Claustrophobia, Panic Attacks and Caffeine Intolerance may NOT be associated with Diastolic Dysfunction: A Pre-Echocardiogram Questionnaire-Based Pilot Study

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Corresponding Author:
Dr. Deepak Gupta,
Anesthesiologist, Wayne State University, 48201 - United States of America

Submitting Author:
Dr. Deepak Gupta,
Anesthesiologist, Wayne State University, 48201 - United States of America

Other Authors:
Dr. Anupama Kottam,
Cardiologist, Wayne State University - United States of America
Dr. Sarwan Kumar,
Internist, Wayne State University - United States of America
Dr. Ashish Mazumdar,
Former Research Assistant, Detroit Medical Center - United States of America

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Appendix A
Table 1
Table 2
Table 3
Table 4
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Author(s): Gupta D, Kottam A, Kumar S, Mazumdar A

Abstract

Background: Diastolic heart dysfunction may explain the enigmatic pathophysiology of panic attacks and related disorders like claustrophobia, subjective/objective intolerance of heated enclosed environments and caffeine intolerance/allergy that can be sometimes indistinguishable from panic attacks symptomatically.

Objectives: To investigate whether clinical history of panic attacks-claustrophobia-caffeine intolerance is more common in patients with undiagnosed diastolic dysfunction who present for their outpatient echocardiogram tests.

Materials and Methods: Consenting adult outpatients who presented for their scheduled outpatient echocardiogram or stress echocardiogram at our University Hospital based Echocardiography Laboratory were asked to complete a questionnaire related to the clinical history of panic attacks, claustrophobia and caffeine intolerance. Spearman Rank Correlation and Partial Correlation Coefficients were used to correlate echocardiographic diastolic function grades with claustrophobia, panic attacks and caffeine intolerance based extracted (CP/CI/CPCI ) scores.

Results: Due to very small (n=40) pilot results (despite planned large-scale study at outset), we were only able to infer that: (a) there was only 75% inter-rater concordance in regards to diagnosing diastolic heart function on echocardiogram; (b) patients with diastolic heart dysfunction were significantly older; (c) 75% patients in our study pool were females; (d) diastolic heart dysfunction was prevalent in 45% patients; (e) there was very little (if any) clinical significance of CP/CI/CPCI scores in regards to predicting diastolic dysfunction grading; and (f) claustrophobia-panic attacks vs. caffeine-intolerance/allergy did not co-exist as co-morbidities in our set of patients.

Conclusion: Per our pre-echocardiogram questionnaire-based pilot study, claustrophobia, panic attacks and caffeine intolerance may NOT be associated with diastolic dysfunction.

Introduction

Diastolic heart dysfunction may explain the enigmatic pathophysiology of panic attacks and related disorders like claustrophobia, subjective/objective intolerance of heated enclosed environments and caffeine intolerance/allergy that can be sometimes indistinguishable from panic attacks symptomatically. Diastolic dysfunction includes impaired isovolumetric ventricular relaxation, poorly compliant left ventricles and higher filling pressures that when transmitted to pulmonary vasculature can potentially mimic panic attacks symptomatically. Eventually, decreased stroke volume/cardiac output can cause effort intolerance.¹

Based on above-mentioned our hypothesis/projected understanding, the purpose of the current study was to investigate whether clinical history of panic attacks and/or claustrophobia and/or caffeine intolerance is more common in patients with undiagnosed diastolic dysfunction who present for their outpatient echocardiogram tests.

Materials and Methods

After institutional review board approval for prospective questionnaire-based study, a written and informed consent for inclusion in the study was taken from the outpatients aged 18 years and above who presented for their scheduled outpatient echocardiogram or stress echocardiogram at our University Hospital based Echocardiography Laboratory. Inpatients, pregnant patients and lactating patients with recent delivery within last 6 months were excluded from the study. After the registration process for echocardiogram, the patients were approached for their consent to participate in the study. They were asked to complete a questionnaire related to the clinical history of panic attacks, claustrophobia and caffeine intolerance while they were waiting for scheduled echocardiograms. Subsequently patients underwent their scheduled echocardiograms or stress
echocardiograms. Cardiac sonographers acquiring the study and echocardiogram-reading clinical cardiologists were blinded to the patients' responses to the study questionnaires. Subsequently, the echocardiogram results were accessed and diastolic function in those echocardiograms were re-assessed and confirmed by the researchers including a research cardiologist who was blinded to the echocardiographers' readings-results as well as to the patient's responses to the study questionnaire.

