

EXERCISE INDUCED BRONCHOSPASM

Eucapnic Voluntary Hyperventilation Is Superior to Methacholine Challenge Testing for Detecting Airway Hyperreactivity in Nonathletes

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Introduction. Response to eucapnic voluntary hyperventilation (EVH) has not been compared with methacholine challenge testing (MCCT) in nonathletes being evaluated for dyspnea on exertion. **Objective.** To determine the airway response to EVH and MCCT in a population of nonathletes who exercise regularly but have symptoms with exertion. **Methods.** We reviewed records for all patients with exercise symptoms who underwent both EVH and MCCT. Presenting symptoms, comorbid diseases, and results of bronchoprovocation (BP) testing were recorded. This study was approved by the institutional review board at our hospital. **Results.** A total of 131 patients (mean age 32.3 ± 11.6 , body mass index (BMI) 27.1 ± 4.7 kg/m², 59.5% male) had an EVH, MCCT, and clinical evaluation performed. Overall, 37 (28.2%) patients had positive BP testing and met criteria for exercise-induced bronchoconstriction (EIB). There were 32 (24.4%) patients with a positive EVH, compared with only 11 patients with a positive MCCT (8.4%). There were 26 patients (19.8%) who had a positive EVH but a negative MCCT, and correlation between the two tests was poor to moderate ($r = 0.11$ – 0.57). A complaint of chest pain and younger age were independent predictors for a positive EVH, whereas a history of tobacco use and a decreased FEV₁/FVC (forced expiratory volume in 1 s/forced vital capacity) predicted a positive MCCT. A previous diagnosis of asthma was an independent predictor for a response to either test. **Discussion.** In a population of nonathletes who exercise regularly and have symptoms with exertion, EIB is common. Correlation between EVH and MCCT in this population is poor, and although the tests are somewhat complementary, a large percentage of patients had a negative MCCT but a positive EVH. **Conclusions.** EIB is common in nonathletes with exercise-induced symptoms, and EVH is the preferred test for this population. **Clinical implications.** EIB is common in nonathletes who exercise regularly. In this population, MCCT will miss most patients with EIB, and MCCT and EVH show only poor-to-moderate correlation. **Capsule summary:** EVH has not been compared with MCCT in nonathletes without a diagnosis of asthma. Our study shows that the two tests are complementary in this population, but EVH is positive more often.

Keywords asthma, bronchoprovocation testing, dyspnea, eucapnic voluntary hyperventilation, exercise-induced bronchoconstriction, methacholine challenge

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) has been described as a transient airway narrowing in response to exertion commonly seen in elite and competitive athletes (1–3). Up to 90% of asthmatics have EIB (4), and exercise is the most common trigger of symptoms in known asthmatics. The prevalence of EIB as measured by the response to eucapnic voluntary hyperventilation (EVH) can be as high as 50% in elite athletes and 19% in the general population (5). Although EIB is often suspected and treated based on a patient's symptoms and history, multiple studies have shown that symptoms are not specific and diagnosis should be based on objective data (6–8).

Accurate and timely diagnosis of EIB is especially important in populations required to engage in high levels of physical activity. Members of the active-duty military

regularly participate in endurance training, meaning those with EIB are more likely to present to a health-care provider complaining of dyspnea on exertion (9, 10). Most military medical centers rely on direct airway challenge testing with methacholine to evaluate the active-duty patient with dyspnea on exertion. Methacholine challenge testing (MCCT) has a very high sensitivity for the diagnosis of asthma, but indirect airway challenges are thought to be more appropriate for the diagnosis of EIB (11, 12).

EVH is an indirect bronchoprovocation (BP) test that serves as a surrogate for exercise. It was specifically designed to mimic the pathophysiology of EIB (13, 14). The test causes airway drying and hyperosmolality through hyperventilation of dry air. This leads to release of mast cell inflammatory mediators (15, 16), resulting in submucosal airway edema and ultimately bronchial smooth muscle contraction and airway narrowing (11). It can be conducted in a controlled environment, where high levels of physical exertion are not required to induce a response. It is easy and inexpensive, and has been well standardized (14, 17).

Studies comparing MCCT with EVH for the diagnosis of EIB have shown roughly equivalent performance, with

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each test diagnosing patients that the other would miss (18–21). Some of these studies enrolled known asthmatics, which could bias results in favor of MCCT. Others enrolled only elite athletes, a group known to have a high prevalence of EIB, which might bias results toward having a positive EVH. This makes their results difficult to generalize to other populations.

