33, 214-225.

Geddes, L.A. (1970). Direct and Indirect Measures of Blood Pressure, Chicago, Yearbook Medical Pub.,

Geer, J.H. (1964). Measurement of the Conditioned Cardiac Response. J. of Comparative & Physiological Psychology, 57, 426-433.

Gettes, L.A., Newberg, D.C. (1977). Cuff pressure oscillations in the measurement of relative blood pressure. Psychophysiology, 14, 198-202.

Gorman, J.M., Askanazi, J., Liebowitz, M.R., Fyer, A.J., Stein, J. Kinney, J.M. Klein, D.F. (1984). Response to Hyperventilation in a group of patients with Panic Disorder. Am. J. of Psychiatry, 141(7), 857-861.

Ginsberg, S. & Furedy, J.J. (1974). Stimulus repetition, change, and assessment of sensitivities and relationship amoung an electrodermal and two plethysmographic components of the orientating response. Psychophysiology, 11, 35-43.

Gorman, J.M. Fyer, A.J., Ross, D.C., Cohen, B.S., Martinez, J.M. Liebowitz, M.R., Klein, D.F. (1985). Normalization of venous Ph, pCO2, and Bicarbonate levels after blocade of panic attacks. Psychiatry Res., 14(1), 57-65.

Gorman, J.M., Fyer, A.J. Gliklich, J., King, D., Klein, D.F. (1981) Mitral valve prolapse and Panic disorders: Effects of ipramine. In D.F. Klein & J. G. Rabkin (Eds.) Anxiety - New Research and Changing Concepts. New York, Raven Press.

Graham, F.K. (1973). Habituation and Dishabituation of Responses innervated by the Autonomic Nervous System. In Peeke, H.V. & Herze, M.J. (Eds.) Habituation. Vol. 1, Behavioral Studies, New York, Academic Press, Pp. 163-218.

Graham, F.K. (1978a) Normality of distributions and Homogeneity of Variance of Heart Rate and Heart Period Samples. Psychophysiology, 15, 487-491.

Graham, F.K. (1978b). Constraints on Measuring Heart Rate and Period Sequentially through Real and Cardiac Time, Psychophysiology, 15, 492-495.

Graham, F.K. (1979). Distinguishing amoung orientating, defence and startle reflexes. In H.D. Kirimal, E.H. van Olst, J.F. Orlebile (Eds.). The orientating Reflex in Humans. Hillsdale, N. J. Erlbaum.

Grossman, P. (1983) Respiration, Stress and Cardiovascular Function, Psychophysiology, 20, 284.

Guyton (1985) Textbook of Medical Physiology, Phil., W.B. Saunders.

Harris, V.A., Katkin, E. S., Lick, J.H. & Habberfield, T. (1976) Paced Respiration and cardiac response to Stress. Psychophysiology, 14, 228.

Hastrup, J.L. (1986) Duration of initial heart rate assessment in Psychophysiology: current practices and implications. Psychophysiology, 23, 15-17.

Hellegrave, R.J., Ogilvie, J.C., Furedy, J.J. (1979) Measuring Baseline - Treatment Differences in Heart rate Variability: Variance versus Successive Difference Mean Square and Beats per Minute versus Interbeat Interval, Psychophysiology, 16, 151-157.

Hord, D.J., Johnson, J.G., Lubin, A. (1964). Differential effects of the law of initial value (LIV) on autonomic variables. Psychophysiology, 1, 79-87.

Hugdahl, K., (1981) The Three systems model of fear and emotion - a critical examination. Behavior Research and Therapy, 19, 75-85.

Jennings, J.R., Stringfellow, J.C., Graham, M. (1974). A Comparison of the statistical distributions of Beat-by-Beat Heart Rate and Heart Period, Psychophysiology, 11, 207-210.

Jennings, J.R. & Wood, C.C. (1976). The e- adjustment procedure for Repeated Measures Analysis of Variance. Psychophysiology, 13, 277-278.

Jennings, R.J., Berg, K.W., Hutcheson, J.S., Obrist, P.A., Porges, S. & Turpin, G. (1981). Publication Guidelines for Heart Rate Studies in Man. Psychophysiology, 18, 226-231.

Jennings, R.J., Tahmoush, A.J., Redmon, D.P. (1980). The non-invasive measurement on peripheral vascular activity. In P. H. Venerables & I. Martin (Eds.). Techniques in Psychophysiology, New York, Wiley.

