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Heart rate and respiratory response to doxapram in patients with panic disorder

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Abstract

Panic disorder (PD) is characterized by anticipatory anxiety and panic, both causing physiological arousal. We investigated the differential responses between anticipatory anxiety and panic in PD and healthy controls (HC). Subjects (15 PD and 30 HC) received an injection of a respiratory stimulant, doxapram, with a high rate of producing panic attacks in PD patients, or an injection of saline. PD subjects had significantly higher scores in anxiety and panic symptoms during both conditions. Analysis of heart rate variability (HRV) indices showed higher sympathetic activity (LF) during anticipatory anxiety and panic states, an increase in the ratio of LF/HF during the anticipatory and panic states and a decrease in parasympathetic (HF) component in PD patients. During doxapram PD subjects increased their LF/HF ratio while HC had a reduction in LF/HF. Parasympathetic component of HRV was lower during anticipatory anxiety in PD. In general, PD showed greater sympathetic and psychological responses related to anxiety and sensations of dyspnea, reduced parasympathetic responses during anticipatory and panic states, but no differences in respiratory response. This confirms previous studies showing that PD patients do not have an intrinsic respiratory abnormality (either heightened or dysregulated) at the level of the brain stem but rather an exaggerated fear response.

Keywords

anticipatory anxiety; panic; heart rate variability (HRV); respiration; autonomic; physiology

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1. Introduction

Panic attacks are defined as discrete, time-limited episodes of acute autonomic arousal accompanied by severe fear and with physical symptoms including palpitations, shortness of breath, nausea or abdominal distress, numbness, sweats, chills, and psychological cognitions such as fear of dying and losing control. Two types of panic attacks have been defined: expected and unexpected. Panic attacks may be situationally-dependent (“expected”) when one is subjected to specific cues or panic triggers or situationally-independent (“unexpected”), when they occur suddenly without any obvious cause. Both are associated with underlying panic disorder (PD), a diagnosis requiring recurring, unexpected panic attacks along with avoidance and fear of future attacks (American Psychiatric Association, 2013). Because expected panic attacks are predictable, patients with PD often experience high levels of autonomic arousal and anxiety in anticipation of situations that trigger them (Helbig-Lang et al., 2012). Patients experience anticipatory anxiety as general distress or worry that can remain incapacitating even after panic attacks have been remitted. Anticipatory anxiety are more strongly associated with avoidance behavior than panic attacks themselves and play an important role in determining severity and impairment of PD. Anticipatory anxiety is therefore different from panic although an important component of PD.

Patients with PD have been reported to suffer from irregular breathing patterns both in vivo (Martinez et al., 1996), in laboratory settings (Papp et al., 1995), and during sleep (Stein et al., 1995), suggesting that respiratory variability may be a marker for PD (Niccolai et al., 2009). One theory is that there exists a dysregulation within the respiratory control system, the “false suffocation alarm” hypothesis of panic (Klein, 1993). This theory proposes that panic attacks occur when the brain suffocation monitors (at the level of autonomic brain stem control) erroneously signals a lack of air. In PD patients this monitor is over-sensitive and causes a physical and psychological state of panic in situations where there is no actual risk of suffocation. In this theory patients with PD should respond to anxiety with an exaggerated respiratory response. Another hypothesis is that patients with PD have normal respiratory physiology but mount a greater fear response when somatic sensations are aroused (Gorman et al., 2000). This theory involves a “fear network” in the brain that is centered in the amygdala and involves interactions with several other brain structures including the hippocampus and medial prefrontal cortex and involves similar pathways seen in conditioned fear responses in animals. A heightened or dysregulated respiratory response is not crucial as part of the anxiety/fear response.

