ORIGINAL RESEARCH

Derivation of a screening tool to identify patients with right ventricular dysfunction or tricuspid regurgitation after negative computerized tomographic pulmonary angiography of the chest

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Abstract: Many dyspneic patients who undergo computerized tomographic pulmonary angiography (CTPA) for presumed acute pulmonary embolism (PE) have no identified cause for their dyspnea yet have persistent symptoms, leading to more CTPA scanning. Right ventricular (RV) dysfunction or overload can signal treatable causes of dyspnea. We report the rate of isolated RV dysfunction or overload after negative CTPA and derive a clinical decision rule (CDR). We performed secondary analysis of a multicenter study of diagnostic accuracy for PE. Inclusion required persistent dyspnea and no PE. Echocardiography was ordered at clinician discretion. A characterization of isolated RV dysfunction or overload required normal left ventricular function and RV hypokinesis, or estimated RV systolic pressure of at least 40 mmHg. The CDR was derived from bivariate analysis of 97 candidate variables, followed by multivariate logistic regression. Of 647 patients, 431 had no PE and persistent dyspnea, and 184 (43%) of these 431 had echocardiography ordered. Of these, 64 patients (35% [95% confidence interval (CI): 28%–42%]) had isolated RV dysfunction or overload, and these patients were significantly more likely to have a repeat CTPA within 90 days ($P = .02$, χ^2 test). From univariate analysis, 4 variables predicted isolated RV dysfunction: complete right bundle branch block, normal CTPA scan, active malignancy, and CTPA with infiltrate, the last negatively. Logistic regression found only normal CTPA scanning significant. The final rule (persistent dyspnea + normal CTPA scan) had a positive predictive value of 53% (95% CI: 37%–69%). We conclude that a simple CDR consisting of persistent dyspnea plus a normal CTPA scan predicts a high probability of isolated RV dysfunction or overload on echocardiography.

Keywords: echocardiography, pulmonary hypertension, emergency medicine, venous thromboembolism, tomography, spiral computed.

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In the past decade, multidetector-row computerized tomographic pulmonary angiography (CTPA) has become the imaging mainstay in the diagnosis and exclusion of acute pulmonary embolism (PE). CTPA can also disclose clinically important alternative diagnoses, most often pulmonary infiltrates suggestive of pneumonia.[1,2] However, CTPA is not without harm and has been known to cause adverse effects, including radiation exposure, contrast nephropathy, and false positive diagnoses.[3-10] Despite these risks, the rate of CTPA recidivism has increased in recent years. For example, in one study, almost 40% of patients who had CTPA in the years 2000–2001 underwent a second CTPA scan that was negative for PE within the next few years.[11]

Approximately 70% of patients who undergo CTPA scanning have dyspnea as a chief complaint, and many of these patients continue to have dyspnea despite normal imaging studies and a negative emergency department (ED) evaluation.[12] Persistent dyspnea is a major reason that many patients return to an ED and often receive a repeat CTPA scan.[11] These data suggest that pathologies

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other than PE are responsible for persistent/recurrent symptoms and recurrent use of health care resources such as CTPA.

Pulmonary hypertension (PH) is a proliferative and sometimes obstructive vasculopathy defined by a mean pulmonary arterial pressure higher than 25 mmHg with a normal pulmonary arterial capillary wedge pressure. If left untreated, PH can cause right ventricular (RV) failure and death. PH has multiple etiologies, including idiopathic, hereditary, connective-tissue disease, HIV, congenital heart disease, and portal hypertension (collectively termed "pulmonary arterial hypertension" [PAH]), or it may occur as a secondary complication of treatable diseases, including left heart disease, chronic lung disease, and sleep-disordered breathing.[13-17] However, although PH has major implications on morbidity and mortality, recent studies suggest that it is frequently overlooked and underrecognized.[18,19] Early diagnosis and treatment improve outcomes. Since RV function determines functional status, exercise capacity, and outcomes in PH, and since RV dysfunction is commonly observed in PH patients, we hypothesized that a substantial portion of patients with persistent dyspnea, despite negative CTPA for PE, have unrecognized RV dysfunction or overload on echocardiography that contributes to persistent symptoms and CTPA recidivism.[20,21] The identification of such patients would allow for the diagnosis and treatment of correctable etiologies (e.g., PAH, chronic heart or lung disease, chronic sleep-disordered breathing). In chronic obstructive pulmonary disease (COPD), RV dysfunction may precede the development of frank PH.[22]

One prior study reported on a subset of ED patients with dyspnea in the PRIDE study who underwent echocardiography as part of standard care.[23] In this sample of 134 patients, the authors found that 20% had RV hypokinesis and 30% had moderate or severe tricuspid regurgitation. However, to our knowledge, no prior literature has examined the frequency of RV dysfunction or overload after negative CTPA. We therefore performed this study on patients with negative CTPA scanning and persistent dyspnea to derive a simple clinical decision rule (CDR) to predict a high probability of RV dysfunction or overload on echocardiography and to test whether RV dysfunction was associated with CTPA recidivism.