Katkin, E.S. & Deitz, S.R. (1973) Systematic Desensitization. In W. F. Prokasy & D. Raskin (Eds.) Electrodermal Activity and Psychological Research. New York, Academic Press.

Khachaturian, Z.A., Kerr, J. Kruger, R. & Schachter, J. (1972). A Methodological Note: Comparison Between Period and Rate Data in Studies of Cardiac Function. Psychophysiology, 5, 539.

Kelly, D. (1966) Measurement of Anxiety by Forearm Blood Flow, British J. Psychiatry, 152, 789-798.

Kelly, D. (1968) The Relationship Between Clinical Diagnosis and Anxiety Assessed by Forearm Blood Flow. British J. Psychiatry, 114, 611-626.

Kelly, D., Brown, C.C., Shaffer, J.W. (1970). A comparison of physiological and psychological measurements of anxious patients and normal controls. Psychophysiology, 6, 429-441

Kelly, D. Walter, C. (1968) The relationship between clinical diagnosis and anxiety assessed by forearm blood flow and other measurements, British J. of Psychiatry, 114, 611-626.

Kelly, D., Mitchell- Heggs, N., Sherman, D., (1971). Anxiety and the Effects of Sodium Lactate assessed clinically and physiologically. British J. Psychiatry, 119, 129-141.

Knight, M.L., Borden, R.J. (1979). Autonomic and Affective reactions of high and low socially-anxious individuals awaiting public performance, Psychophysiology, 16, 209-213.

Kotona, P.G., Jih, F. (1975). Respiratory Sinus Arrhythmia; Noninvasive measure of parasympathetic Cardiac Control. J. of Applied Physiology, 39, 801-805.
Kubicek, W.G., From, A.H., Patternson, R.P., Witsoe, D.A., Caseda, A., Lilleki, R.G., Resek, R. (1970). Impedance Cardiography as a non-invasive means to monitor cardiac function. J. of Association for the Advacement of Medical Instrumentation, 4,79-84.

Lacy, B.C. (1950). Individual differences in somatic response patterns. J. comp. physiol. psychol., 43, 338-350.

Lacy, J.L. (1967). Somatic Response Patterning and Stress: Some Revisions on Activation Theory. in M.H. Appley amd R. Trumbull (Eds.) Psychological Stress: Issues in Research, New York, Appleton-Century-Crofts, Pp. 14-37.

Lacy, B. C. & Lacy, J.I. (1974) studies in Heart Rate and Other Bodily Processes in Sensorrimotor Behavior. In P.A. Obrist, A.H. Black, J. Brener, and L.V. Dicara (Eds.). Cardiovascular Psyphysiology: Current Issues in Response Mechanism, Biofeedback and Methodology., Chicago,Aldine, Pp. 85-92.

Lacy, J.L. & Lacy, B.C. (1962) The law of initial value in the longitudional study of autonomic constitutions: Reproducability of Autonomic responses and response patterns over a four year interval. Annals of the New York Academy of Science, 38, 1257-1290.

Lacy, J.I., Kagan, J., Lacy, B.C., & Moss, H.A. (1963). The Viseral level: Situational Determinants and Behavioral Correlates of Autonomic Response Patterns. In P.H. Knapp (Ed.), Expression of the Emotions in Man, New York ,International Universities Press

Lader, M.H. (1975). The Psychophysiology of Mental Illness. London, Routledge and Kegan Dawl.

Lader, M.H. (1976). The Peripheral and Central Roles of Catecholamines in the Mechanism of Anxiety. In Klein, D.F., Gittleman-Klein, R. (Eds.) Progress in Psychiatric Drug Treatment, vol. 2, New York, Brunner-Mazel.

Lader, M.H. (1967). Palmer Skin Conductance measures in Anxiety and Phobic States. J. Psychosomatic Research, 11, 271-281.

Lader, M.H. & Mathews, A. (1970). Physiological Changes during Spontaneous Pannic Attacks. J. of Psychosomatic Research, 14, 377-382.

Lader, M.H. & Wing, L. (1966). Physiological Measures, Sedative Drugs and Morbid Anxiety, London , Oxford University Press.

Lande, S.D. (1981) Physiological and Subjective meaning of anxiety during flooding. Behavior Research and Therapy, 18, 162-163.

Lane, J.D., Greenstat, L., Shapiro, D., Rubisntein, E. (1983). Pulse transit time and blood pressure: an intensive analysis, Psychophysiology, 20, 45-49.

Lang, P.J. (1968). Fear reduction and fear behavior: Problems in treating a construct. In J.M. Schlien (Ed), Research in Psychoterapy, (vol 3). Washington D.C.: American Psychological Association.

