Respiratory Medicine (2011) 105, 1014–1021

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An algorithmic approach to chronic dyspnea

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Received 14 October 2010; accepted 8 December 2010
Available online 7 January 2011

KEYWORDS
Algorithm;
Diagnosis;
Dyspnea

Summary
Question: The objective of the study was to prospectively evaluate an algorithmic approach to the cause(s) of chronic dyspnea.
Materials/patients/methods: Prospective observational study. The study group consisted of 123 patients with a chief complaint of dyspnea of unknown cause present for >8 weeks. Dyspnea severity scores were documented at entry and after therapy. Patients underwent an algorithmic approach to dyspnea. Therapy could be instituted at any time that data supported a treatable diagnosis. Whenever possible, accuracy of diagnosis was confirmed with an improvement in dyspnea after therapy. Tests required, spectrum and frequency of diagnoses, and the values of individual tests were determined.
Results: Cause(s) was(were) diagnosed in 122/123 patients (99%); 97 patients had one diagnosis and 25 two diagnoses. Fifty-three percent of diagnoses were respiratory and 47% were non-respiratory. Following therapy, dyspnea improved in 63% of patients.
Conclusions: The prospective algorithmic approach led to diagnoses in 99% of cases. A third of patients were diagnosed with each tier of the algorithm, thus minimizing the need for invasive testing. Specific diagnoses led to improvement in dyspnea in the majority of cases. Based on the results of this study, the algorithm can be revised to further minimize unnecessary tests without loss of diagnostic accuracy.

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doi:10.1016/j.rmed.2010.12.009

Introduction

Dyspnea is a frequent, sometimes disabling complaint. It is among the most common reasons for seeking medical attention.[1] Three prior studies have evaluated cohorts of patients with a chief complaint of dyspnea to try and diagnose the cause of dyspnea as well as the value of specific tests.[2–4] The results of these three studies showed that the spectrum of diagnoses associated with dyspnea was broad and included a number of cardiorespiratory as well as non-cardiorespiratory disorders. They also demonstrated the diagnostic value of pulmonary function tests (PFTs) including methacholine bronchoprovocation challenge (BPC), chest roentgenogram (CXR) and cardiopulmonary exercise testing (CPET).[2–4] None of these studies, however, employed a prospective algorithmic approach that was applied in a systematic way to all patients.[3]

The goal of our study was to use an algorithmic approach to the diagnostic evaluation of outpatients referred with undiagnosed chronic dyspnea (i.e.>8 weeks). The algorithm (i.e. the specific tests and sequence) was based upon the prior studies[2–4] as well as a review of the literature on causes of dyspnea.[5] It focused on the initial use of PFTs including BPC to diagnose Chronic Obstructive Pulmonary Disease (COPD) and asthma[4] the CXR to detect parenchymal lung and pleural disorders[4] and blood tests to detect anemia and heart failure. CPET followed when PFTs, CXR, and blood tests failed to detect or suggest a cause.[2–4] The algorithm was designed with four primary goals in mind: 1) to diagnose the cause(s) of dyspnea in every patient if possible; 2) to sequence the testing to try and optimize efficiency; 3) to use a beneficial response to therapy as a way to help confirm diagnoses whenever possible; and 4) to use the results of this study to streamline and revise the diagnostic algorithm.

Patients and methods

Patients

The protocol was approved by the Institutional Review Board of Cooper University Hospital. (Approval #05-039.) Patients gave informed written consent.

Conflicts of interest: No author of this paper has any financial or personal conflict of interest related to the material presented herein. There was no study sponsor.

Patients referred to our university pulmonary practice between September 2005 and December 2006 were eligible for enrollment if they had a chief complaint of shortness of breath present for at least eight weeks, it occurred at least three days per week, interfered with normal activities, and was of unknown cause.

