



# Do asthma patients with panic disorder really have worse asthma? A comparison of physiological and psychological responses to a methacholine challenge



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## ABSTRACT

**Background:** Panic disorder (PD) has been linked to worse asthma outcomes. Some suggest that asthmatics with PD have worse underlying asthma; others argue that worse outcomes are a result of their tendency to over-report symptoms. This study aimed to measure physiological and psychological responses to a simulated asthma attack (methacholine challenge test: MCT) in asthmatics with and without PD.

**Methods:** Asthmatics with (n = 19) and without (n = 20) PD were recruited to undergo a MCT. Patients completed subjective symptom questionnaires (Panic Symptom Scale, Borg Scale) before and after a MCT. Physiological measures including heart rate (HR), and systolic and diastolic blood pressure (SBP/DBP) were also recorded.

**Results:** Analyses, adjusting for age and sex, revealed no difference in methacholine concentration required to induce a 20% drop in forced expiratory volume in one second (FEV<sub>1</sub>: F = 0.21, p = .652). However, PD patients reported worse subjective symptoms, including greater ratings of dyspnea (F = 8.81, p = .006) and anxiety (F = 9.44, p = .004), although they exhibited lower levels of physiological arousal (i.e., HR, SBP/DBP). An interaction effect also indicated that PD, relative to non-PD, patients reported more panic symptoms post-MCT (F = 5.05, p = .031).

**Conclusions:** Asthmatics with PD report higher levels of subjective distress, despite exhibiting lower levels of physiological arousal, with no evidence of greater airway responsiveness. Results suggest that worse outcomes in PD patients may be more likely due to a catastrophization of bodily symptoms, rather than worse underlying asthma. Interventions designed to educate patients on how to distinguish and manage anxiety in the context of asthma are needed.

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**Abbreviations:** ACQ, Asthma Control Questionnaire; ADIS-IV, Anxiety Disorders Interview Schedule for DSM-IV; BMI, Body Mass Index; DBP, Diastolic Blood Pressure; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revised; ED, Emergency Department visits; FEV<sub>1</sub>, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GLM, General Linear Model; HSCM, Hôpital du Sacré-Coeur de Montréal; HR, Heart Rate; MCT, Methacholine Challenge Test; PC<sub>20</sub>, Provocative Concentration; PD, Panic Disorder; PSS, Panic Symptom Scale; SBP, Systolic Blood Pressure; SD-VAS, Subjective Distress Visual Analogue Scale.

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## 1. Introduction

Asthma is characterized by chronic airway inflammation in response to a variety of stimuli [1,2] causing respiratory symptoms such as shortness of breath [1]. The high economic and quality of life-related burden of asthma has led to the evaluation of potential risk factors for asthma morbidity [3,4]. Over the last 20 years, research has linked chronic negative mood states to worse objective measures of asthma [5–7]. Panic disorder (PD) affects between 6 and 24% of asthmatics [8–10], which is 3–10 times more prevalent than the general population [11]. PD is

characterized by sudden, recurrent panic attacks, which are episodes of intense fear or discomfort associated with cognitive (e.g., fear of losing control) and physiological (e.g., shortness of breath) symptoms [12]. Studies have also shown that comorbid PD and asthma tends to be associated with worse outcomes, e.g., excessive use of bronchodilators and more emergency department (ED) visits [13–16].

Two potential pathways have been proposed to explain the PD-worse asthma outcomes association: one postulates a direct physiological pathway where panic leads to physiological changes (e.g., increased cardiorespiratory reactivity such as heart rate, carbon dioxide partial pressure, and respiratory rate) [17,18] via increased autonomic nervous activation that may be causally linked to asthma [5–7]. The other proposes that PD patients' tendency to catastrophize bodily sensations is associated with increased symptom reporting, resulting in greater treatment-seeking, independent of worse asthma [16,19–23]. Previous evidence supports both hypotheses, but has suffered from methodological weaknesses: a failure to objectively diagnose asthma [22,24], often relying upon self-reported diagnoses which are subject to bias [25]; a failure to use a validated psychiatric interview to diagnose PD [22,26], over-relying on questionnaire measures of panic-like anxiety which are insufficient to confirm PD diagnoses; and the use of resting spirometry as the sole objective measures of asthma [23,27], which may appear normal when asthma is well controlled [28]. In order to test the extent to which asthmatics with PD have physiologically worse asthma, bronchial provocation tests are needed. Based on the American Thoracic Society (ATS) recommendations [29], the methacholine challenge test (MCT) would be a good alternative since this standardized challenge permits to assess several objective measures of asthma such as bronchial hyperresponsiveness, which to our knowledge has not been done in asthmatics with and without PD.