Lang, P.J. (1980) Anxiety: Toward a psychophysiological definition. In H.S. Akiskal & W. L. Webb (Eds.) Psychiatric diagnosis: Explorations of biological prediction, New York, Spectrum.

Lang, P.J., (1971). The Application of Psychophysiological methods to the Study of psychotherapy and behavior modification. In A. E. Bergin and S.L. Garfields (Eds) Handbook of Psychotherapy and Behavior Change New York, Wiley.

Lang, P.J., (1977). The Psychophysiology of Anxiety. In J.D. Cone and R.P. Hawkins (Eds.) Psychiatric Diagnosis: Exploration of Biological Criteria New York, Spectrum.
Lang, P.J., Melamed, B.G., & Hart, J.H. (1974). Automating the desensitization procedure: A psychophysiological analysis of fear modification. In M.J. Kietzman (Ed.)., Experimental Approaches to Psychopathology, New York, Academic Press.

Lang, P.J., Rice, D.G., Sternbach, R.A. (1972) The Psychophysioly of Emotion. In N.S. Greenfield and R.A. Sternbach, Handbook of Psychophysiology, New York, Holt, Rinehart and Winston.

Lapierre, Y.D., Knott, V.J., Gray, R. (1984). Psychophysiological correlates of sodium lactate. Psychopharmacology Bull., 20, 50-57.

Larson, P.B., Scheideman, N., Pasin, R.D. (1986). Physiological basis of cardiovascular psychophysiology. In M.G.H. Coles, E. Donchin and S.W. Porges (Eds). Psychophysiology, Systems Processes and Applications, New York, Guilford Press.

Lawler, J.E., Obrist, P.A. (1974). Indirect Indices of Contractile Force. In P.A. Obrist, A.H. Black, J. Brener, and

L.V. Dicara (Eds.). Cardiovascular Psychophysiology: Current Issues in Response Mechanism, Biofeedback and Methodology. Chicago, Aldine, Pp. 85-92.

Lick, J.R. and Katkin, E.S. (1976). Assessment of Anxiety and Fear. In M. Hersen and A., Bellack, (Eds.). Behavioral Assessment: A practical handbook. New York, Pergamon.

Liebowitz, M.R., Fyer, A.J., Gorman, J.M., Dillon, D., Appleby, I.L., Levy, G., Anderson, S., Levitt, M. Palij, M. Davies, S.O., (1984). Lactate provocation of panic attacks. I. clinical and behavioral findings, Arch. Gen. Psychiatry, 41(8), 764-770.

Liebowitz, M.R., Fyer, A.J., Gorman, J.M., Dillon, D., Appleby, I.L., Levy, G., Anderson, S, Levitt, M. Palij, M. Davies, S.O., (1984). Lactate provocation of panic attacks. II. Biochemical and physiological findings, Arch, Gen, Psychiatry, 42(7), 764-770.

Lindsley, D.B. (1951). Emotion. In S.S. Stevens (Ed) Handbook of Experimental Psychology. New York, Wiley, 473-516.

Lockhart, R.A. (1972). Interrelations between amplitude, latency, rise time and the Edelberg recovery measure of the Galvonic skin response. Psychophysiology, 9, 437-442.

Lovallo, W. & Zeiner, A.R. (1975). Some Factors influencing the Vasomotor response to Cold Pressor Stimulation. Psychophysiology, 13, 499.
Lown, B. & DeSilva, R.A. (1978). Roles of Psychologic Stresst and Autonomic Nervous System Changes in Provocation of Ventricular Premature Complexes. American J. Cardiology, 41, 979-985.

Lum, L.C. (1976) The syndrome of habitual chronic hyperventilation. In O. Hill (Ed.) Modern Trends in Psychosomatic Medicine (vol. 3), London, Butterworth

Lum, L.C. (1981). Hyperventilation and Anxiety State. J. of the Royal Society of Medicine. Jan., 74 Pp 1-4.

Lykken, D.T. (1972). Range Correction Applied to Heart Rate and GSR data. Psychophysiology, 9, 373-379.

Lykken, D.T. & Venables, P.H. (1971). Direct Measurement of Skin Conductance: a proposal for Standardation. Psychophysiology, 8, 656-672.

Malmo, R.B. (1959) Activation: A Neuropsychological dimension. Psychological Reviews, 66, 367-386.

Malmo, R.B. and Shagrass, C. (1949). Physiology Study of Symptom Mechanism in Psychiatric Patients under Stress. Psychosomatic Medicine, 11, 25-29.