Diagnostic protocol (Fig. 1)

Tier I

At the initial visit, each patient filled out a "Mahler Baseline Dyspnea Index"[6,7] and then underwent Tier I testing which consisted of a history and physical examination (H&P), chest roentgenogram (CXR), pulmonary function tests (PFTs), and blood tests. PFTs included spirometry, lung volumes by plethysmography, diffusing capacity (DLCO), and a methacholine bronchoprovocation challenge (BPC). If the forced expiratory volume in 1 s (FEV_1) was <70% of predicted, BPC was not performed in order to avoid potentially dangerous drops in lung function; instead, nebulized albuterol (2.5 mg) was administered followed by spirometry. Predicted values for PFTs were based on published literature.[8–10] BPC was performed with the tidal volume nebulizer.[11–13] PFTs provided the primary basis for diagnosing asthma or COPD. Normal spirometry with a positive MIC and response to therapy was considered diagnostic of asthma. Baseline obstruction with (near) normalization post bronchodilator (BD) or following therapy was also considered diagnostic of asthma. Baseline obstruction with failure to achieve normalization post BD as well as following maximum therapy (plus a low DLCO) was considered diagnostic of COPD. Emphysema without airflow obstruction was diagnosed based on (near) normal spirometry, a low DLCO and a Chest computerized tomographic (CT) scan that showed significant emphysema.

Blood tests included blood count (CBC), basic chemistries, thyroid stimulating hormone (TSH), and brain natriuretic peptide (BNP). (BNP or pro-BNP as mandated by insurance).

At the initial visit, the physician predicted the cause of dyspnea, first after the H&P and then after PFTs. These predictions were later compared with final diagnoses.

The completion of Tier I represented a branch point. If the H&P, blood tests, CXR, and PFTs strongly supported a diagnosis (e.g. PFTs consistent with asthma), therapy was prescribed. If dyspnea improved, the diagnosis was considered confirmed. Alternatively, if Tier I results (+/− therapy) did not confirm a diagnosis, Tier II was routinely performed unless Tier I results suggested a diagnosis which could be confirmed by a specific Tier III study. In those cases Tier II (CPET) was bypassed.

Tier II- cardiopulmonary exercise testing (CPET)

Tier II (CPET) was performed if there was no diagnosis after Tier I or an additional cause was suspected. If CPET confirmed a diagnosis and no additional cause was suspected, no further testing was done. If CPET did not confirm a diagnosis, the results were used to select specific Tier III studies. Exercise capacity was characterized as normal or reduced based on maximal oxygen uptake (VO_2 max),[14] and any limitation was categorized as respiratory or circulatory. It should be noted that echocardiography (echo) was not included as part of Tier II. The CPET was performed in the pulmonary laboratory by a pulmonologist. Neither the equipment nor the expertise to perform and interpret an echocardiogram was available.

Studies specific for that limitation were then ordered. For example, if the CPET showed a circulatory limitation an echocardiogram (echo) was typically obtained. Alternatively, if the CPET suggested ischemia a nuclear cardiac stress test or stress echo was ordered. (It may well be desirable in the future to combine standard CPET with echocardiography in centers designed for the diagnosis and evaluation of patients with unexplained dyspnea.).

CPET results were part of the diagnostic criteria for obesity and non-physiologic (i.e. psychogenic) dyspnea. A reduced VO_2/kg plus a normal VO_2 max without cardiorespiratory dysfunction (and normal Tier I studies) was