Statistical Analysis

Despite initially planned larger sample size, the study was only completed, then closed and analyzed for 43 consenting patients as a pilot. Additionally, collected responses/data of four page long questionnaires per patient as well as two page long echocardiogram parameters per patient (Appendix A) were respectively reformatted (only for analysis) into 8-point questions-based Extracted Scores (Table 1) and 4-point diastolic function grade per American Society of Echocardiography (Table 2). The data was analyzed and compared with Spearman Rank Correlation and Partial Correlation Coefficients to deduce whether there was any correlation of diastolic function grades (Table 2) with claustrophobia, panic attacks and caffeine intolerance based scores (Table 1). The proportions were compared with Chi Square test (Fisher Exact Tests). Means were compared with Analysis of Variance (ANOVA). A p value of < 0.05 was considered significant.

Results

In these pilot results for 43 patients, two patients were excluded as after completion of questionnaires, they did not undergo their scheduled echocardiograms due to clinical reasons unrelated to our research; and another patient was excluded as diastolic dysfunction could not be graded due to underlying mitral stenosis. Among the remaining 40 patients whose data were finally analyzed as above-mentioned by the researchers, diastolic function had not been graded/reported by clinical cardiologist in four patients and among remaining 36 patients, there was 75% inter-rater concordance in regards to diastolic function grading between clinical cardiologist and research cardiologist while in the remaining 25% patients, research cardiologist's blinded assessment resulted in upgrading the diastolic dysfunction scores as compared to clinical cardiologist's report.

In regards to 40 patients finally analyzed (Table 3), patients were significantly (P< 0.01) older in age if the assessed diastolic function grade was abnormal (non-zero) however patient's sex was not a confounding factor even though 75% among the analyzed patients were females. Prevalence of abnormal diastolic function grade was 45% during our study. Sensitivity, specificity, positive predictive value and negative predictive value for Claustrophobia-Panic (CP) Scale/Score, Caffeine-Intolerance (CI) Scale/Score and Claustrophobia-Panic-Caffeine-Intolerance (CPCI) Scale/Score were low most likely due to low power (sensitivity), high type I error (1-specificity) and high type II error (1-sensitivity) except for 73% specificity of CI Scale/Score and 67% sensitivity of CPCI Scale/Score in regards to diastolic function grading. Similarly likelihood ratios (both positive and negative) weighted for prevalence were close to or equal to 1 that meant little clinical significance of CP/CI/CPCI scores in regards to predicting diastolic dysfunction grading. As far as Spearman correlation coefficients were concerned (Table 4), patient's age showed strong positive correlation with echocardiogram based diastolic function grading (r=0.66; P< 0.01). Similarly, CP scores and CI scores had significant positive correlation with CPCI scores (P< 0.01) because CPCI scores are numerical sum total of CP scores and CI scores. These significant correlations persisted and even became stronger for CP:CPCI and CI:CPCI correlations when effects of other variables were controlled in the 6x6 partial correlation matrix (Table 4). Moreover, after controlling for other variables, a strong negative partial correlation appeared between CP scores and CI scores (r=-0.9; P< 0.01) suggesting the non-existence of claustrophobia-panic and caffeine-intolerance as co-existing co-morbidities in our set of patients.

Discussion

PANIC ATTACK

A panic attack by definition is a conglomerate of at least four symptoms among the following: palpitations, heart pounding or a rapid pulse, sweating, trembling or shaking, breathing problems, such as shortness of breath or feeling smothered, feeling of choking, chest pain or chest discomfort, abdominal discomfort, upset stomach or nausea, feeling faint, dizzy, light-headed or unsteady on your feet, feeling unreal or detached from yourself, fear of losing control, fear of dying, numbness or tingling in arms, legs or other parts of the body, chills or hot flushes etc. Panic attack symptomatology is often indistinguishable from cardiac pathology symptomatology that can include chest pain, shortness of breath, stomach discomfort, dizziness,
and a sense of impending death. While panic attacks themselves may not be deadly, patients with panic disorder have reduced heart-rate variability (HRV) that increases risk for cardiac arrhythmia and sudden death.\(^3,4\) Low baseline high frequency HRV may reflect inflexibility of autonomic nervous system in anxiety disorders involving hypervigilance with perceptive difficulty to disengage from perceived threats.\(^5\) Eventually underperforming parasympathetic nervous system and overactive sympathetic nervous system result in long term low HRV at baseline.\(^6\) Similarly, although initial reports of correlation of panic disorder and mitral valve prolapse (MVP) have not been substantiated as cause-and-effect relationship, the elusive unknown mechanism should not deter the appreciation of high rates for co-existence of both disorders.\(^7\)