Mathews, A. M. & Lader, M.H. (1971) An Evaluation of Forearm Bloob Flow as a Physiological Measure. Psychophysiology, 8, 509-524.

Mathews, A. M. & Gelder, M.G. (1969) Psychophysiological investigations of brief relaxation training. J. of Psychosomatic Research, 13, 1-12.

Martin, B. (1961). The Assessment of Anxiety by Physiological behavioral Measures. Psychological Bulletin, 58, 234-255.

Martin, B. & Stroufe, L.A. (1970). Anxiety. In C.G. Costello (Ed.) Symptoms of psychopathology, A handbook. New York, Wiley.

Mavissakalian, M. & Michelson, L. (1982). Patterns of Psychophysiological Change in the Treatment of Agoraphobia. Behav. Res. Ther., 20(4), 347-356.

McCaul, K.D. Solomon, S. & Holmes, D.S. (1979) The Effects of paced Respiration and expectations on physiological responses to threat. J. of Personality and Social Psychology, 37, 564-571.

McCullum, M., Burch, W.R., Roesler, R. (1969) Personality and Respiratory responses to sound and light. Psychophysiology, 6, 291-300.

McGuinness, D. (1973). Cardiovascular responses during habituation and mental activity in anxious men and women. Biological Psychology, 1, 115-123.

Meyers, A.W., & Craighead, W.E. (1978). Adpation periods in clinical psychophysiology research: A recommendation. Behavior Therapy, 9, 355-362.

Mills, J.N. (1973). Biological aspects of circadian rhythms London, Plenum.

Miller, J.C., Horvach, S.M., (1978). Impendance Cardiography, Psychophysiology, 15, 80-91.

Miller, L.H., Shmavonian, B.H. (1965) Replicability of two GSR indices as a function of stress cognitive activity. J. Personality Soc. Psychology, 2, 753-756.

Montgomery, G.K., (1977). Effects of Performance Evaluation and Anxiety on Cardiac Responses in Anticipation of Difficult Problem Solving, Psychophysiology, 14, 251-257.

Nesse, R.M., Cameron, O.G., Curtis, G.C., McCann, D.S., Huber-Smith, M.J. (1984). Adrenergic function in patients with panic anxiety. Archives of General Psychiatry, 41, 771-776.

Newlin, D.B., Levenson, R.W. (1979). Pre-injection period: measuring Beta-adrenergic influences on the heart. PsychoPhysiology, 16: 546-553.

Obrist, P.A., Howard, J.L., Lawler, J.E., Galosy, R., Meyers, K. Gaebelein, C.J., (1974a). cardiac-somatic interaction. In P. A. Obrist, A. H. Black, J. Brener, and L.V. Dicara (Eds.). Cardiovascular Psychophysiology: Current Issues in Response Mechanism, Biofeedback and Methodology. Chicago, Aldine, Pp. 132-162.

Obrist, P.A., Webb, R.A., Sutterer, J.R., amd Howard, J. (1970a). The Cardiac -Somatic Relationship, some reformulations. Psychophysiology, 6, 569-587.

Obrist, P.A., Webb, R.A., & Sutterer, J.R. (1969). Heart Rate and Somatic Changes during Aversive Conditioning and Simple Reaction Time Tasks. Psychophysiology, 5, 696-723.

Odegaard, O. (1932). The Psychogalvonic Reactivity in Affective Disorders. J. Medical Psychology, 25, 3-12.

Oken, D., Grinker, R.R., Heath, H.A., Korchin, S.J., Sabskin, M., Schwartz, N.B. (1962) Relation of physiological responses to affect expression, Archives of General Psychiatry, 6, 336-351.

Papillo, J.F., Pijacki, R., Tursky, B. (1984). A Comprehensive Software package for the Management of Psychophysiological Experimentation. Psychophysiology, 21, 159.

Papillo, J.F., Tursky, B., Freidman, R. (1981). Perceived changes in the intensity of arterial pulsations as a function of applied cuff pressure. Psychophysiology, 18, 283-287.

Paul, G.L., Bernstein, D.A. (1973). Anxiety and Clinical Problems: Systematic desensitization and related techniques. New York: General Learning Press.

Pennebaker, J.W. (1981) Stimulus characteristics influencing estimation of heart rate. Psychophysiology, 18, 3-10.

Porges, S.W., & Coles, M.G.H. (1976). Psychophysiology, Penn., Dowden, Hutchinson & Ross.