At the Walter Reed Army Medical Center (WRAMC) Pulmonary Disease Clinic, we see a predominantly active-duty population that is required to exercise on a regular basis. In order to maximize sensitivity for detection of EIB, we routinely perform both EVH and MCCT on patients presenting with unexplained exercise symptoms. We sought to evaluate the performance characteristics of EVH and MCCT in a population of nonathletes presenting for evaluation of dyspnea on exertion.

METHODS

Patients

Using an exempt protocol approved by the Department of Clinical Investigation at our institution (IRBNet ID# 351388-1), we conducted a retrospective review of patients seen in the WRAMC Pulmonary Disorders Clinic between June 2003 and February 2009. Patients were active-duty military soldiers, retirees, or their dependents. Patients were included if they had both EVH and MCCT performed as part of their work-up and had exercise-related complaints. Both hard-copy physical charts and electronic medical records (EMRs) were reviewed. Presenting symptoms, comorbid diseases, the presence of known or suspected environmental allergies, current medications, tobacco history, baseline spirometry, and the clinical diagnosis as determined by a pulmonologist were abstracted. Patients were excluded if they had a previous diagnosis of asthma verified by BP or bronchodilator testing.

Bronchoprovocation Testing

Prior to both tests, patients were instructed to stop long-acting bronchodilators and inhaled corticosteroid (ICS) at least 2 and preferably 4 weeks before testing, and short-acting bronchodilators and caffeine 24 hours prior to testing. The protocol for EVH testing has been described previously (13, 14, 22). Briefly, subjects breathed a dry gas consisting of air at room temperature (22°C) enriched to 5% carbon dioxide, a concentration shown to maintain arterial carbon dioxide levels within the range documented during exercise. The gas flow rate applied to the system was equivalent to a minute ventilation of $30 \times \text{FEV}_1$ (forced expiratory volume in 1 s), and it was monitored continuously with a rotameter. Although ventilation was not directly measured during the study, subjects were coached to maintain a constant volume in the 3.5 L meteorological balloon to keep pace with the gas flow through the system. Repeat FEV_1 measurements were taken immediately after the test and at 0, 5, 10 and 20 minutes. FEV_1 was measured according to the American Thoracic Society

(ATS) criteria (23, 24). EVH challenge was considered positive if FEV_1 dropped by $\geq 10\%$ within 20 minutes of study completion (14, 22).

MCCT was performed in the same laboratory using the standardized, 5-breath dosimeter technique described by ATS guidelines (25). Serial concentrations of methacholine were prepared from dry powder. Subjects were given five timed breaths at concentrations of 0.0625, 0.25, 1, 4, and 16 mg/mL while wearing a nose clip. This was followed by measurements of FEV_1 . The PC20 (concentration at which FEV_1 drops 20% from baseline) was calculated in accordance with ATS guidelines (25), and MCCT was considered positive when the PC20 was ≤ 16 mg/mL.

On 5 June 2008, the pulmonary laboratory switched to a two-concentration dosimeter protocol, which affected only eight subjects (6.1%). These subjects were given a series consisting of one, three, and six breaths at a dose of 2 mg, followed by three and six breaths at a dose of 32 mg. Methacholine was administered by an electronic, software-controlled (automatic) APSpro dosimeter (Viasys Healthcare) designed to deliver doses equivalent to those given using the original method. This protocol has previously been described in the literature (26).

Because it is more efficient, it is common practice at our clinic to order both BP tests on the same day. EVH is always performed first, with MCCT a minimum of 3 hours later. The patient's FEV_1 must return to within 10% of baseline prior to MCCT if EVH was performed earlier in the day. This protocol is based on data collected at our institution, which showed that when both tests are performed sequentially, EVH has a minimal refractory period with no significant effect on an MCCT done at least 90.5 ± 4.5 minutes later (27).

Statistics

All means are followed by standard deviation. Comparisons between categorical variables were performed using Chi-square and Fisher's exact tests where appropriate, and differences between means using the independent samples *t*-test. Bivariate correlations were performed using Spearman's correlation coefficient. To test for clinical, historical, or spirometric variables that might predict a positive EVH or MCCT, multivariate modeling was carried out using logistic regression. All variables that had a *p*-value $\leq .10$ in univariate analysis were entered into the multivariate models. Data were analyzed using PASW 17 (Formerly Statistical Package for Social Sciences 17.0, SPSS Inc., Chicago, IL).

