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Title:
Diagnostic performance of pulmonary embolism imaging in patients with history of asthma

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ABSTRACT

Asthma and pulmonary embolism (PE) can present with overlapping symptoms, and distinguishing between these two conditions can be challenging. Asthma may limit imaging for PE due to either worsened ventilation defects on ventilation/perfusion scan (VQ) or increased motion artifact on CT pulmonary angiography (CTPA).

Methods

We identified adults evaluated for PE with VQ or CTPA from 2012-2016. Patients with chronic lung disease (other than asthma) were excluded. Studies were classified as negative, positive, or non-diagnostic. Follow-up of negative cases were reviewed to determine rate of repeat exam (within one week) and false-negative rate (defined as diagnosis of venous thromboembolism within 90 days).

Results

We reviewed 19,412 adults (age 52 ±18 years, 70% women) evaluated for PE (60% with VQ, 40% with CTPA); 23% had history of asthma. Non-diagnostic results were comparable for those with and without asthma for both VQ (asthma 3.3%; non-asthma 3.8%; p=0.223) and CTPA (asthma 1.6%; non-asthma 1.5%; p=0.891). History of asthma was not associated with higher repeat exam after negative imaging for VQ (asthma 1.9%; non-asthma 2.1%; p=0.547) or CTPA (asthma 0.6%; non-asthma 0.6%; p=0.796), nor was history of asthma associated with higher false negative rate for VQ (asthma 0.4%; non-asthma 0.9%; p=0.015) or CTPA (asthma 1.9%; non-asthma 1.5%; p=0.347).

Conclusion

History of asthma in the preceding ten years was not associated with impaired diagnostic performance of PE imaging for either VQ or CTPA.

Key word: Pulmonary embolism, asthma, ventilation-perfusion scan, CT pulmonary angiography

INTRODUCTION

Asthma and pulmonary embolism (PE) have overlapping clinical presentations, and distinguishing these two entities is an ongoing challenge, particularly in the emergency department (ED)(*1,2*). Additionally, asthmatics are prone to development of PE (*3,4*), which may further complicate evaluation.

Presence of PE is frequently assessed with an imaging study, either ventilation/perfusion scan (VQ) or CT pulmonary angiography (CTPA). In our institution, we have adopted an algorithm in which patients with a clear chest radiograph preferentially undergo VQ in order to reduce radiation exposure(*5*). Since asthma is a chronic disease, and frequently encountered in young adults(*6*), these patients often undergo repeated imaging evaluations, and may therefore benefit from efforts to reduce diagnostic radiation exposure(*7-9*).

Unfortunately, asthma has potential limitations for both VQ and CTPA, which have not previously been characterized. Bronchoconstriction from asthma can cause multiple ventilation(*10*) and matched perfusion defects(*11*), which can complicate interpretation and may lead to increased rate of non-diagnostic or false negative interpretations on VQ. Respiratory motion is known to result in non-diagnostic CTPA exams(*12*), and may be more prevalent in acutely dyspneic asthmatic patients.

A previous series in pregnant women at our institution suggested the subgroup of patients with asthma may have higher rate of non-diagnostic perfusion-only scans (no ventilation portion) or CTPA(*13*). This result motivated our research question—is the performance of PE imaging impaired by history of asthma?

This is a particularly important consideration for underserved populations, and with the overall increasing asthma prevalence in the United States(*14*). Our patient population has a high rate of asthma (13% of Medicaid enrollees(*15*)), as well as the highest rate of ED visits for asthma in New York State, with 35,000 visits in the Bronx during 2016 (244 per 10,000 people)(*16*). Due to our high patient volume, and our imaging algorithm with high VQ use in our ED, we have performed a large number of both VQ and CTPA studies. These factors give us the opportunity to assess whether the reliability of VQ or CTPA is impaired in the setting of asthma.