Posey, J.A., Getty, L.A., Williams, H., Moore, A. (1969). The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure. Cardio. Res. Cent. Bull., 8, 15-25.

Rachman, S. and Hodgeson, R.I. (1972) Synchrony and Desynchrony in Fear and Avoidance. Behavior Research and Therapy. 12, 311-318.

Roth, W.T., Tinklenberg, J.R., Doyle, C.M. (1979). Mood States and 24-hour cardiac Monitoring. J. of Psychosomatic Research, 20, 179-186.

Sayers, B. McA. (1973). Analysis of Heart Rate Variability. Ergonometrics, 16, 17-32.

Schacter, S. & Singer, J. (1962). Cognitive, Social and Physiological determinats of Emotional Stress, Psychological Review, 69, 379-399.

Schwartz, G.E., Weinberger, D.A., Singer, J.A. (1981). Cardiovascular differentation of happiness, saddness, anger and fear following imagery and exercise, Psychosomatic Med., 43, 343-364.

Schwartz, G.E. (1978) Psychobiologival Foundations of Psychotherapy and Behavior Change. In S.L. Garfield and A.E. Bergin (Eds) Handbook of Psychoetherapy and Behavior Change: An Empirical Analysis. New York, Wiley.

Schwartz G.E. (1977). Biofeedback and physiological pattering in human emotion and consciousness. In J. Beatty, J. and H. Legewie (Eds) Biofeedback and behavior, New York, Plenum

Shimizu, H. (1978). Reliable and Precise identification of R-wave in the EKG with a simple peak detector, Psychophysiology, 15, 499-501.

Shean, G.D. & Stange, P.W. (1971). The effects of varied respiratory rate and volume upon finger pulse volume. Psychophysiology, 8, 401-405.

Sherwood, A., Allen, M., Obrist, P.A., Langer, A.W. (1986) Evaluation of Beta adrenergic influences on cardiovascular and

metabolic adjustments to physical and psychological stress. Psychophysiology, 23, 89-104.

Shandry, R. (1981) Heart beat perception and emotional experience. Psychophysiology, 11, 76-85.

Shapiro, D., Greenstat, L., Lane, J.D., Rubinstein, E. (1981). Tracking Cuff System for beat to beat recording of blood pressure. Psychophysiology, 18, 129-136.

Shimizu, H. (1977). Digital Cardiac Meter with D.A. Converter. Psychophysiology, 14, 417-419.

Siddle, D.A.T., Turpin, G. Spinks, J.A. and Stevenson, D. (1980). Peripheral measures. In van Praag, H.M., Lader, M.H. Rafelson, O.J. and Sachar, E.J. (Eds.), Handbook of biological psychiatry: part II - Brain mechanism and abnormal behavior - psychosiology, New York, Marcel Dekker, 45-78.

Smith, T.W., Houston, B.K., Zurawski, R. (1984). Finger Pulse Volume as a measure of Anxiety in Response to Evaluative Threat. Psychophysiology, 21, 260-265.

Smith, T.M., Houston, B.K., Stucky, R.J. (1984) Effects Threat of Shock and Control over Shock on Finger Pulse Volume, Pulse Rate and Systolic Blood Pressure. Biological Psychology, 20, (1), 31-42.

Smyth, H.S., Sleight, P., Pickering, G.W. (1969). Reflex Regulation of Arterial Pressure during Sleep in Man. A Quantative Method of assessing Baroceptor Sensitivity. Circulation Research, 24, 109-121.
Sneiderman and Pickering G.W. (1986). Cardiovascular measures of physiologic reactivity. In K.A. Matthews, S.N. Weiss, T. Detre, T. M. Dembrowski, B. Falkner, S.B. Manuck, R.B. Williams, (Eds.) Handbook of Stress, Reactivity and Cardiology. New York, Wiley.

Sneiderman, McCabe and Hausman (1984). Neurogenic Influences Upon the Heart., In (Eds.) J.A. Herd, A. M. Gotto, P.G. Kaufman, S.W. Weiss, Cardiovascular Instrumentation, and Application in Biobehavioral Science, N.I.H. Publication #84-1654.

Stead, E.A., Warren, J.B., Merrill, A.J. and Brannon, E.S. (1945). Cardiac Output in male subjects as measured by the technique of right atrial catherization: normal values with observations and the effects of anxiety and tilting. J.of Clinical Investigation, 24, 346-331.

Steptoe, A. (1980). Toward a definition of Psychophysiology.

Psychophysiology, 1, 90-91.