RESULTS

A total of 149 patients had both an EVH and an MCCT performed between June of 2003 and February of 2009. Of these, 18 patients were excluded because testing data were incomplete. A total of 131 patients (age 32.4 ± 11.6 , body mass index (BMI) 27.1 ± 4.7 kg/m², 59.5% male) were analyzed. The majority were Caucasian (62.6%) or African

TABLE 1.—Medical history, presenting symptoms, and baseline spirometry.

	N = 131
Medical history	
Current tobacco use	23 (17.6%)
Previous asthma diagnosis	40 (30.5%)
Aspirin/NSAID use	25 (19.1%)
History of antihistamine use	50 (38.2%)
Symptoms	
Dyspnea	115 (87.8%)
Exercise symptoms	113 (86.3%)
Cough	74 (56.5%)
Chest tightness	66 (50.4%)
Wheezing	59 (45.0%)
Night cough	34 (26.0%)

Note: Current tobacco use was defined as smoking tobacco products (cigarettes, cigars, etc.) with the past month.

TABLE 2.—Baseline spirometry prior to BP test/response to BP test.

	Liters $\pm$ SD	% Predicted $\pm$ SD
EVH		
Baseline spirometry:		
FEV ₁	3.48 $\pm$ 0.83	88.5 $\pm$ 13.6
FVC	4.48 $\pm$ 1.12	93.5 $\pm$ 14.2
FEV ₁ /FVC		78.1 $\pm$ 6.7
Mean drop in FEV ₁		
All patients	−6.6% $\pm$ 6.2	
Positive EVH (n = 31)	−15.5% $\pm$ 6.2	
MCCT		
Baseline spirometry:		
FEV ₁	3.47 $\pm$ 0.85	88.1 $\pm$ 13.4
FVC	4.46 $\pm$ 1.13	92.8 $\pm$ 14.4
FEV ₁ /FVC		78.4 $\pm$ 6.7
Mean PC20		
Positive MCCT (n = 11)	6.8 $\pm$ 4.8 mg/mL	

American (28.2%) and the remainder were Hispanic (6.1%) or Asian (3.1%). Relevant medical history and presenting symptoms are shown in Table 1, and mean values on baseline spirometry performed prior to each BP test along with results are shown in Table 2. Less than half of the patients (38.2%) had a history consistent with atopy, which is defined as any allergy diagnosis or a prescription for an antihistamine.

EVH and MCCT were positive in 32 (24.4%) and 11 (8.4%) patients, respectively. The mean time between studies was 9.7 ± 110.8 days, and 58 of 131 (44%) patients had both tests performed on the same day, whereas 6 patients (4.6%) had tests performed more than 6 months apart. There were 5 patients with a negative EVH but a positive MCCT, and 26 patients with a negative MCCT but a positive EVH. The mean fall in FEV₁ when EVH was positive was $-15.5 \pm 6.2\%$, and the mean PC20 was 6.8 ± 4.8 mg/mL. Table 3 shows the timing and duration of positive EVH responses, Table 4 lists EVH responses by whether or not MCCT was positive, and Figure 1 displays the drop in FEV₁ at each time point post-EVH.

Figure 2 shows a scatter plot for each patient's maximum percentage drop in FEV₁ after MCCT versus EVH. The overall correlation between maximum percentage drop in

TABLE 3.—Characteristics of positive EVH responses.

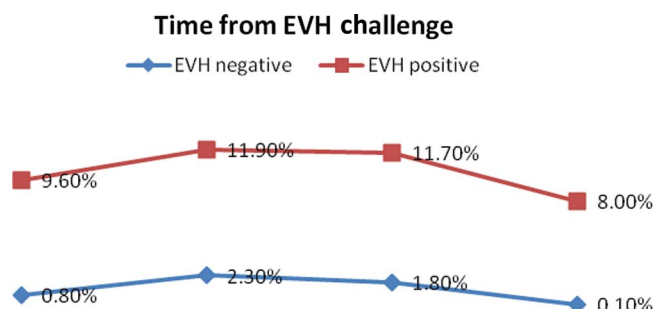
Timing (first drop $\geq$ 10%)	No. of patients (%)	Duration	No. of patients (%) ^a
0 minutes	7 (24.1%)	5 minutes	6 (20.7%)
5 minutes	10 (34.5%)	10 minutes	6 (20.7%)
10 minutes	8 (27.6%)	15 minutes	3 (10.3%)
20 minutes	4 (13.8%)	20 minutes	2 (6.9%)

Note: ^aEight patients: only one trial $\geq 10\%$, two patients: test stopped after $\geq 10\%$ drop, and two patients: $\geq 10\%$ at 20 minutes.