METHODS

Setting and Patient Selection

We performed a retrospective cohort study of patients evaluated for PE at Montefiore Medical Center, a multisite urban academic medical center with three inpatient sites and four emergency rooms. The Institutional Review Board approved this retrospective study, and the requirement to obtain informed consent was waived. A search of adult patients (≥18 years of age) who underwent VQ or CTPA from 2012 through 2016 was performed using Looking Glass Clinical Analytics (Streamline Health), a data mining tool designed to interact with our institution's electronic health records. CTPA exams were identified as any contrast enhanced CT chest exam which contained the abbreviation "PE" in the report—this expression is used in the exam title, technique description, or clinical indication for most CTPA exams. Patient age, self-reported race and ethnicity, and Charlson

Comorbidity Index (CCI)(*17*) at the time of exam were recorded. The clinical setting of the exam (emergency department, inpatient, or outpatient) was also recorded.

Patients were excluded if a diagnosis of a chronic lung disease within the preceding ten years was identified by our search method. Chronic lung diseases were defined as interstitial pneumonia, fibrotic lung disease, chronic bronchitis, emphysema, bronchiectasis, pneumoconiosis, and sarcoidosis. Perfusion-only lung scans (usually performed in pregnant patients), incomplete CTPA or VQ, or exams which did not address PE were excluded. Patients with an ICD diagnosis of asthma within the preceding 10 years formed the asthmatic group. The remaining patients formed the control group. A subset of asthma patients was also identified by whether asthma medication had been prescribed in the preceding year (rescue medications, inhaled corticosteroids, leukotriene modifiers, or biologics).

Study Classification and Follow-up Review

All studies were classified as negative, non-diagnostic, or positive. We use this trinary interpretation scheme for VQ in our clinical practice(*18*), and this is reflected in the exam reports. CTPA scans were classified as negative if this was explicitly stated in the report. If an exam stated there was no central PE but was described as limited, this was also considered negative(*19*). Exams that were described as non-diagnostic, or could only exclude embolus in the main, right, or left pulmonary artery, were counted as non-diagnostic. Exams describing acute or chronic pulmonary embolism were counted as positive. Reports were classified as negative, non-diagnostic, or positive based on text

searches; remaining cases unable to be classified this way were reviewed and classified manually.

Follow up care after PE imaging was reviewed. We determined the rate of repeat exam within one week. False negative cases were defined as the development of PE or deep vein thrombosis (DVT) within 90 days after an initial negative PE imaging study. To identify false negative cases, patients with a negative exam who had documentation of an ICD 9 or 10 diagnosis of PE or DVT within the 90 day follow up period were identified, and these medical charts were all reviewed to confirm development of PE or DVT. The denominator for determining false negative rate was the number of patients with follow up in our system beyond 90 days (determined as documentation of an ICD code) plus the number of patients with confirmed PE or DVT diagnosis within 90 days.

The cohort data were sampled and reviewed manually to determine accuracy. Review of the exam report for every 10th case demonstrated 99.5% accuracy for classifying exam result (10/1940 misclassification). Review of the medical chart for every 100th case demonstrated overall 95% accuracy (9 errors out of 194 reviewed cases: 1 erroneous exam result, 1 missed repeat exam, 4 misclassifications of asthmatic as non-asthmatic, and 3 misclassifications of non-asthmatic as asthmatic). Review of every 100th CTPA exam demonstrated 78 out of 78 exams were tailored to or performed for PE diagnosis.

Statistical Analysis

Categorical variables were compared with Chi-square test and continuous variables were compared with student's t-test. Significance level was set at two-tailed $p<0.05$.

RESULTS

We identified 23,586 adults who were evaluated for PE with either VQ or CTPA during the five-year study period from 2012 through 2016. Of these, 3,608 patients carried an ICD diagnosis of a chronic lung disease within the preceding 10 years, and were excluded. Of the remaining 19,978 patients, 566 patients were excluded (418 patients had perfusion only exam for pregnancy, 75 had incomplete VQ scan, 58 had CT not performed for PE or not addressing PE, and 15 had incomplete CTPA).

The study cohort comprised 19,412 patients (age 52 ±18 years). The study population was predominantly women (70.0%; 13,590/19,412). A large portion self-identified as African-American (38%; 7,443/19,412) or Hispanic (37%; 7,267/19,412). VQ was used to evaluate 11,598 patients (60%) and CTPA was used to evaluate 7,814 patients (40%). Asthma was present in 23% (4,515/19,412) of the cohort, 25% (2,926/11,598) of patients evaluated with VQ, and 20% (1,589/7,814) of patients evaluated with CTPA (Figure 1).