Stern, R.M. & Anchel, C. (1968). Deep Inspirations as stimuli for Responses of the Automatic Nervous System. Psychophysiology, 5, 132-141.

Sternberg, D.E. (1984). Biologic Tests in Psychiatry. Psychiatric Clinics of North America, 7(3), 639-650.

Stevenson, I.P., Duncon, L.H., Wolf, S., Ripley, H.S., and Wollf, H.G. (1949). Life Situations, Emotions and Extrasystolies. Psychosomatic Med., 11, 257-272.

Stenvenson, I. & Ripley, H. (1952) Variations in respirations and in respiratory systems during changes in emotions. Psychosomatic Medicine, 14,, 476-490.

Stroufe, L.A. (1971) Effects of Depth and Rate of Breathing on Heart Rate Variability. Psychophysiology, 8, 648-655.

Suess, W.M., Alexander, A.B., Smith, D. D., Sweeny, H.W., Marion, R.J. (1980). The Effects of Psychological Stress on Respiration: A preliminary Study of Anxiety and Respiration, Psychophysiology, 17, 535-540.

Taylor, C.D., Kraemeer, H.C., Bragg, D.A., Miles, L.E., Rule, B., Savin, W. M. DeBusk, R.F. (1982). A New System for Recording and Processing of Heart Rate and Physical Activity in Outpatients. Compt. Biomed. Res. 15, 7-17.

Turpin, G., Siddle, D.A., (1978). Cardiac and Forearm Plethysmography Responses to High Intensity Auditory Stimuli, Biological Psychology, 6, 267-282.

Turpin, G., Siddle, D.A., (1978). Cardiac and Forearm Plethysmography Responses to High Intensity Auditory Stimuli, Biological Psychology, 6, 267-282.

Tursky, B. & O'Connell, D.N. (1966) Survey of Practice in Electrodermal Measurement, Psychphysiology, 2, 237-240.

Tursky, B., Papillo, J/F., Preidman, R. (1981). The perception and discrimination of arterial pulsations: implications for the behavioral treatment of hypertension. J. of Psychosomatic Research. 26, 485-493.

Tursky, B., Shapiro, D., Schwartz, G.E. (1972) Automated constant cuff pressure system to measure average systolic and diastolic blood pressure in man. IEEE transactions on

Biomedical Engineering, 19, 271-276.

Tyrer, P. (1976). The Role of Bodily Feelings in Anxiety. Institute of Psychiatry- Maudsley Monographs, No. 23, Oxford University Press.

Tyrer, P., Lee, I., Alexander, J. (1980) Awareness of cardiac function in anxious, phobic and hypochondrical patients. Psychological Medicine, 10, 171-174.

Van Egeren, L.F., Feather, B.W., Hein, P.L. (1971). Desentization of phobias: Some physiological propositions. Psychophysiology, 8, 213-228.

Varni, J.G., Clarke, E., Giddon, D.B. (1971) Analysis of Cyclic Heart Rate Variability, Psychophysiology, 8, 406-413.

Venerables, P.H. & Christie, M.J. (1973). Mechanism, Instrumentation, Recording Techniques and Quantification of Responses. In W.F. Prokasy and D.C. Raskin (Eds.), Electrodermal Activity in Psychological Research, New York, Academic Press, Chap. 1.

White, B.V. & Gilden, E.F. (1937) 'Cold Pressor Test' in tension and Anxiety, A cardiochronographic study. Arch. Neuro, Psych, 38, 964-984.

Wilder, J.(1962). Basimetric approach (law of Initial Value) to biological Rhythms., Annals of the New York Academy of Science, 98, 1211-1220.

Weiner, J.S. & Hellman, K. (1960). The Sweat Gland. Biological Review, 35, 141-186.

Weiss, T., Dell bo, A.D., Reichek, N., Engelman, K. (1980). Pulse transit time in the analysis of autonomic nervous system affects on the cardiovascular system. Psychophysiology, 17, 202-207.