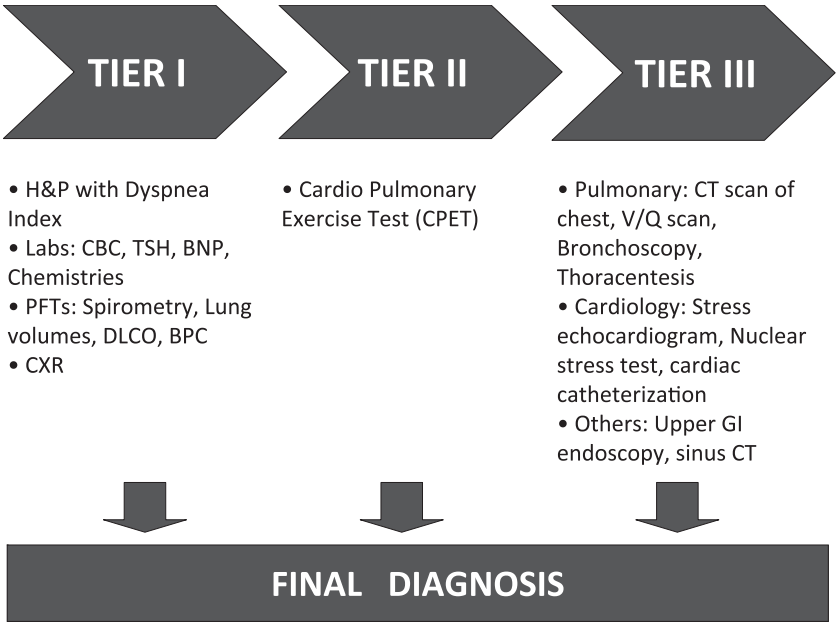

Figure 1 Diagnostic protocol.

considered consistent with obesity-related dyspnea.[14,15] A normal CPET and Tier I was consistent with non-physiologic (psychogenic) dyspnea. Two patients had a CPET that showed a reduced VO_2 max with a circulatory limitation where the subsequent echos were normal, they reported significant inactivity before onset of dyspnea and the dyspnea resolved with exercise training. They were diagnosed with "deconditioning." Two patients had normal Tier I and II (CPET) testing, symptoms typical of post-nasal drip syndrome (PNDS) with nasal congestion and dyspnea resolved with standard treatment for PND. Two patients with typical history (and previous diagnosis) of fibromyalgia had normal Tier I and II (CPET) testing and improved with treatment of their fibromyalgia.

The study design allowed any diagnostic evidence to be followed promptly. As stated above, if Tier I strongly suggested a diagnosis, CPET was bypassed, and a Tier III study obtained (e.g., chest CT scan for suspected ILD on CXR). Furthermore, whenever the data supported a diagnosis, treatment could be instituted.

Tier III — focused organ-specific testing

Tier III tests tended to be single-organ-focused and included invasive studies. Tests included Chest CT scanning, bronchoscopy, echocardiogram (resting or exercise), nuclear stress testing, and cardiac catheterization. Tier III studies were ordered based on the composite results of Tier I +/− Tier II.

Response to therapy and Follow-up

Therapy was instituted whenever a diagnosis was considered probable and therapy was available. When the treatment led to at least a moderate (based on Mahler Transitional Dyspnea Index[7]) improvment in dyspnea, the diagnosis was considered confirmed. The converse was true; if expected therapy did not lead to improvement, that diagnosis was deemed incorrect and the work up resumed.

Statistical analysis

Mean differences between groups were tested for significance using independent samples t-testing (two-sided, $p \leq 0.05$) with correction for equal variance assumptions where indicated.

Results

One hundred forty-eight consecutive patients met study criteria. Six declined to participate and 19 failed to complete the protocol. One hundred twenty-three patients (48 men and 75 women) completed the protocol. Demographic data are presented in Table 1.

Final diagnoses

A cause(s) of dyspnea was determined in 122/123 (99%) patients. Ninety-seven had a single diagnosis and 25 two diagnoses (total, 147 diagnoses). No diagnosis was determined for one patient. Almost half (47%) the diagnoses were non-respiratory (Fig. 2). The spectrum and frequency of diagnoses is shown in Table 2.

Tier evaluations and number of diagnostic tests performed

A total of 524 diagnostic tests were performed on the 123 patients (mean, 4.3/patient). (CBC, BNP, TSH, and chemistries were counted as a "single blood test". PFTs were also counted as a "single test".) After Tier 1, 162 additional

Table 1 Baseline characteristics of patients ($n = 123$).

Age (years	60.2 ± 15.1
Gender (*n*, %)	
Male	48 (39.0)
Female	75 (61.0)
Body mass index (BMI) (kg/m^2)	32 ± 8.4
BMI > 30 (%)	57
BMI > 40 (%)	25
Mean Duration of dyspnea (months)	24.5 ± 33.9
Dyspnea score	6 ± 2.3

tests (67 CPET and 95 Tier III) were performed (mean 1.3 per patient). Fifty-three/123 patients underwent at least one Tier III test.