**CLAUSTROPHOBIA**

Claustrophobia, typically classified as an anxiety disorder, often presents as panic attack, resulting from many situations or stimuli, including but not limited to elevators crowded to capacity, windowless rooms, and even tight-necked clothing. This can be indistinguishable from the symptomatology of subjective/objective intolerance of heated enclosed environments especially during winters requiring fans in those enclosed environments as similar to the subjective anti-distress effects of fans used inside the magnetic resonance imaging scanners.\(^8\) When confined, claustrophobics may present with sweating, accelerated heart rate, increased blood pressure, hyperventilation, shaking, panic attacks, light-headedness, nausea, fainting, fears of actual harm or illness. Though claustrophobia is a prevalent phobia with two major fear(s) of restriction and suffocation, the majority of claustrophobics are not receiving treatment for it.\(^9,10\)

**CAFFEINE INTOLERANCE**

Although almost all of American population ingests coffee regularly, a fraction of population is allergic/intolerant to caffeine.\(^11,12\) Caffeine allergy (intolerance) presents with heart, breathing and anxiety symptoms besides rashes, and facial swelling. Study in healthy volunteers found decreased myocardial flow reserve (exercise-induced) with 200mg caffeine.\(^13\) Additionally, caffeine related calcium influx and subsequent reversible ‘contracture’ (incomplete myocardial relaxation) accentuates left ventricular filling pressure and diastolic pressure during myocardial ischemic episodes in the setting of pacing-induced tachycardia.\(^14\)

This plethora of panic disorders has overlapping presentations and hence besides avoiding the precipitating factors, various medications have been tried for these disorders. Calcium channel blockers (CCBs) like verapamil, diltiazem and nimodipine, have been tried for anxiety disorders but evidence is very weak.\(^15\) Similarly, pregabalin that exerts alteration in voltage-sensitive calcium channels (mechanism dissimilar to cardiac CCBs) have shown some prominence in management of anxiety disorder.\(^16,\ 17\) Similarly, though beta blockers decrease heart rate and systolic blood pressure, the subjective anxiety has not responded to beta blockers and may actually worsen with propranolol.\(^18\)

Therefore, our assumption was to explore (isolated/co-existent) diastolic heart dysfunction explaining out above-mentioned enigmatic pathophysiology: (a) poor correlation of MVP and Panic attacks in previous echocardiogram based trials presumably due to incomplete investigations about the diastolic parameters in those trials; (b) low baseline HRV as a presumable explanation for fragility of the diastolic heart parameters and presentation as acute dysfunction/failure in response to sudden surge in anxiety-related sympathetic activity; and (c) incomplete response of panic attacks to beta-blockers alone presumably projecting that besides heart rate control, these patients may also need angiotensin II receptor blockers, angiotensin-converting-enzyme inhibitors and calcium channel blockers to normalize the stiff and poorly relaxed diastolic hearts.\(^19\) However, due to very small (n=40) pilot results (despite planned large-scale study at outset), we were able to infer only the following: (a) there was only 75% inter-rater concordance in regards to diagnosing diastolic heart function on echocardiogram; (b) patients with diastolic heart dysfunction were significantly older; (c) 75% patients in our study pool were females; (d) diastolic heart dysfunction was prevalent in 45% patients; (e) there was very little (if any) clinical significance of CP/CI/CPCI scores in regards to predicting diastolic dysfunction grading; and (f) claustrophobia-panic attacks vs. caffeine-intolerance/allergy did not co-exist as co-morbidities in our set of patients.

Our study had many limitations. Logistically the contemplated larger study was not completed that could have (with strong statistical power) validated or refuted the current pilot results. The current pilot results did not differentiate isolated vs. co-existent diastolic heart dysfunction wherein cardiac co-morbidities might have confounded our results (type I and II errors). The only positive findings were the obvious/natural positive correlation of increased stiffening of hearts with aging of patients, and
selection bias related high prevalence of diastolic heart dysfunction in patients (not healthy volunteers) presenting for their scheduled outpatient echocardiograms. The pilot results may need further explorations for the validity of extracted/deduced/analyzed CP/CI/CPCI scores in future studies in healthy volunteers among whom only allowable symptomatology will include variable non-zero numerical scoring per CP/CI/CPCI scores (Table 1) and variably graded isolated diastolic heart dysfunctions (Table 2) on their otherwise normal echocardiograms.

Conclusion
Per our pre-echocardiogram questionnaire-based pilot study, claustrophobia, panic attacks and caffeine intolerance may NOT be associated with diastolic dysfunction but this may NOT preclude exploring this aspect in future with larger studies that can validate/refute the results after correcting the poor statistical power and type I&II errors of the current pilot.

References