The populations undergoing VQ and CTPA were distinctly different (table 1). Patients who underwent CTPA were older (CTPA 56 years ±18; VQ 50 years ±18; $p<0.001$) and less predominantly women (CTPA 65% [5,106/7,814] women; VQ 73% [8,484/11,598] women; $p<0.001$). Patients who underwent CTPA also tended to be sicker, as quantified by CCI (CTPA 2.0 ±2.9; VQ 1.2 ±2.3; $p<0.001$). These differences were observed in patients with and without asthma. Patients with asthma were slightly younger (asthma 51 years ±17; non-asthma 52 years ±19; $p<0.001$) and more predominantly women (asthma 80% [3,625/4,515] women; non-asthma 67% [9,965/14,897] women;

p<0.001). Patients with asthma had higher CCI (asthma 2.0 ±2.6; non-asthma 1.4 ±2.5; p<0.001), not surprising since asthma contributes 1 point to the CCI.

The most common clinical setting for PE evaluation was in the emergency department (60%, 11,724/19,412), followed by inpatient (30%, 5,904/19,412). PE evaluation was rarely performed in the outpatient setting (4%, 768/19,412), and clinical setting was not available for 5% (1,016/19,412) of cases. VQ was more commonly used in the emergency department (VQ 66% [7,702/11,598]; CT 51% [4,022/7,814]; p<0.001), and less commonly used inpatient (VQ 23% [2,638/11,598]; CT 42% [3,266/7,814]; p<0.001).

Rate of non-diagnostic results did not significantly differ between asthmatic and non-asthmatic populations for either VQ (asthma 3.3% [97/2,926]; non-asthma 3.8% [330/8,672]; p=0.223) or CTPA (asthma 1.6% [25/1,589]; non-asthma 1.5%; [95/6,225] p=0.891). Asthmatic patients had a lower rate of positive PE study for both VQ (asthma 5.5% [162/2,926]; non-asthma 6.9% [596/8,672]; p=0.010) and CTPA (asthma 12.0% [191/1,589]; non-asthma 16.3% [1,012/6,225]; p<0.001; table 2).

The presence of asthma was not associated with higher rate of repeat PE imaging within one week following an initial negative exam (table 3). This was observed for both VQ (asthma 1.9% [51/2,667]; non-asthma 2.1% [163/7,746]; p=0.547) and CTPA (asthma 0.6% [8/1,373]; non-asthma 0.6% [33/5,118]; p=0.796). Patients with a negative VQ were more likely than patients with a negative CTPA to have a repeat exam (VQ 2.1% [214/10,413]; CTPA 0.6% [41/6,491]; p<0.001). History of asthma was associated with a lower rate of false negative VQ scan (asthma 0.4% [10/2,463]; non-asthma 0.9% [57/6,273]; p=0.015). History of asthma was not associated with different rate of false negative CTPA (asthma 1.9% [23/1,190]; non-asthma 1.5% [59/3,838]; p=0.348).

The subgroup of asthmatic patients who had documented medication prescription in our health system in the preceding year consisted of 2,626 patients (58% of asthma group), of whom 1,666 had VQ and 960 had CTPA. Exam results, repeat exam after negative result, and false-negative result were similar to the broader asthma cohort, and with similar comparison to the non-asthma group, with the exception that the difference in positivity rate of VQ in asthmatics with documented medication compared to non-asthmatics was not statistically significant (Table 4).

DISCUSSION

History of asthma was not associated with impaired diagnostic ability for either VQ or CTPA when evaluating for PE. Any additional artifact or limitation in these exams that might be attributed to asthma is therefore unlikely to alter the reliability or accuracy of PE imaging.

The rate of non-diagnostic exam did not differ in asthmatics compared to non-asthmatics for either VQ or CTPA. This is important for managing asthmatic patients with dyspnea or chest pain—we can be assured that history of asthma does not change the likelihood that the patient will have a diagnostic exam. We interpret VQ scans using a trinary approach (positive, negative, or non-diagnostic), rather than probability terminology(*18*). The probability terminology can be ambiguous to both exam readers(*20*) and clinicians(*21*). The trinary approach clearly communicates results to clinicians, without increasing the possibility of false negative exam. This provides a concise positive or negative result, keeping in line with interpretation strategies for other diagnostic studies.