Fig. 3 shows the flow of patients through the tiers. Forty-five patients were diagnosed from Tier I. Sixty-seven patients underwent CPET (Tier II), 60 who lacked a diagnosis after Tier I and 7 who had a diagnosis (asthma 5, anemia 2), but for whom additional causes were suspected (none were found). Thirty-eight patients were diagnosed after CPET (particularly obesity and non-physiologic, psychogenic dyspnea). Therefore, a diagnosis was made in 83/123 patients (67%) by the end of Tier II. Thirty-nine patients were diagnosed from Tier III studies. One patient had no diagnosis.

Although Tier I established a diagnosis in 45 patients, suspicion that additional diagnoses might be present led to Tier II evaluation in 7 and Tier III studies in 8; no additional diagnoses were found. Similarly, 7 patients diagnosed by Tier II went on to Tier III studies that were, again, of no additional diagnostic value.

Accuracy of physician predictions

Physicians' predictions following H&P were accurate 55% of the time compared with final diagnoses. When PFT results were added, accuracy increased to 72%.

Table 2 Final diagnoses by category.

	# patients	%
1. Respiratory diagnoses	78	53
a. Airflow obstruction	55	37
i. Asthma	29	20
ii. Asthma/COPD	13	9
iii. COPD	13	9
b. Interstitial lung diseases	12	8
i. Usual interstitial pneumonitis (UIP)	7	5
ii. Sarcoidosis	4	3
iii. Lymphangioleiomyomatosis	1	1
c. Other pulmonary disorders	11	7
i. Emphysema without airflow obstruction	3	2
ii. Pulmonary hypertension	3	2
iii. Chronic pneumonia	1	1
iv. Lung cancer	1	1
v. Kyphoscoliosis with ventilatory limitation	1	1
vi. Pleural disease	2	1
2. Cardiovascular and circulatory diagnoses	23	16
a. Congestive heart failure/ cardiomyopathy (includes diastolic dysfunction, systolic dysfunction, and ischemic heart disease)	9	6
b. Valvular heart disease	5	3
c. Other circulatory disorders	12	8
i. Anemia	5	3
ii. Inferior vena caval obstruction	1	1
iii. Chronotropic insufficiency	1	1
iv. Peripheral vascular disease	1	1
3. Non-cardiopulmonary diagnoses	46	31
a. Obesity	24	16
b. Non-physiologic (psychogenic)	15	10
c. Deconditioning	2	1
d. Fibromyalgia	2	1
e. Pregnancy	1	1
f. Post-nasal drip	2	1
Total diagnoses	147	100

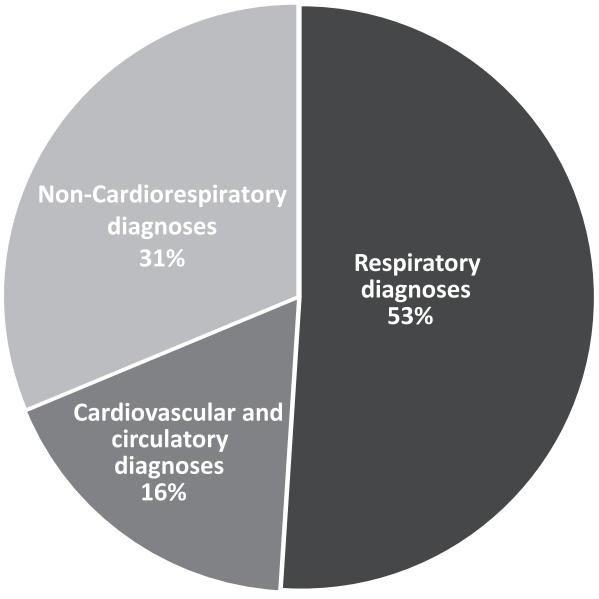

Figure 2 Diagnoses by category.