In addition to respiratory distress, other prominent symptoms of PD include cardiac symptoms such as chest pain and palpitations. Many studies have reported cardiac differences between PD patients and HC characterized by increased resting heart rate (Larsen et al., 1998; Wilkinson et al., 1998; Friedman and Thayer, 1998; Cohen et al., 2000; Cuthbert et al., 2003; Blechert et al., 2007; Garakani et al., 2009; Martinez et al., 2010; Wise et al., 2011), and decreased heart rate variability (HRV) (Friedman and Thayer, 1998; Sloan et al., 1999; Cohen et al., 2000; Gorman and Sloan, 2000; McCraty et al., 2001; Yeragani et al., 1993; 1998; 2003; Garakani et al., 2009; Melzig et al., 2009; Wise et al., 2011; Hovland et al., 2012). Decreased HRV is a risk factor for increased mortality in patients with

cardiovascular disease (Kleiger et al., 1987; Bigger et al., 1992a; 1992b; Tsuji et al., 1996; Liao et al., 1997; La Rovere et al., 1998; Gerritsen et al., 2001; Camm et al., 2004), and has been proposed as a marker for cardiac disease (Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996).

Evidence suggests that patients with PD are at increased risk for cardiovascular disease. In a German national health interview and examination survey using over four thousand participants of the general population showed a strong association between PD and cardiovascular diseases independent of depression (Tully and Baune, 2014). Another study examining the association between PD and coronary heart disease using a large national managed care database found that PD patients had nearly a 2-fold increase risk for coronary heart disease after adjusting for factors of age, tobacco use, obesity, depression and use of medications (Gomez-Caminero et al., 2005). Still another interesting study showed myocardial ischemia during panic attack induced by CO₂ inhalation (Soares-Filho et al., 2014).

Because decreased HRV is a result of decreased vagal function, autonomic imbalance and decreased parasympathetic activity decreased HRV may be a common pathway for PD and cardiovascular disease (Thayer and Lane, 2007). In general, studies have indicated sympathetic overactivity, parasympathetic hypoactivity, and an imbalance between the two systems in patients with PD.

Researchers have attempted to re-create panic attacks in the laboratory using various behavioral and physiological models including hyperventilation and tilt table challenges and a multitude of panicogenic agents including lactate, yohimbine, pentagastrin, and flumazenil (Esquivel et al., 2008). Doxapram, a respiratory stimulant acting on the carotid body chemoreceptors, has been used in anesthesiology and has the benefit of a rapid onset, short duration, and low blood-brain barrier penetration (Folgering et al, 1981; Calverley, 1983; Hirsh and Wang, 1974; Yost, 2006). Doxapram has been shown to cause panic attacks in patients with PD more often than in HC (Lee et al., 1993; Abelson et al., 1996a,b; Abelson et al., 2007; Fujimura et al., 2009), including studies by our group (Gutman et al, 2005; Kent et al, 2005, Garakani et al, 2007).

The aims of this paper are to further explore the physiological and behavioral characteristics of panic attacks and the differences between panic and anticipatory anxiety. With regard to the former, previous research indicates that, contrary to a prominent theory about PD, no fundamental abnormalities in respiratory physiology are found in patients with PD. We now wish to test this finding by administering a respiratory stimulant, doxapram, to patients with PD to test whether respiratory response differs between patients with PD and HC or whether differences in response are seen in other areas such as autonomic nervous system control of the heart and subjective sense of fear. With respect to the second aim, both panic attacks and worry about future attacks (anticipatory anxiety) are essential features of PD. Studies have suggested that anticipatory anxiety are more strongly associated with avoidance behavior than panic attacks themselves and play an important role in determining severity and impairment of PD. We wishes to test whether in fact there are behavioral and physiological differences between the two anxious states under controlled laboratory conditions.

2. Methods

2.1. Participants

Fifteen patients with PD (9 men, 6 women, mean age 39.40, SD= 12.94) and 30 healthy controls (14 men and 16 woman, mean age= 35.37, SD= 8.23) participated. All participants read and signed informed consent approved by the Institutional Review Boards of the Mount Sinai School of Medicine. Subjects were given a diagnostic clinical interview by a clinician and administered the Structured Clinical Interview for DSM-IV Disorders by a trained clinical interviewer (First et al., 2002). Subjects who passed both interviews were given a physical exam, which included medical history, routine blood tests, urinalysis, urine toxicology, and electrocardiogram.