This study aimed to determine whether asthmatics with (versus without) PD had greater non-specific bronchial responsiveness and if they simply report more symptoms and subjective distress in response to a MCT. It was hypothesized that asthmatics with, versus without, PD would exhibit greater airway responsiveness; report greater subjective distress; and experience exaggerated physiological arousal during a MCT.

## 2. Methods

### 2.1. Participants

Patients were recruited from the asthma clinics of Hôpital du Sacré-Coeur de Montréal (HSCM) from September 2011 to December 2013. To be included, patients had to have a primary diagnosis of asthma (chart evidence of previous positive MCT and/or bronchodilator reversibility), be non-smoking, and be between the ages of 18–70. Eligible patients underwent spirometry, and only patients with a forced expiratory volume in one second [FEV<sub>1</sub>] >70% (predicted) and >1.5 L participated. PD patients had to meet current Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revised (DSM-IV-TR) criteria for a primary psychiatric diagnosis of PD. Patients in the control group could not meet DSM-IV-TR criteria for any current or past Axis I disorder. Patients were excluded for chart evidence of a medical condition that was more severe than asthma and evidence of cognitive or language deficit that would have impaired providing informed consent. A total of 228 patients were screened for inclusion (see Fig. 1). Of the 122 initially eligible patients, 83 patients refused participation or were subsequently ineligible, resulting in a final sample of 39 patients.

### 2.2. Study procedure

The Ethics Committee of HSCM approved this study (#2003-10-198; 2010-95) and written consent was obtained from all participants. Consenting patients completed an initial screening interview (including demographic, medical, and psychological measures) performed routinely at the asthma clinics with the consent of the attending patients. Patients meeting initial eligibility criteria completed the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) on the phone to confirm all psychiatric diagnoses. A supervised, trained, clinical psychology PhD student conducted the interviews. Patients were then scheduled to undergo the MCT. At the laboratory, patients were asked to complete the Asthma Control Questionnaire (ACQ) and, prior to starting the MCT and following the final methacholine dose, patients were administered the Panic Symptom Scale (PSS) to assess panic symptoms. After each concentration of methacholine, the Borg Scale and the Subjective Distress Visual Analogue Scale (SD-VAS) were administered, assessing perceived breathlessness and anxiety symptoms. Physiological measures were recorded throughout the MCT, including heart rate (HR), and systolic and diastolic blood pressure (SBP/DPB) (Datascope Accutorr Plus, New Jersey, USA).

### 2.3. Methacholine challenge test protocol

As per the ATS recommendations [29], patients inhaled incremental two-fold concentrations of methacholine chloride from 0.03 to 16 mg/ml through a Wright nebulizer (output of 9.3 L/min) following a diluent (0.9% sodium chloride) [30]. When FEV<sub>1</sub> fell by at least 20%, the test was stopped and the technician, who was blind to the patient's psychiatric status, administered inhaled albuterol.

## 3. Measures

### 3.1. Baseline measures

#### 3.1.1. Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV)

The ADIS-IV [31] was used to confirm the diagnosis of PD. It is a widely used semi-structured interview for the diagnosis of mood, anxiety, substance abuse, and somatoform disorders. Good to excellent inter-rater reliability (e.g., PD,  $k = 0.72$ ) has been reported for the various dimensional ratings [32].

#### 3.1.2. Anxiety Sensitivity Index (ASI)

In order to assess trait anxiety sensitivity, patients completed the ASI [33], a 16-item self-report questionnaire measuring the extent to which individuals are fearful of anxiety-related symptoms. It yields scores from 0 to 64, with higher scores indicating higher anxiety sensitivity [34]. The ASI has high internal consistency ( $\alpha = 0.83$ ) and test-retest reliability [35], and is highly correlated with diagnoses of PD [36].

#### 3.1.3. Asthma Control Questionnaire (ACQ)

In order to assess asthma control levels in the week prior to the MCT, patients completed the ACQ [37], a 7-item questionnaire that measures asthma symptoms and bronchodilator use. Each item is ranked on a 7-point scale (0 = good control, 6 = poor control), with lower scoring indicating better asthma control. The ACQ has demonstrated high intraclass coefficient (ICC = 0.90) and good cross-sectional validity ( $r = 0.76$ ) [37,38].

### 3.2. Experimental measures

#### 3.2.1. Borg Scale

The Borg Scale [39] is a self-report questionnaire that was used

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