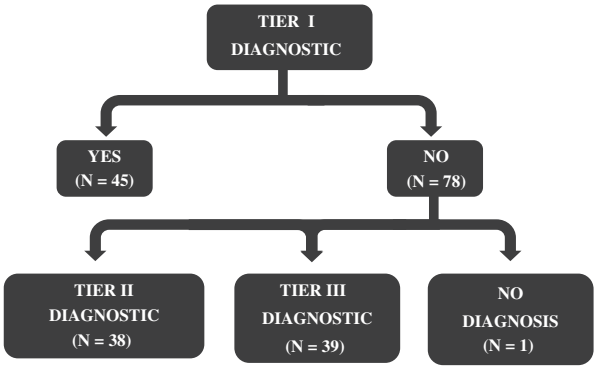

Figure 3 Flow of patients through tiers.

Diagnostic accuracy of patient-reported histories of asthma and COPD

Only 17/31 patients reporting a history of asthma had asthma-related dyspnea (positive predictive value (PPV) 0.55). Only 13/29 patients reporting a history of COPD had COPD-related dyspnea (PPV 0.45).

Diagnostic accuracy of smoking history for COPD

Of the 123 patients, 23 were current smokers, 49 ex-smokers, and 51 non-smokers. COPD (or isolated emphysema) was diagnosed in 29 patients. All were either current or former smokers. A smoking history had a Positive predictive value (PPV) of 0.40 for COPD. A non-smoking history had a negative predictive value of 1.0; (i.e., no non-smoker was diagnosed with COPD). There was a significant difference in mean pack-years between smokers with COPD (49.6 $\pm$ 21.8, range 10–114), versus those without COPD (33.2 $\pm$ 25.7, range 2–100). ($p = 0.002$), but there was considerable overlap. No patient with <10-pack-year history had COPD.

Diagnostic value of blood tests

One hundred and nineteen patients had hemoglobin measured. Seventeen of the 119 hemoglobin levels (14%) were low[16] including 5 patients <10 gm/dl (9.6, 9.3, 9.1, 8.6, and 7.7). Anemia was determined to be a factor in all 5; dyspnea improved with increase in hemoglobin. In patients with hemoglobin >10, other causes of dyspnea were found.

One hundred and fifteen patients had a pro-BNP ($n = 72$) or BNP ($n = 43$). In ninety-five patients, the values were normal and in 20 they were elevated. Ninety-three/95 normal values were true negatives, and 2 were false negatives (i.e., cardiomyopathy was the final diagnosis). Nine/20 elevated values were true positives (diagnosis of cardiomyopathy) and 11 were false positives. TSH and chemistries were of no value in this study.

Diagnostic value of CXR

Sixty-nine/121 patients (57%) had a normal and 52 (43%) an abnormal CXR. (Two patients did not have a CXR.) All 12 patients with interstitial lung disease (ILD) had CXRs consistent with the diagnosis. Only 9/29 (31%) of patients with COPD had CXR findings consistent with COPD (hyperinflation or bullae). Three patients with emphysema without airflow obstruction all had normal CXRs. Ninety percent (26/29) of asthmatics had normal CXRs. Three had hyperinflation. Seven of 9 patients with cardiomyopathy had cardiomegaly with interstitial changes, and 2 had normal CXRs. The patients with lung cancer, fibrothorax with pleural effusion, and scoliosis had the expected CXR abnormalities. The patient with pneumonia had a normal CXR. (Diagnosis made by CT scan and response to therapy). In 13/14 patients with dyspnea due to isolated obesity, CXR was normal. In summary, all patients with non-physiologic (psychogenic) dyspnea or other non-cardiorespiratory diagnoses (except 1 patient with obesity) had normal CXRs. Most (90%) of asthmatics and the majority (69%) of patients with COPD had normal CXRs. All patients with ILD and most patients with cardiomyopathy (78%) had abnormal CXRs consistent with the diagnosis. Therefore, while a normal CXR is to be expected in non-physiologic causes of dyspnea, it is also commonly seen with asthma and COPD.

Diagnostic value of PFTs

Twenty-nine patients had COPD or isolated emphysema without airflow obstruction. Mean FEV_1 was 59% of predicted (range 34–110), mean FEV_1/FVC ratio was 55% (range 36–100%), and mean DLCO was 47% of predicted (range 30–66). Three of the 29 had emphysema with minimal or no airflow obstruction; (FEV_1s were 110%, 82%, and 72% of predicted, FEV_1/FVC ratios of 0.73, 0.64, 0.76). For all 3, DLCO was low (39%, 41%, and 44% of predicted) and chest CT scans showed extensive emphysema.