Whitney, R.J. (1953) The measurement of volume changes in human limbs., J. of Physiology, 121, 1

Wilson, R.S. (1974) CARDIVAR: The statistical analysis of heart rate data. Psychophysiology, 11, 76-85

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11.0 Appendex 1

Lactate Study
Modified API Scale

Pt. Name_____ ID #_____ Inf 1 2 3 Mod_____

Date _____ M.D. Name_____ Panic: Yes_____ No_____

Time of Panic_____

Scale: 0 = No 1 = Slight 2 = Moderate 3 = Severe Clean: Yes_____ No_____

	Base	Pre Needle -35	Pre Inf. -5	+10	+20
Do you feel faint?					
Are you afraid of dying?					
Are you afraid in general?					
Do you have palpitations?					
Is it hard for you to breathe or catch your breath?					
Do you have an urge to urinate?					
Do you have an urge to defecate?					
Do you feel dizzy or lightheaded?					
Do you feel confused at all?					
Do things and people seem unreal?					
Do you feel detached from part or all of your body?					
Is it hard for you to concentrate?					
Are you sweating at all?					
Is it difficult for you to speak?					
Would it be difficult for you to do your job (apart from being hooked up now)?					
Do you have any twitching, trembling or inner shakiness?					
Do you feel nauseous, queasy?					
Are you afraid of going crazy?					
Are you afraid of losing control?					
Do you have any tingling?					
Are you experiencing any chest pain or discomfort?					
Do you have any difficulty in swallowing?					

Lactate Study
Modified AFI Scale

	Base	Pre Needle -35	Pre Inf. -5	+10	+20
Is your mouth dry?					
Do you feel weak?					
Do you have a desire to flee?					
Do you feel depressed?		-			
Do you feel you will embarrass or humiliate yourself?					
Do you feel everyone is watching you?					

Form 90.10 Adm (REB) (6-76)

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IRB #

909-B-EP

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Consent Form For the Study of the Induction of Anxiety Attacks By Sodium Lactate

(Patient)

PURPOSE

The purpose of this study is to see if sodium lactate given intravenously induces an anxiety attack; whether there are patterns of change in heart rate, respiratory rate, blood pressure, and electrical resistance of the skin associated with these attacks; and whether successful treatment of the anxiety attacks which occur spontaneously, will lead to lessened sensitivity to the effect of sodium lactate.

PROCEDURE

The infusion will be done in a laboratory at the New York State Psychiatric Institute , on two consecutive days. On the first day (baseline) you will be shown the laboratory to become familiar with it and the staff. We shall also monitor your heart rate, respiratory rate, brain waves, muscle activity, blood pressure, electrical resistance and temperature of your skin, and tape record samples of your speech. You will also have a needle in your arm for one half hour after which we will draw a small sample of blood (one ounce.)

These measurements will also be made on the second or infusion day. We also may conduct psychological testing, ask questions, as well as ask you to fill out questionnaires - so as to measure how anxious you become, if you do. The whole procedure will last 4-5 hours.

On infusion day, but not on the baseline day, you will be given intravenous infusions in one arm and have small samples of blood removed periodically from the other arm. To avoid repeatedly sticking you to obtain blood samples, we shall leave a small plastic tube in your artery so we can withdraw samples without discomfort. In order to place such a tube, you will first be given a small injection of a local anesthetic (xylocaine) into your wrist and then a tiny needle will be inserted. The plastic tube is then threaded into the artery. The risk entailed in placing the arterial tube are the possibility of a local bruise from the needle and, very rarely a localized infection. Rarely, an allergic reaction to the local anesthetic can occur. There is a very remote possibility of injury to the artery occurring when performing the needle puncture. This would require surgical repair. You will be responsible for all medical costs that may accrue because of any untoward effects of this research.

A third needle may also be placed in a vein of the forearm and connected to a small suction pump. The pump allows us to draw small samples of blood at very short intervals (every two minutes). This method of sampling can pick up very short-lived changes in the blood. The samples will be used to measure levels of adrenalin and noradrenalin. The total amount of blood taken will be no more than 5 ounces, about 1/3 of that given when one donates blood.

The infusion will consist of sterile water, a solution of sodium lactate and small quantities of salt water. Sterile water and salt water are commonly used intravenous fluids and will have no effect upon you other than filling your bladder with urine as if you took the same quantity of fluid by mouth. Sodium lactate fluid is commonly used as an intravenous treatment of certain illnesses. Its use in the present context is not its usual use. It has been found to produce anxiety in some people, and not in others. Aside from the risk of producing an anxiety attack, sodium lactate in this dose involves no forseeable risks.

During the test, psychiatrists, psychologists and nurses specially trained for this will be present. Should you develop a panic attack, we shall immediately stop the infusion. The attack (as most real-life spontaneous attacks), is expected to be of a brief duration. The professional staff will stay with you during and after the attack, should you have one, to offer assistance and comfort. There may be mild sleepiness for 24 yours after the infusion.