TABLE 4.—EVH responses (PC20 > 16 vs PC20 $\leq$ 16 mg/mL).

Dose	N	Age (years)	FEV ₁	VE target (L/minute) ^a
PC20 > 16 mg/mL				
EVH <10	94	33.2 $\pm$ 12.0	89.9 $\pm$ 13.5	116.6 $\pm$ 33.4
EVH 10–19.9	24	29.9 $\pm$ 9.9	86.3 $\pm$ 12.9	110.3 $\pm$ 26.9
EVH ≥ 20	2	27.5 $\pm$ 6.4	90 $\pm$ 19.8	151.6 $\pm$ 27.7
PC20 $\leq$ 16 mg/mL				
EVH <10	5	39.0 $\pm$ 16.6	73.6 $\pm$ 15.8	107.5 $\pm$ 48.7
EVH 10–19.9	4	26.0 $\pm$ 5.9	88.8 $\pm$ 13.0	129.8 $\pm$ 52.3
EVH ≥ 20	2	24.0 $\pm$ 0.0	83.0 $\pm$ 7.1	117.7 $\pm$ 37.0

Note: ^aBased on FEV₁ $\times$ 35 for males, and FEV₁ $\times$ 30 for females.

FIGURE 1.—FEV₁ decrease at 0, 5, 10, and 20 minutes post-EVH.

FEV₁ was moderate ($r = 0.31$; $p < .001$). The correlation between percent FEV₁ fall after EVH and PC20 was poor when all patients with a PC20 ≤ 16 mg/mL ($r = 0.11$; $p = .75$) were included, but improved significantly when only the seven patients with PC20 ≤ 8 mg/mL were analyzed ($r = 0.57$; $p = .18$). Correlation was poor when both tests were performed on the same day ($r = 0.26$; $p = .05$), and moderate when they were performed on different days ($r = 0.36$; $p = .001$). When EVH was positive, the mean drop after MCCT was $-12.2 \pm 9.4\%$, and when MCCT was positive, the mean drop after EVH was $-10.9 \pm 8.3\%$. The sensitivity for MCCT detecting a positive EVH was 20.7% overall, and was 25% and 19% when both tests were performed on the same day versus different days, respectively.

Individual patient characteristics showing a trend ($p < .10$) toward association with a positive EVH or MCCT on univariate analysis were entered into multivariate logistic regression models for each test (Table 5). A previous physician diagnosis of asthma predicted a positive EVH or MCCT. A mean lower FEV₁/FVC (forced vital

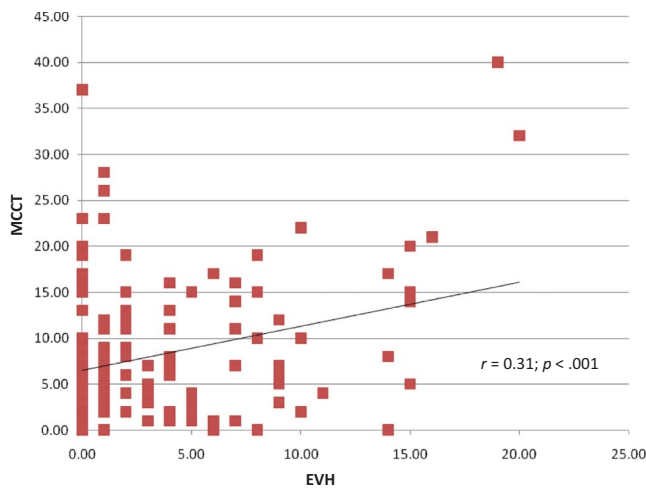


FIGURE 2.—Scatter plot displaying the maximal drop in FEV₁ on both MCCT and EVH.

TABLE 5.—Multivariate analysis.