2.2. Subjects Selection

All patients met DSM-IV criteria for PD with or without agoraphobia, with at least one panic attack per week in the four weeks prior to enrollment and/or a Mobility Inventory score of 3.3 (alone) or 2.5 (accompanied). Subjects were excluded if they had ever met DSM-IV criteria for schizophrenia, bipolar disorder, obsessive compulsive disorder, or any eating disorder. Participants were also excluded if they met DSM-IV criteria for substance abuse or dependence within six months of study entry or had Hamilton Depression Scale score of greater than 15. Subjects were excluded if they were currently on effective medication for PD. All subjects had to be off any psychotropic medication for at least 2 weeks (4 weeks for fluoxetine) before the baseline visit. Healthy controls consisted of individuals with no major Axis I diagnosis including major depressive disorder, PD, generalized anxiety disorder, PTSD, OCD, schizophrenia, bipolar disorder or substance use disorders. All subjects were free of medications affecting the cardiovascular system.

2.3. Physiological recordings and drug administration

Subjects were fitted with the LifeShirt System, a noninvasive ambulatory recording device that continuously acquires and stores respiratory (respiratory rate and volume) and ECG signal onto a computer memory card for later analysis (VivoMetrics, Inc.). The LifeShirt vest is calibration for respiratory measures by having the subject breathe in and out of a respiratory bag of known volume (800cc) and give an approximation of tidal volume and minute ventilation. The lifeShirt system program identifies artifacts in the ECG waveform using R-wave and RR interval periods. Heart rate variability is sampled at a rate of 1000 Hz.sec. Heart rate component variables consisted of low frequency (LF), high frequency (HF), total spectral power and the ratio of LF/HF. Subjects had two PET scans, typically one day apart. They were told they would receive either an injection of 0.5 mg/kg of doxapram, a respiratory stimulant, which has a high rate of producing panic attacks, or an injection of saline on either of the two days to minimize expectancy effects. In fact, all subjects received doxapram and saline in a randomized order. PET scan results will be reported separately.

2.4. Psychological rating scales

Scales administered on screening day included the following: (1) Clinical Global Impression of Severity (CGI-S), a widely used 7-point clinician-rated instrument to assess global

severity and improvement (Guy, 1976); (2) Panic Disorder Severity Scale (PDSS), a 7-item clinician-rated scale providing ratings of the core features of PD (panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations, and the degree of work and social impairment/interference due to PD (Shear et al., 1997); (3) Hamilton Depression scale (HAM-D), a multiple item questionnaire used to provide an indication of depression in adults (Hamilton, 1960); (4) Hamilton Anxiety scale (HAM-A), a 14 item symptom-orientated questionnaire administered by a clinician to assess level of anxiety (Hamilton, 1959); (5) Penn State Worry Questionnaire (PSWQ), a 16-item questionnaire that aims to measure the trait of worry, using Likert-like ratings from 1 (not at all typical of me) to 5 (very typical of me) (Meyer et al., 1990); and (6) Anxiety Sensitivity Index (ASI), a 16 item questionnaire assessing the discomfort with and belief that bodily sensations are dangerous (Shear et al., 1997). The PDSS and CGI scales were not assessed in HC.

Assessments were made by a rater blinded to injection type (saline or doxapram) during PET scans included the Acute Panic Inventory (API), 10-point Anxiety Scale, and Borg (breathlessness, dyspnea) Scale. The API is a 27-item questionnaire that measures anxiety and physiological sensations (Dillon et al., 1987). The 10-point Anxiety Scale is a 0-to-10 Likert-type scale that measures level of anxiety (Houtman and Bakker, 1989). The Borg (Breathlessness) Scale is a 1-to-10 level scale that measures level of sensation of effort to breathe (Borg, 1982).

2.5. Experimental Session

An IV angiocath was inserted in the antecubital vein and a 0.9% saline drip started. Patients were then moved to a sound-attenuated room. Subjects rested in the room for 10 minutes baseline period followed by a 10 minute physiological recording period. Then, the positron emission tomography (PET) scan ligand 5 μ Ci of 18F-fluorodeoxyglucose was injected into the port in the intravenous tubing, followed by the administration of doxapram over 30 s or a saline injection. Patients rested quietly in the room for 35 min, and were then positioned in the scanner. Respiratory and heart rate measures were collected continuously during the testing. Acute Panic Inventory (API) and Borg scales were obtained 10 minutes before doxapram/placebo injection and at 30 minutes post-injection. The 10-point Anxiety Scale was obtained at -10 minutes, +10 minutes, +20 minutes and at +30 minutes. Symptoms of anxiety experienced during the period of time before each doxapram or saline infusion are considered to represent anticipatory anxiety, whereas spikes in anxiety occurring during the infusions are candidates for panic attacks.