You may be videotaped during your participation in the study of lactate infusions and panic attacks. The purpose of the videotape recording is to further research in the nature of panic attacks. The tape will be used solely for research purposes and will be seen only by mental health professionals without use of your name of other identifying information. You may at any time during the taping stop it without prejudicing your participation in other aspects of the research.

TREATMENT AND MEDICATION

After the test, psychiatrists at the Psychiatric Institute will supervise your treatment with tricyclic antidepressant medication and psychotherapy. The usual drugs used for this condition are imipramine (Tofranil) or similar drugs. The drug treatment is not part of the research directly. It is the usual treatment we offer all patients with this condition.

The possible adverse effects of imipramine are sleepiness, lightheadedness, dryness of mouth, constipation and tremor. High doses can also have adverse cardiac effects in individuals with pre-existing heart disease.

FOLLOW-UP AND REINFUSIONS

We expect the treatments with usual drugs to be fully effective, i.e. to completely stop your panic attacks. This is the usual result. When that occurs, we shall retest you with the same intravenous infusions as before. We shall do this shortly after the panic attacks have ceased. The procedure will be the same as before.

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after the second infusion you will continue your usual treatment. When you have been well for six months, you will enter the next part of the study, the purpose of which is to compare the effects of sodium lactate on patients with a history of anxiety attacks, who have been successfully treated and are taken off the medication, with the effects of sodium lactate on similar patients whose medication is continued. At this point, you will either be switched slowly to an active placebo or will continue your usual medication (see below). Neither you nor your doctor will know which medicine you are on. The appearance of the medications will be identical. Six weeks after this switchover, we will again retest you with an infusion of sodium lactate identical to the first two. During this six week period, you will see your doctor weekly and will be asked to answer a short questionnaire at each visit. After the third infusion, you will be informed as to what you were taking; those on the active placebo will be taken off it, and if necessary, put back on imipramine.

The active placebo used will be methscopolamine bromide (Pamine). Methscopolamine bromide produces mild side effects similar to those of imipramine (dry mouth, constipation), but does not affect the central nervous system. It is a commonly used drug approved by the FDA for treatment of certain intestinal problems such as spastic colon and duodenal ulcer. Its use here as an active placebo is not its usual use. The amount of methscopolamine you will take will be less than the doses prescribed in clinical use.

The risk to you of taking methscopolamine bromide in the doses and duration used is that you may experience discomfort of its side effects. The common side effects are: dry mouth, constipation, lightedheadedness, blurred vision and faster heart rate. If you experience significant discomfort, your doctor may stop the medication and treat you as clinically indicated. Though neither you nor your doctor will be aware of whether you are taking methscopolamine bromide (Pamine), or your usual tricyclic antidepressant, this information will be available to the doctor at all times should the unlikely need for it arise.

The risk of discontinuing medication is that your condition might worsen. During the period you may be on placebo you will be closely monitored and emergency consultation will be available to you through the Depression Evaluation Service, 212 960-2368, 2367, or the emergency service of Presbyterian Hospital 212 694-2500. Ask for the psychiatrist on call.

Your participation (or withdrawal), and the results of the project will be known only to the investigators and their assistants. They will consider such information strictly confidential. Should the results be used for publication or presentation at scientific meetings, the identity of the participants will not be divulged.

The benefits to me rest in the value of my participation in providing increased knowledge about the disease and the potential of finding better treatments.

You may withdraw from this study at any time. In such instance, we would continue to provide treatment as we would have had you continued in the program. We expect

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that the course of treatment will take 2 to 8 weeks. We are not responsible for providing treatment after that. If further care is required, we shall help you obtain it.

Should any of the information we gather from you be used for scientific publications or presentation, your anonymity will be strictly preserved. Your records will be kept in locked files and access to them will be restricted to the research staff.

The investigators are available to answer questions at any time. Their telephone number is 212 960-2368 or 2367. The investigators are Michael R Liebowitz, M.D., Abby Fyer, M.D., Donald Dillon, Ph.D, and Donald F. Klein, M.D.

The New York State Psychiatric Institute - Columbia University Institutional Review Board has approved recruitment of subjects for this study.

I understand that I can contact the Institutional Review Board (960-5758) if I have any complaints or questions about my rights as a research subject.

I understand that if as a result of my participation in this research, injuries occur from the known or unknown risks of the research described to me, immediate medical care and treatment, including hospitalization if necessary, will be available. Emergency medical treatment will be provided free of charge. I understand, however, that funds are not available to cover the costs of additional medical treatment or other compensation.

I have been given a copy of this consent.

NAME _____ SIGNATURE _____

ADDRESS_____

_____

DATE_____