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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.

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 oversensitive 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

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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 and 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 CO_2 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 et al., 1983; Hirsh and Wang, 1974; Yost, 2007). 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, 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, S.D. = 12.94) and 30 healthy controls (14 men and 16 woman, mean age = 35.37, S.D. = 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 (800 cc) 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 s. 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