2.6. Statistics

Behavioral scale differences pre and post each intervention (saline/doxapram) were tested using independent-samples t-tests. Change scores for each behavioral measure were calculated (post minus pre values) and tested using independent-samples t-tests. Data from physiological recordings were analyzed using repeated measures analysis of variance (ANOVA). Independent group factors were diagnosis (patients, controls) by time (pre vs. post injection) by condition (saline, doxapram), using condition (baseline, post-drug) and time (5 minute mean periods). Correlation analysis (Spearman's rho) was performed

between the four heart rate variability measures (LF, HF, total power and LF/HF ratio) and the three behavioral scale measures (anxiety scale, API and Borg scale). The level of statistical significant was set at $p < 0.05$, two tailed.

3. Results

Age was not significantly different between the groups. All clinical ratings obtained during screening were as expected significantly higher in the PD group than HC including the HAM-D ($p < 0.001$), HAM-A ($p < 0.001$) and ASI ($p < 0.001$), with a trend for higher scores in the PSWQ ($p < 0.056$) in PD subjects than HC.

3.1. Behavioral and Clinical scales

Table one gives the means and standard deviations for the Borg, Anxiety and API scales between PD patients and HC before and after saline and doxapram administration. With one exception (pre-doxapram, Borg scale), patients had significantly higher scores on all three scales both before and after the infusion of doxapram as well as saline. Table two gives the means and standard deviations of the change scores from pre to post doxapram/saline injection in the API, Anxiety and Borg ratings. These show a significantly greater increase in API, Anxiety and Borg scores after doxapram injection in the PD group than HC. The placebo (saline) injection did not produce a significantly different change in API, Anxiety or Borg measure between the two groups. Table three gives the means and standard deviations of behavioral, respiratory and heart rate measures, before and after each condition (doxapram or saline) per group (PD or HC). Significant group by time conditions were found for only the three behavioral measures. Minute ventilation, tidal volume and respiratory frequency, while demonstrating robust effects of doxapram, did not show a statistically significant difference between groups.

Table four gives the spectral analysis of heart rate before and after each condition per group. Significant group by time by condition interactions were found for the HF component and the ratio of LF/HF components of heart rate. HF component of HR was higher in healthy controls than in PD patients prior to saline administration (anticipatory state) ($p < 0.04$). Both controls and patients had an increase in HF during post saline injection. Prior to doxapram administration controls had higher HF levels and increased more post doxapram than patients. The ratio of LF/HF showed PD patients had a greater ratio prior to saline with a decrease post saline injection while controls were lower prior to saline injection and had a smaller drop post injection. During doxapram PD patients had a lower ratio than controls but increased to a higher level than controls post injection while controls had a small decrease post doxapram. In HC anticipatory anxiety as measured by the Anxiety Scale prior to doxapram administration correlated with a decrease in LF component of heart rate ($r = -.55$; $p < 0.004$; $n = 26$), the ratio of LF/HF ($r = -.53$; $p < 0.005$; $n = 26$), an increase in HF ($r = .50$; $p < 0.009$; $n = 26$) and an increase in HRV (RMSSD) ($r = .39$; $p < 0.048$; $n = 26$). In PD patients panic anxiety post doxapram administration correlated with a decrease LF ($r = -.95$; $p < 0.001$; $n = 7$), HF ($r = -.81$; $p < 0.029$; $n = 7$), and total power of heart rate ($r = -.79$; $p < 0.036$; $n = 7$).