With the trinary approach, the occurrence of VQ studies interpreted as non-diagnostic is low, less than 4% for both asthmatic and non-asthmatic populations. Furthermore, the rate of false-negative VQ is also low, less than 1% in this series. False negative rate was not significantly higher in asthmatic patients for either VQ or CTPA. Overall, negative predictive value was greater than 98% for both VQ and CTPA, for patients with and without history of asthma. Asthmatics demonstrated a statistically significant lower rate of false negative VQ exam, however the baseline numbers for this are small and the clinical significance is unclear. The need for a follow up exam, after an initial negative exam, also did not differ between asthmatic and non-asthmatic patients. This indicates that history of asthma does not alter the need to further evaluate for PE.

Interestingly, asthmatic patients were slightly less likely to have a PE than non-asthmatic patients. Asthmatic patients in general are reported be at increased risk for VTE(*3,4*). However, in the acute setting where the patient's symptoms have already brought them to medical attention, it is not surprising that asthmatic patients are less likely to have PE—as they have an alternative diagnosis at presentation that may explain their symptoms.

Asthma is a common disease in patients presenting with alarming symptoms of chest pain and/or dyspnea, which overlap with symptoms of PE. Asthma may be the cause of the episode or a comorbidity. PE is a frequent and concerning differential diagnosis in these patients. The initial workup for PE is based on clinical and laboratory assessment, however the diagnosis is ultimately dependent on imaging, usually VQ or CTPA. Both of these modalities use ionizing radiation and have limitations regarding sensitivity and specificity. VQ has the potential for false negative results for smaller PEs which may or may

not be clinically significant(*22*), or false positives due to non-embolic causes of pulmonary artery narrowing(*23*). CTPA has the possibility of false positive results due to motion artifact, heterogeneous contrast filling, or beam hardening artifact(*24,25*). Based on prior data from asthmatic pregnant patients(*13*), we were concerned that history of asthma—with ventilation defects, air-trapping, and increased respiratory motion—might increase the limitations for either of these exams.

Our practice setting provided us a good opportunity to address concerns regarding asthma in both CTPA and VQ exams. First, asthma is particularly prevalent in our practice, present in 13% of Medicaid enrollees in Bronx, NY(*15*), and was even higher in our cohort (23%, similar to the prior cohort of pregnant patients studied in our medical system(*13*)). Second, our practice algorithm recommends VQ scan when the chest radiograph is normal and the patient is stable enough to tolerate the exam(*5*)—this provided us with a large sample size of VQ studies to review, and accounts for the older age and higher CCI in the CTPA group. The CTPA group was also less predominantly women, likely due to additional benefit of reducing radiation to the chest (breast tissue) in women(*7,9*).

Asthmatic patients in our cohort were found to be slightly younger, and more often women; these are the patients that are most susceptible to radiation from chest imaging. While the continued development of modern CT scanners may narrow the radiation dose difference between VQ and CTPA(*26-28*), use of VQ may be beneficial for young patients in certain practice settings, and will perform reliably regardless of the diagnosis of asthma.

This analysis is limited by the ability to assess the acuity of a patient's asthma. Asthma exacerbation is likely in the differential for most patients presenting with shortness of breath or chest pain, especially if there is any documented history of asthma.

Patients may be empirically treated for multiple conditions, including asthma, and it is therefore difficult to know the true etiology of a patient's symptoms. In fact, it is our standard practice for patients who are wheezing to recommend bronchodilator therapy prior to performing VQ scan, and our results reflect that practice. VQ is advised to be performed after bronchospasm has resolved, in order to decrease ventilatory defects(*29*). We addressed this issue with our subgroup analysis, restricted to the patients with documented prescription for asthma medication in the preceding year. This accounted for a slight majority of the asthma cohort (58%). The characteristics of this subgroup was similar to the broader asthma cohort, and demonstrated similar comparison to the non-asthma group, indicating that our results hold for patients with more active or more recent history of asthma.