	OR	CI	p-Value
Eucapnic voluntary hyperventilation			
Age	0.95	0.90–1.00	.06
Dyspnea	3.08	0.33–28.4	.32
Chest tightness	3.30	0.05–10.8	.049
History of asthma	4.82	1.56–14.9	.01
Night cough	4.57	0.46–4.57	.52
Methacholine challenge test			
FEV ₁	0.95	0.90–1.01	.11
FEV ₁ /FVC	0.86	0.75–0.99	.04
Tobacco use	21.1	2.92–151.9	.003
History of asthma	7.2	1.1–49.1	.04
Night cough	2.86	0.52–15.7	.23

Note: Univariate analysis included age, dyspnea, chest tightness, history of asthma, night cough, wheezing, cough, exercise symptoms, baseline spirometry (FVC, FEV₁, FEV₁/FVC), allergies, tobacco use, BMI, and aspirin/NSAIDs use. OR = odds ratio; CI = 95% confidence interval.

capacity) predicted a positive MCCT, as did current tobacco use. A complaint of chest tightness was significantly more common when EVH was positive, and older patients showed a trend toward being less likely to have a positive EVH. A third model was constructed using a positive result on either BP test as the dependent variable. For this model, a previous diagnosis of asthma showed significance ($p = .002$, odds ratio (OR) 5.25 (95% confidence interval (CI): 1.87–14.79)) and a complaint of chest tightness a trend toward significance ($p = .09$, OR 2.52 (95% CI: 0.87–7.25)) in multivariate analysis.

DISCUSSION

We evaluated the performance of EVH and MCCT in patients referred for mild, predominately exercise-induced symptoms. No previous comparisons between these two BP tests in a nonasthmatic, nonathlete population have been published. Although some patients had been given a diagnosis of asthma by a physician in the past, no patient

had documented BP testing or a positive bronchodilator response prior to the EVH and MCCT performed in our laboratory. Correlation between the two tests was poor overall, EVH was positive approximately three times as often as MCCT, and 26 patients had a positive EVH but a negative MCCT. Previous reports from our laboratory using an identical EVH protocol showed that the two tests have a similar sensitivity and specificity for asthma or EIB (18, 21). In reports from other laboratories, Filuk et al. (19) found that MCCT is positive more often than EVH, whereas Holzer et al. (20) and Pederson et al. (28) found that EVH is positive more often. Correlation between PC20 or FEV₁ drop on MCCT and FEV₁ drop or dose of hyperventilation on EVH has also varied, with some finding high levels of agreement, $r = 0.80$ – 0.90 (29, 30), and others finding values closer to $r = 0.50$ – 0.60 (18, 19, 21). We found a similar correlation between FEV₁ drop after EVH and patients with a PC20 ≤ 8 mg/mL, but it was otherwise much lower. There are a number of differences across studies that make comparisons to ours and to each other difficult. Patient populations varied, with some studies enrolling elite athletes (20, 28), and others known asthmatics (18, 21, 29, 30).

Our population consisted of nonathlete, dyspneic, regular exercisers without confirmed asthma who had both EVH and MCCT performed. We found that 24.4% of these patients were positive on EVH. Mannix et al. found that 19% of the 212 nonathlete, regular exercisers without asthma that they studied had a positive EVH. They concluded that the rate of EIB in this population approaches that seen in elite athletes. The high rate of EIB seen in elite athletes is postulated to be due to effects on the airway after large volumes of air have been conditioned by the lungs during repetitive training. It may be that lesser degrees of consistent training by nonelite athletes has a similar effect, and leads to positive findings on EVH.

Prior studies demonstrated that elite athletes with EIB can have a negative MCCT but a positive indirect airway challenge (12, 20, 28). Our study is the first one to show that a large number of patients (19.8%) from a population of nonathletes who exercise regularly could have a positive EVH with a negative MCCT. This has important clinical consequences both in and out of the military. Because members of the active-duty military are required to exercise regularly, untreated EIB could cause them to be discharged from the military due to failure to pass the Army Physical Fitness Test (APFT), which includes a 2-mile run. Even worse, it could put the patient at risk for excess morbidity during forced training (6). With regular exercise being recommended by major medical organizations and millions of patients participating in physical training and rehabilitation, we believe these results have important implications outside the military as well.