4. Discussion

Our investigation explored the differential physiological and behavioral responses between anticipatory anxiety and panic states in PD and HC. As expected we found higher scores in anxiety and panic symptoms in the PD group than in HC during both states. We found in our analysis of spectral heart rate components that PD subjects had decreased HF component of HR compared to HC throughout each condition (pre/post saline and pre/post doxapram) of the study, which was particularly lowest in the PD subjects during the anticipatory anxiety phase. We also found PD subjects to have decreased HRV compared to HC throughout each condition. This is in agreement with other studies that have shown decreased HF activity and HRV in PD subjects during conditions of acute stress, in association with threat stimuli and elevated state anxiety (Melzig et al, 2009; Wang et al., 2013). Conversely we found an increase in the ratio of LF/HF in PD subjects compared to HC which was highest in the PD subjects during the anticipatory anxiety state. Both PD and HC had decreased parasympathetic activity (lower HF) and greater sympathetic activity (LF/HF) during the pre-saline period (anticipatory anxiety state) with a compensating response of increase in HF and decrease in LF/HF post saline period. This may represent a rebound to baseline once the subjects realized they were not going to panic, having received the injection without a reaction occurring (i.e. without any physical symptoms or sensations).

Similarly, Wang et al. (2013) showed that PD subjects had greater LF/HF than HC and had a significant increase in LF/HF ratio during threatening stimuli than HC. In the same way patients with generalized anxiety disorder have been found to have decreased parasympathetic activity and reduced HRV in response to compulsive worrying (Thayer et al, 1996). Melzig et al. (2008) postulated that increased anticipatory anxiety of threat may reflect both decreased prefrontal cortical modulation of the amygdala and a decrease in vagal autonomic modulation and may be a possible endophenotype for forms of anxiety, particularly anxiety characterized by anticipatory anxiety. Others have shown that anticipatory anxiety may be worse for the patient than actual panic attacks. High levels of anticipatory anxiety are more strongly associated with avoidance behavior and may be more important in determining severity and impairment than frequency of panic attacks (Rachman and Lopatka, 1986; Craske and Barlow, 1988; Craske et al., 1988; Cox et al., 1991).

While both groups had a significant increase in respiratory values these were not significant between groups. One possible explanation for the lack of respiratory differences is that doxapram may have caused ceiling effect in respiratory response to be able to tease out more subtle fear related responses in respiration.

A study limitation was the small number of subjects in some of the statistical analysis that were performed, in particular the correlation analysis of behavioral scales with heart rate variability indices, even though significant correlations were found these need to be confirmed in larger studies.

In summary, this study gives further evidence that PD subjects have an abnormal autonomic nervous system which can be further dysregulated during periods of anticipatory anxiety and panic attacks. This dysregulation of vagal modulation may also be associated with

dysregulation of the prefrontal cortex and amygdala activity. If PD patients have decreased prefrontal cortex activation they may be less able to inhibit amygdala activity thereby increasing physiological responses seen during states of anxiety arousal. Further studies, particularly imaging studies are needed during the different states of anxiety in order to evaluate these possibilities. Additionally, increased autonomic arousal in relation to anticipatory anxiety and panic may increase the risk of coronary artery disease as patients with PD are known to have greater risk of coronary artery disease and sudden cardiac death. Decreased HRV, increased sympathetic predominance and decreased vagal function may increase the risk for cardiac morbidity in this population, particularly in PD patients with coronary artery diseases. It will also be important to determine whether treatment of PD modifies any of these putative risk factors. Our study showed greater sympathetic and psychological responses to anxiety and sensations of dyspnea, reduced parasympathetic responses during anticipatory and panic states, but no significant differences in respiratory parameters between PD patients and HC. This provides further evidence that PD patients do not have respiratory abnormalities but rather an exaggerated fear response.

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Highlights

- We investigated the differential physiological and behavioral responses between anticipatory and panic states in panic disorder and healthy controls.
- We found in our analysis of spectral heart rate components that panic disorder subjects had decreased high frequency component of heart rate compared to healthy controls.
- We also found panic disorder subjects to have decreased heart rate variability compared to healthy controls.
- We found an increase in the ratio of low/high frequency of heart rate in panic disorder subjects compared to healthy controls which was highest in panic disorder subjects during the anticipatory anxiety state.
- Both panic disorder and healthy controls had decreased parasympathetic activity (lower HF) and greater sympathetic activity (LF/HF) during the anticipatory anxiety state period.