Additional limitations of this study primarily stem from its retrospective nature performed in one medical system and dependence on medical record keeping. ICD codes were used to classify patients as asthmatic or non-asthmatic, presence of underlying chronic lung disease, and to identify the development of venous thromboembolism. The development of VTE was likely underestimated in this study, primarily due to dependence on ICD coding to identify potential false negative cases and incomplete follow up of all patients within our system. However, these limitations should not bias results toward asthmatic or non-asthmatic patients. Differences between the asthmatic and non-asthmatic groups, with higher proportion of females and slightly younger age in the asthmatic group, are an additional limitation of this study.

There were important differences between patients evaluated with VQ or CTPA—including age, gender, and exam setting—which reflects our clinical practice and precludes

comparison between VQ and CTPA in this study. CTPA had a higher rate of positive exams and false negative exams compared to VQ—however, both of these findings likely reflect the older age and higher rate of comorbidities in patients who underwent CTPA. The higher positivity rate for CTPA also reflects the higher sensitivity of CTPA for small PE(*30,31*).

CONCLUSION

The decision to image for pulmonary embolism is complex and must take into consideration the benefits and limitations of VQ and CTPA. History of asthma does not impair the diagnostic performance of either of these modalities.

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Key points:

Question: Does history of asthma impair the diagnostic performance of imaging for pulmonary embolism?

Pertinent findings: Asthmatic patients did not demonstrate higher rate of non-diagnostic studies or false negative results for either VQ or CTPA.

Implications for patient care: Our results should assure physicians that history of asthma will not impair the diagnostic performance of either VQ or CTPA.

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FIGURE 1. Flowchart of study design with patient sample sizes.