Because other investigators have concluded that EVH and MCCT are complementary to each other (18–21), we attempted to help physicians tailor their work-up for dyspnea on exertion by constructing logistic regression models using baseline patient characteristics. We hoped this might help clinicians decide which BP test would be

preferred based on specific symptoms or aspects of the medical history. However, because EVH was positive almost three times as often, it would be hard to argue against it being the initial test of choice when EIB is suspected in a similar population. Using EVH followed by MCCT (if EVH is negative and the pretest probability for EIB is high) would be consistent with recommendations from existing guidelines (4, 22) and reviews (6).

Evaluating the performance of tests used to diagnose EIB is difficult (31). Although patients who drop their FEV₁ on EVH have increased levels of sputum inflammatory mediators (32) and are responsive to treatment (15, 16), we cannot say for certain whether all positive BP studies represent clinically significant disease. Consensus guidelines have documented tobacco use and a decreased baseline FEV₁ as reasons for a false positive MCCT. We found that tobacco use and lower FEV₁ predicted a positive MCCT, which suggests the possibility that a portion were false positives.

Most would consider a patient with exercise-induced dyspnea and a positive BP test to have EIB (4), but it is difficult to establish definitively that EIB is solely responsible for their symptoms (33). It is also notable that the overall positive predictive value that exercise symptoms had for EIB was poor, as only 28.2% had a positive response to either EVH or MCCT. The patients we studied had additional testing when clinically appropriate, and clinicians should correlate all BP results with the clinical presentation and response to treatment. An algorithmic approach that includes indirect BP, direct BP, and field testing as needed should be used to evaluate unexplained dyspnea (4).

Our study has several limitations, the most of important of which is the retrospective design, which subjects our data to work-up and other known or unknown biases. Many patients received a previous diagnosis of asthma and some had been using ICS with long- and short-acting bronchodilators in different combinations, which could have blunted the airway response to one or both tests. Our clinic protocol for BP testing requires patients to stop ICS and long-acting bronchodilators 2–4 weeks and short-acting bronchodilators 24 hours prior to testing though, and an asthma diagnosis predicted a positive, not a negative BP response. Our patient population may not be representative of all nonathlete, regular exercisers due to the selection bias inherent in studying only those who had both EVH and MCCT performed. However, because the prevalence of positive EVH results we found was comparable to that found by others in a similar population who did not have both tests (5), we feel our findings can be generalized. Because EIB can change over time, the delay between testing could have artificially decreased the correlation between the two tests. Still, correlation was better when tests were performed on different days as opposed to the same day, so this effect was likely minimal. Finally, this analysis would have been optimal had both tests been performed in a randomized fashion on two separate days. Because EVH was always done first when both tests were conducted on the same day, if there was any refractory

effect on the airways, the response to MCCT would have been decreased. We feel this was unlikely, given that our same day protocol was based on data showing that a 3-hour delay after EVH should not cause residual blunting of an airway response to MCCT (27). In addition, the percentage of positive MCCT results was similar whether both tests were performed on the same or on different days, 6.9% versus 9.6%, respectively, and MCCT showed higher sensitivity for detecting a positive EVH when both tests were on the same day.

CONCLUSIONS

In summary, we present the first study comparing room-air EVH to MCCT in a regularly exercising, nonathlete population. We have confirmed their high prevalence of EIB, and we have shown that EVH is superior to MCCT for identifying EIB in nonathletes. The two tests are not highly correlated, and MCCT will occasionally identify patients who have negative results on EVH. Although EVH may be the superior test in this setting, for a patient with a high pretest probability who is required to exercise regularly, both tests should be ordered before EIB is ruled out. A positive EVH result does not rule out other causes of dyspnea and testing for alternative etiologies should be done when clinically appropriate.

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Author's contribution

Brian Cohee: Performed retrospective data gathering, conducted background research, and wrote the introduction, methods, and discussion sections. He also participated in editing the full article and attested for the accuracy and completeness of the data.

Rob Walter: Performed retrospective data gathering, preparation of graphs and figures, and editing of the article.

Anita Shah: Reviewed interpretations of ultimate diagnosis and edited the article.

Chris King: Participated in study design and edited the article.

Stuart Roop: Developed the initial study concept and edited the article.

Aaron Holley: Developed the initial study concept and study design, performed statistical analysis, wrote the abstract and results section, reviewed interpretations of the ultimate diagnosis, and edited the full article and attested for the accuracy and completeness of the data.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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