Table 1

Behavioral measures of Breathlessness (Borg scale), Anxiety level, and Acute Panic Inventory pre and post Saline and doxapram administration

Measure	Group	N	Mean	Std. Deviation	Significance
Pre saline Borg	Patients	15	1.50	1.899	
	Controls	30	.05	.201	t= 2.95; p<0.01; df=14.16
Post saline Borg	Patients	15	1.200	1.9254	
	Controls	30	.033	.1269	t= 2.34; p<0.034; df=14.06
Pre Saline Anxiety	Patients	15	3.20	1.897	
	Controls	30	1.53	1.525	t= 3.18; p<0.003; df=43
Saline Anxiety 10 min.	Patients	10	2.9000	2.37814	
	Controls	23	1.1304	.69442	t= 2.31; p<0.044; df=9.67
Saline Anxiety 20 min.	Patients	10	2.4000	1.42984	
	Controls	23	1.0000	.30151	t= 3.07; p<0.013; df=9.35
Saline Anxiety 30 min.	Patients	15	2.67	2.193	
	Controls	30	1.23	.728	t= 2.46; p<0.026; df=15.56
Pre saline API	Patients	15	8.40	9.927	
	Controls	30	.97	2.141	t= 2.87; p<0.012; df=14.66
Post saline API	Patients	15	10.33	12.482	
	Controls	30	1.03	2.399	t= 2.86; p<0.012; df=14.52
Pre doxapram Borg	Patients	15	.53	1.343	
	Controls	30	.03	.183	N.S.
Post doxapram Borg	Patients	15	4.73	3.990	
	Controls	30	1.98	2.621	t= 2.42; p<0.025; df=20.24
Pre doxapram anxiety	Patients	15	2.73	2.738	
	Controls	30	1.17	.531	t= 2.20; p<0.045; df=14.53
Doxapram Anxiety 10 min.	Patients	10	6.2000	2.61619	
	Controls	23	1.5652	.78775	t= 5.50; p<0.001; df=9.72
Doxapram Anxiety 20 min.	Patients	10	4.4000	2.11870	
	Controls	23	1.2609	.68870	t= 4.58; p<0.001; df=9.84
Doxapram Anxiety 30 min.	Patients	15	6.33	3.716	
	Controls	30	2.57	2.239	t= 3.61; p<0.002; df=19.24

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Measure	Group	N	Mean	Std. Deviation	Significance
Pre doxapram API	Patients	15	7.27	9.603	t= 2.70; p<0.017; df=14,13
	Controls	30	.57	.935	
Post doxapram API	Patients	15	43.80	15.298	t= 7.12; p<0.001; df=43
	Controls	30	14.63	11.669	

Table 2

Change scores of behavioral measures taken before and after saline and doxapram injection

	Panic Disorder N=12	Healthy Controls N=27		
Variable	Mean +/- SD	Mean +/- SD	t-value	df p-level
Borg Saline	0.17+/- 2.72	-0.02+/- 0.23	0.356	37 0.72
Anxiety Saline	-0.42+/-1.98	-0.33+/-1.33	-0.155	37 0.88
API Saline	2.42+/-10.35	0.11+/-2.04	1.126	37 0.27
Borg Doxapram	4.75+/-4.22	1.80+/-2.58	2.696	37 0.01
Anxiety Doxapram	3.75+/-4.61	1.37+/-2.27	2.173	37 0.04
API Doxapram	39.42+/-16.80	13.96+/-11.55	5.505	37 0.001

BORG= Borg breathlessness scale, API= Acute Panic Inventory scale, ANX= Anxiety 10 point scale (30 minutes post-injection minus pre-injection value).

Table 3
Repeated Measures between PD and NC by time (pre, post) by Condition (Saline, Doxapram) Behavioral and respiratory measures