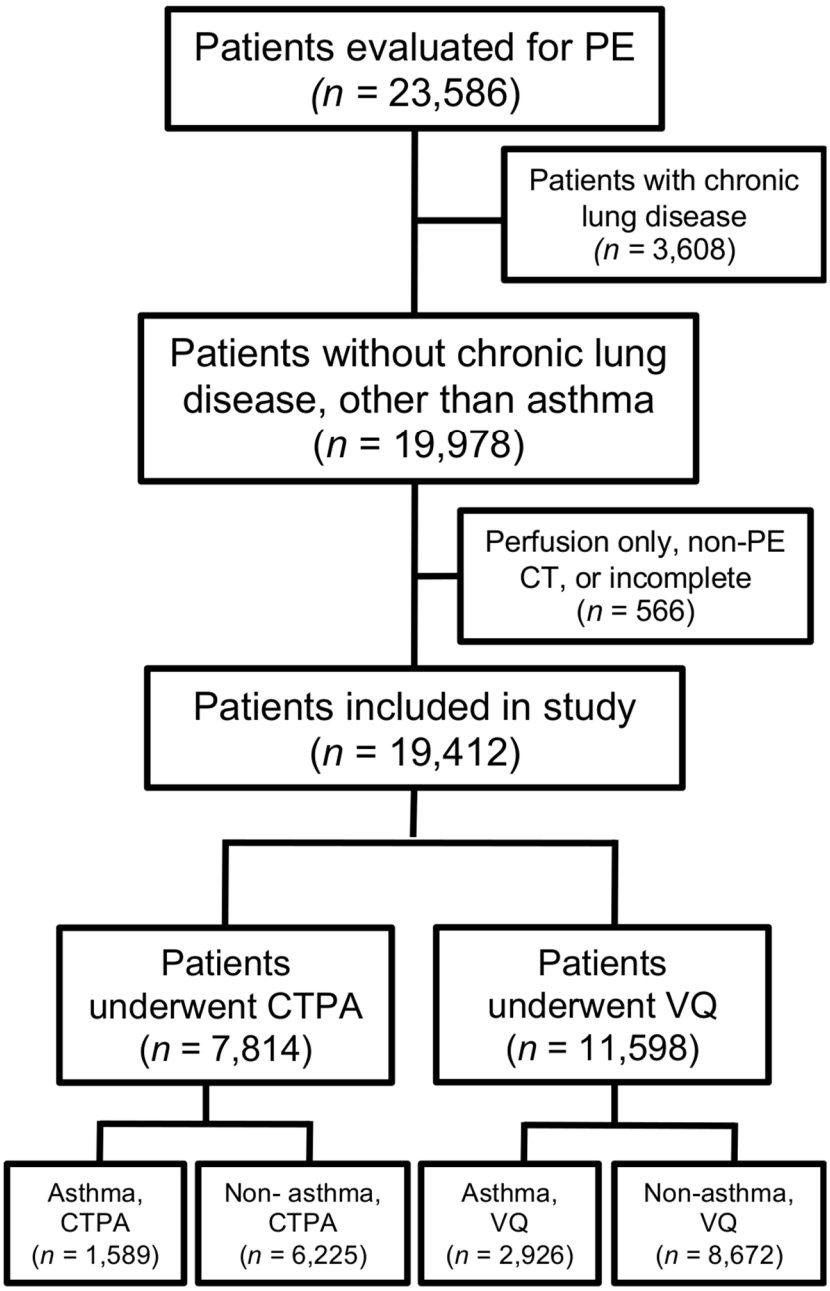

Table 1. Patient characteristics and exam setting by modality and presence or absence of asthma.

	All (n=19,412)	VQ group (n=11598)	CTPA group (n=7814)	p-value	Asthmatics (n=4515)	Non-asthmatics (n=14,897)	p-value
Age (years)	52 ±18	50 ±18	56 ±18	*p<0.001*	51 ±17	52 ±19	*p<0.001*
Gender (%female)	70%	73%	65%	*p<0.001*	80%	67%	*p<0.001*
CCI*	1.5 ±2.6	1.2 ±2.3	2.0 ±2.9	*p<0.001*	2.0 ±2.6	1.4 ±2.5	*p<0.001*
Exam Setting							
Emergency Department	60%	66%	51%		61%	60%	
Inpatient	30%	23%	42%		32%	30%	
Outpatient	4%	5%	2%		5%	4%	
Unavailable	5%	6%	5%		2%	6%	
				p<0.001			*p<0.001*

* CCI, Charlson Comorbidity Index

Table 2. Exam results by modality and presence or absence of asthma.

	Negative	*p-value*	Non-diagnostic	*p-value*	Positive	*p-value*
VQ						
Asthmatics (n=2,926)	2,667 (91.1%)	*0.005*	97 (3.3%)	*0.223*	162 (5.5%)	*0.010*
Non-asthmatics (n=8,672)	7,746 (89.3%)		330 (3.8%)		596 (6.9%)	
CTPA						
Asthmatics (n=1,589)	1,373 (86.4%)	*<0.001*	25 (1.6%)	0.891	191 (12.0%)	*<0.001*
Non-asthmatics (n=6,225)	5,118 (82.2%)		95 (1.5%)		1,012 (16.3%)	

Table 3. Outcomes following an initial negative exam.

	Initial exam negative	Repeat exam within one week	*p-value*	False negative result or follow up beyond 90 days	False negative result	*p-value*
VQ						
Asthmatics	2667	51 (1.9%)	*0.547*	2463	10 (0.4%)	*0.015*
Non-asthmatics	7746	163 (2.1%)		6273	57 (0.9%)	
CTPA						
Asthmatics	1373	8 (0.6%)	*0.796*	1190	23 (1.9%)	*0.347*
Non-asthmatics	5118	33 (0.6%)		3838	59 (1.5%)	

Table 4. Sub-group of asthmatic patients with documented asthma medication prescription in the preceding year compared to the non-asthmatic group.

	Negative	Non-diagnostic	*p-value*	Positive	*p-value*	Repeat exam after negative	*p-value*	False-negative	*p-value*
VQ									
Asthma with medic-ation (n=1,666)	1,511 (90.7%)	60 (3.6%)	*0.689*	95 (5.7%)	*0.072*	27 (1.8%)	*0.634*	4/1430 (0.3%)	*0.015*
Non-asthmatics (n=8,672)	7,746 (89.3%)	330 (3.8%)		596 (6.9%)		163 (2.1%)		57/6273 (0.9%)	
CTPA									
Asthma with medic-ation (n=960)	833 (86.8%)	15 (1.6%)	*0.932*	112 (11.7%)	*<0.001*	6 (0.7%)	*0.944*	18/716 (2.5%)	*0.063*
Non-asthmatics (n=6,225)	5,118 (82.2%)	95 (1.5%)		1,012 (16.3%)		33 (0.6%)		59/3838 (1.5%)	