Forty-two/80 BPCs demonstrated bronchial hyperresponsiveness (BHR). Twenty-nine/42 patients (69%) with a positive BPC had asthma or asthma/COPD; BPC was false positive in 13 (i.e. no improvement with asthma treatment, another cause of dyspnea determined.) The mean provocative concentration causing a 20% decrease from the baseline FEV_1 (PC_{20}) for true positives was 0.88 mg/ml ($\pm$1.13), while the mean PC_{20} for false positives was 2.68 mg/ml ($\pm$2.31) ($p = 0.023$). No patient with negative BPC had asthma. Thirteen patients with asthma (or asthma/COPD) did not undergo BPC due to a baseline $FEV_1 < 70\%$. For these patients, asthma was diagnosed based upon improvement following treatment; FEV_1 increased an average of 41%, FVC an average of 42%, and mean post-treatment FEV_1 was normal at 84% of predicted (range 71–106%).

A reduction in DLCO (<75% of predicted)[17] was present in 78/122 patients (64%). It was useful despite this high prevalence. It was reduced in all patients with COPD (see above) and ILD (mean 35% of predicted, range 20–64). It was normal in all patients with non-physiologic (psychogenic) dyspnea.

Diagnostic value of CPET

Sixty-seven patients underwent CPET. Results were normal in 36 and abnormal in 27. Effort was sub-optimal in 4. In 26/29 patients with a normal CPET (90%), a non-cardiorespiratory disorder was found. There were 3 "falsely negative" studies (2 ILD, 1 cardiomyopathy). In 25/27 patients with an abnormal CPET (93%), the physiologic abnormality was consistent with the final diagnosis (i.e. true positive test). Excluding the 4 patients with sub-optimal effort and the 7 in whom the CPET was done for a suspected additional cause of dyspnea (established diagnoses of asthma in 5 and anemia in 2), CPET accurately guided the work-up in 51/56 patients.

Tier III studies

There were 95 Tier III studies (81 non-invasive and 14 invasive). In some cases, one Tier III study led to one or more additional Tier III studies to more precisely define the diagnosis (e.g. abnormal stress test lead to cardiac catheterization, abnormal chest CT scan led to bronchoscopy). The 81

non-invasive studies included 36 chest CT scans, 30 echocardiograms (resting +/− exercise), 10 nuclear stress tests, 4 ventilation/perfusion (V/Q) scans, and 1 sinus CT scan. There were 11 normal and 25 abnormal chest CTs. All 25 abnormal CT scans were diagnostically useful (ILD, sarcoidosis, emphysema with or without airflow obstruction, pneumonia, lung cancer, and pleural disease). Of the 30 echocardiograms, 20 were abnormal and 10 normal. Eighteen/20 abnormal echoes were true positive (showing abnormalities − left ventricular diastolic, systolic, or valvular dysfunction or evidence of right-sided dysfunction − eventually determined to be the etiology of dyspnea). A normal echocardiogram ruled out a cardiovascular cause of dyspnea 100% of the time (10/10). There were 10 nuclear cardiac stress tests (3 true+, 1 false+, 6 true- for ischemic heart disease). Two/four V/Q scans were diagnostic (1 atrial septal defect with right to left shunt, 1 pulmonary hypertension due to chronic pulmonary embolism). The sinus CT showed chronic sinusitis.

The 14 invasive studies included 7 heart catheterizations, 4 bronchoscopies, one upper gastrointestinal endoscopy, 1 thoracentesis, and one skin biopsy. All 4 bronchoscopies were diagnostic (3 sarcoidosis and 1 lung cancer). Six/seven heart catheterizations were positive (aortic stenosis, cardiomyopathy, chronic pulmonary thromboembolism, idiopathic pulmonary hypertension, atrial septal defect with pulmonary hypertension, and mitral stenosis with pulmonary hypertension). The thoracentesis demonstrated pleural effusion. The UGI endoscopy showed Barrett's epithelium in patient with dyspnea due to gastroesophageal reflux disease (GERD). In each case, dyspnea improved with treatment.