Variable	Group	Condition 1		Condition 2		Statistics		
		Pre S	Post S	Pre D	Post D	Group	Time	Condition Grp/Time/Condition
BORG	PD	1.50 + 1.90	1.20 + 1.93	0.53 + 1.34	4.73 + 3.99	F=19.70	F=23.66	F=20.60 df=1,43
	NC	0.05 + 0.20	0.03 + 0.13	0.03 + 0.18	1.98 + 2.62	p<0.001	p<0.001	p<0.014
API	PD	8.40 + 9.92	10.33 + 12.48	7.27 + 9.60	43.80 + 15.30	F=50.66	F=115.43	F=114.50 df=1,43
	NC	0.97 + 2.14	1.03 + 2.40	0.57 + 0.94	14.63 + 11.67	p<0.001	p<0.001	p<0.001
ANX	PD	3.20 + 1.90	2.67 + 2.19	2.73 + 2.74	6.33 + 3.72	F=25.78	F=17.71	F=16.76 df=1,43
	NC	1.53 + 1.53	1.23 + 0.73	1.17 + 0.53	2.57 + 2.24	p<0.001	p<0.001	p<0.038
TV	PD	386.5 + 211.5	444.5 + 227.9	331.4 + 76.8	624.2 + 193.5	F=1.72	F=36.19	F=6.03 df=1,36
	NC	357.2 + 172.9	344.3 + 164.5	313.1 + 110.5	533.3 + 217.6	p=NS	p<0.001	p=NS
RR	PD	19.0 + 4.3	17.1 + 3.5	18.1 + 4.5	21.1 + 09.4	F=0.46	F=0.74	F=1.59 df=1,36
	NC	21.8 + 10.9	18.9 + 6.5	20.7 + 5.8	19.7 + 5.7	p=NS	p=NS	p=NS
MV	PD	6.64 + 2.78	7.62 + 4.07	5.76 + 1.48	12.96 + 4.84	F=0.07	F=19.95	F=6.59 df=1,36
	NC	8.25 + 9.81	6.33 + 3.20	6.26 + 2.48	10.61 + 5.45	p=NS	p<0.001	p=NS
HR	PD	78.2 + 1.5	77.8 + 11.6	79.4 + 27.1	99.9 + 26.8	F=9.12	F=44.10	F=9.86 df=1,36
	NC	70.6 + 6.6	69.3 + 7.7	68.6 + 8.7	80.0 + 9.5	p<0.005	p<0.001	p<0.078

Pre S= pre-saline, post S= post-saline, Pre D= pre-doxapram, post D= post-doxapram

BORG= Borg breathlessness scale, API= Acute Panic Inventory scale, ANX= Anxiety 10 point scale

TV= Tidal volume (mil-liters), RR= respiratory rate (breaths/minute), MV= minute ventilation (liter/minute), HR= heart rate (beats/minute)

Table 4

Repeated Measures between PD and NC by time (pre, post) by Condition (Saline, Doxapram) of spectral analysis of heart rate

Variable	Group	Condition 1		Condition 2		Statistics	
		Pre S	Post S	Pre D	Post D	Grp	Time Cond Grp/Time/Cond
LFnorm	PD	0.683 + 0.961	0.545 + 0.105	0.557 + 0.098	0.570 + 0.207		
	NC	0.593 + 0.189	0.550 + 0.161	0.583 + 0.146	0.548 + 0.201	F=0.15 p=NS	F=5.60 p<0.025 F=1.17 p=NS F=3.34 p<0.078
HFnorm	PD	0.195 + 0.067	0.329 + 0.114	0.272 + 0.091	0.289 + 0.126		
	NC	0.298 + 0.186	0.350 + 0.159	0.296 + 0.139	0.325 + 0.170	F=1.59 p=NS	F=5.12 p<0.031 F=0.48 p=NS F=7.34 p<0.011
Total Power	PD	2389.5 + 1475.2	2818.5 + 2674.4	4248.5 + 4861.7	1910.6 + 2515.6		
	NC	2651.5 + 2636.4	2478.1 + 2765.1	2846.8 + 3096.4	2032.5 + 1944.5	F=0.12 p=NS	F=12.42 p<0.001 F=0.43 p=NS F=2.73 p=NS
LF:HF	PD	4.14 + 2.18	1.94 + 0.96	2.43 + 1.39	3.18 + 2.27		
	NC	3.13 + 2.21	2.37 + 2.34	2.89 + 2.30	2.66 + 2.62	F=0.04; p=NS	F=6.72 p<0.015 F=0.12 p=NS F=5.96 p<0.021

Pre S= pre-saline, post S= post-saline, Pre D= pre-doxapram, post D= post-doxapram