Response to therapy

Follow-up dyspnea scores were obtained in 110 patients three months post therapy. Seventy-two were improved, 31 unchanged, and 7 worse. Thirty one of 37 patients with "pure airway disease" (asthma or COPD with no secondary diagnoses) had moderate or greater improvement. For asthma, mean improvement was 3.2. In 18/23 the improvement was moderate or better. One patient with no improvement had occupational asthma but refused to change the work environment. Two patients with airway disease were lost to follow-up. Patients with cardiomyopathy had moderate improvement (mean 3.2). There was marked improvement in all patients with dyspnea due to anemia, gastroesophageal reflux disease (GERD), post-nasal drip, pregnancy, and pneumonia.

Thirteen/fourteen with isolated obesity showed no change. Eight/twelve patients with ILD showed some improvement (mean 2.6). For the 11 patients with non-physiologic (psychogenic) dyspnea, 4 showed marked improvement, 1 moderate improvement, and 6 no change.

Discussion

This is the fourth prospective study of patients presenting with chronic dyspnea and the first to establish and follow an algorithm. Pratter et al.[4] studied patients presenting with chronic dyspnea and demonstrated that a diagnosis could usually be established and that PFTs with BPC, imaging, and CPET all had diagnostic value. The data of DePaso et al.[2] demonstrated again the capacity to achieve a diagnosis in a majority of cases and the value of BPC. Martinez et al.[3] echoed the above findings and showed that CPET was valuable in determining the etiology of dyspnea, that "CPET results are a useful guide to further diagnosis and treatment". Martinez et al. also noted that their study and the two that preceded theirs, "suffered from a lack of a standardized subsequent testing protocol and lack of routine bronchoprovocation testing". The algorithm in the current study was based upon these earlier studies[2–4] and upon an exhaustive review of the literature on dyspnea.[5] We believe that it incorporates important prior findings into an organized approach.

The approach used in this study was useful; a diagnosis was made in 99% of patients. Tier I findings (H&P, PFTs, blood tests, and CXR) diagnosed 45 patients, Tier II (CPET) diagnosed an additional 38, and focused Tier III studies an additional 39. Thus each Tier diagnosed approximately one third of the patients. Invasive testing was minimized; there were only 14 invasive studies, and 13 of them diagnosed the cause of dyspnea.

The data demonstrate that Tiers I and II together acted as a "check and balance" system which ensured that a significant physiologic abnormality was not missed. If Tier I and Tier II were both normal, a non-cardiorespiratory diagnosis was always made and Tier III studies were uniformly negative. If Tier I or II demonstrated abnormalities that were non-diagnostic, those abnormalities were nevertheless valuable in guiding Tier III studies.

Our data generated a number of key points: One, patients presenting with dyspnea have a wide range of underlying diagnoses; a narrow subspecialty focus is likely to be less successful than a broader multidisciplinary perspective. Two, Objective data is vital; clinical suspicion based upon H&P alone cannot replace physiologic testing. The value of BPC was re-confirmed; BPC should be performed early in any approach to dyspnea when baseline spirometry is normal. The results of CPET establish some diagnoses and lead to specific testing for others. Third, response to therapy is a helpful in diagnosing conditions where effective therapy is available. It allows the clinician to determine whether a patient with laboratory evidence for a diagnosis (e.g. positive BPC as evidence for asthma) actually responds to therapy that is expected to work. Although response to therapy does not prove the diagnosis, it does add additional evidence.

The most important contribution of this study is the algorithm, with specific sequenced testing for Tiers I and II. In addition to the algorithm, our data generate new points relevant to dyspnea: Obesity was disproportionately represented in patients with dyspnea compared to the general population. Anemia can cause dyspnea; hemoglobin is a valuable early test. P-BNP (not available for the prior studies) is valuable although not diagnostic for suggesting a cardiovascular disorder.

As with any clinical study, this one is open to criticisms. First, both dyspnea and response to therapy are subjective, making any objective study difficult; while we found an explanation for dyspnea in 99% of patients, there is no independent gold standard for comparison. There is also no comparator or standard practice in the literature against which we can directly compare our algorithm. Therefore, while we believe it is a useful approach that is likely to be

more cost effective and efficient than the "routine", non algorithmic approach typically used in clinical practice, we do not have proof that this is true. Second, the algorithm was not a rigid sequence, as any data suggesting a diagnosis could lead to treatment. It was in a sense an "open algorithm"; potentially diagnostic clinical data (such as a positive BPC) were pursued, but if diagnosis-specific treatment was not fruitful, the patient was returned to the algorithm and its specified sequence. Third, CPET data are complex, and others could disagree with their interpretation. Fourth, any equivocal data were reviewed and agreed upon by consensus of all the investigators, a process neither available nor realistic in most clinical settings. Fifth, the choice of Tier III studies was based upon study data and not upon a set sequence, and thus required clinical judgment. It is also possible that some Tier III tests (and even CPET) were redundant and we could have made the diagnosis without them. We do not believe this was a common occurrence since our goal was to stop the work-up as soon as we felt a diagnosis (diagnoses) was firmly established, but it certainly remains a possibility. Alternatively, even though we made a diagnosis (or diagnoses) in almost every patient it is still possible that there were additional diagnoses present that we missed in some patients that further testing might have demonstrated. We feel that despite these issues, the findings are relevant to clinical medicine. Nevertheless, it should be pointed out that our patient population had been specifically referred to us as pulmonologists. Therefore, it is quite possible that the frequency and distribution of diagnoses associated with dyspnea would prove to be different in an internal medicine or cardiology subspecialty practice. In addition, the relative value and optimal sequence of diagnostic tests might prove to be significantly different from our algorithm. We believe, however, that a systematic, organized approach analogous to what we used in this study would likely prove to be beneficial in these settings.

Based on our results we would revise the algorithm, specifically Tier I. We would recommend physician judgment in deciding whether to obtain blood studies if the PFTs or CXR strongly support a specific diagnosis. While we would suggest, based on the low diagnostic yield in this study, that a TSH or blood chemistries do not need to be automatically obtained, they are low cost and occasionally may be helpful (e.g. a high TSH suggesting hypothyroidism or a high CO_2 suggesting obesity hypoventilation). If baseline spirometry is normal we would not routinely obtain full lung volumes. We would only obtain a P-BNP if there was at least some clinical suspicion for cardiovascular dysfunction. Furthermore, Tier I studies could be done sequentially during one or more visits rather than all at once. PFTs could be obtained and if normal or non-diagnostic a Chest X-ray could then be obtained. If the Chest X-ray is normal or non-diagnostic a CBC and P-BNP could be obtained to evaluate for heart failure and anemia, respectively.

In conclusion, the findings of this study strengthen and extend those of prior studies. The algorithm used in this prospective study of chronic dyspnea helped organize the approach and generally enabled the identification of a cause or causes of dyspnea. It led to specific diagnoses, specific treatment, and good clinical outcomes in most patients while minimizing invasive studies. Nevertheless, our approach can be streamlined further as noted above. The most important finding is that the physician by following a systematic (algorithmic) approach has a high likelihood of being successful in diagnosing the cause of chronic dyspnea and, in the majority of patients, achieving improvement in dyspnea and exercise tolerance through specific treatment.

Acknowledgements

All authors participated in the design of the study, IRB submission, enrolled patients, followed the protocol, and analyzed results. All authors helped write and edit the paper and approved the final manuscript.

We wish to thank Hiren Shingala, MD for help with the tables and figures and Barry Milcarek PhD and Krystal Hunter MBA for study design and statistical assistance.

There was no outside writing assistance involved in the preparation of this manuscript.

Conflict of interest

The authors of this study believe they have no "conflict of interests" to report. Dr. Pratter has been a speaker for AstraZeneca up until September 30, 2010. He received honorariums totaling ten thousand dollars for 2010. He is no longer speaking for this or any other pharmaceutical company.

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