METHODS

Study design

This was a secondary analysis of a 4-center prospective, noninterventional study of diagnostic accuracy. The details of the methods have been published previously.[12] For the main analysis, we included only patients who had a CTPA negative for PE, had persistent dyspnea, and had transthoracic echocardiography performed within 1 week of enrollment.

Study setting and population

Patients undergoing CTPA scanning for suspected PE were prospectively enrolled at 4 academic medical centers in the United States: Carolinas Medical Center, Charlotte, North Carolina; Northwestern Memorial Hospital, Chicago, Illinois; Wake Forest University Baptist Hospital, Winston-Salem, North Carolina; and Baystate Hospital, Springfield, Massachusetts. All patients provided written informed consent. The study was approved by the institutional review boards of the 4 participating centers. The study protocol was registered on ClinicalTrials.gov before enrollment (identifier NCT00368836).

Experienced research coordinators initiated the screening process with discovery of an order entry for a CTPA scan from anywhere within the hospital, 6 days per week, 12 hours per day. Based on preliminary work that showed that CTPA scans were ordered in equal proportions for inpatients and ED patients, the screening process was designed to produce equal proportions of enrolled inpatients and outpatients.[24] Inclusion criteria required that patients had 1 of 15 signs or symptoms of PE and 1 of 21 known risk factors for PE (Table 1) and had a CTPA scan ordered.[6] Patients were excluded if they were unlikely to provide follow-up (e.g., imprisonment, homelessness, no telephone, history of noncompliance) or if they were hemodynamically unstable or intubated, had prior fibrinolytic treatment within 48 hours, had PE diagnosed within the last 6 months and were currently receiving systemic anticoagulation, had known active tuberculosis, or refused to give consent. Patients were enrolled within 24 hours of CTPA imaging.

Study protocol

CTPA images were obtained at each site as part of standard care with 64-channel multidetector equipment, capable of $\leq$2.5-mm collimation.[6] Intravenous contrast was given to all patients according to local protocol; a computer-controlled mechanized timing injector was used in all cases. Images were obtained with energy, pitch, and rotation settings as required for the patient's body habitus.

Contiguous 1.25-mm-thick images were routinely reconstructed at mediastinal (width: 400 Hounsfield units [HU]; center: 0 HU) and lung (width: 1,600 HU; center: 600 HU) window settings. All patients had reconstructions that included transverse, coronal, and sagittal views. Images were converted to a digital file with a Dig-

Table 1. Predictor variables: demographics and symptoms and comorbidities

	Echo done (n = 184)		Echo not done (n = 247)			Echo with isolated RV dysfunction or overload (n = 64)		Echo with normal RV and LV function (n = 75)		
	n	%	n	%	P	n	%	n	%	P
Inpatient, acute care	93	51	86	35	.001	24	38	38	51	.120
Inpatient, rehabilitation	2	1	3	1	.903	2	3	0	0	.123
ED patient	84	46	150	61	.002	36	56	34	45	.199
Male	77	42	83	34	.080	20	31	33	44	.123
Hispanic	10	5	13	5	.938	2	3	2	3	.872
Black	62	34	80	32	.775	20	31	23	31	.941
Native American	1	1	0	0	.246	0	0	1	1	.354
White	118	64	161	65	.821	42	66	50	67	.897
Asian	1	1	0	0	.246	0	0	1	1	.354
Alternate diagnosis more likely than PE	96	52	124	50	.685	31	48	39	52	.675
Chest pain reproduced on palpation	29	16	49	20	.277	10	16	13	17	.787
Pleuritic chest pain	47	26	83	34	.071	17	27	19	25	.869
Substernal chest pain	29	16	60	24	.030	10	16	15	20	.503
Angina-like pain	4	2	8	3	.506	2	3	2	3	.872
Unilateral arm or leg swelling	33	18	35	14	.289	12	19	15	20	.853
New onset dyspnea	129	70	174	70	.940	44	69	54	72	.675
Dyspnea worse than usual/persistent	31	17	50	20	.372	8	13	11	15	.711
Syncope	6	3	4	2	.263	3	5	3	4	.842
Chest pain	67	36	97	39	.545	24	38	29	39	.888
Confusion	5	3	9	4	.592	1	2	3	4	.392
Upper abdominal pain	9	5	24	10	.062	4	6	5	7	.921
Upper back pain	17	9	30	12	.338	4	6	9	12	.246
Hemoptysis	6	3	6	2	.604	2	3	2	3	.872
Dizziness	30	16	51	21	.254	10	16	14	19	.636
Cough	69	38	117	47	.041	25	39	25	33	.483
Limb swelling	15	8	12	5	.163	5	8	7	9	.750

Note: Echo: echocardiography; ED: emergency department; LV: left ventricular; PE: pulmonary embolism; RV: right ventricular.

ital Imaging and Communications in Medicine format, devoid of any annotations or protected health information, and were transferred to an independent reference reading (IRR) laboratory (Medical Metrics, Houston). Radiologists read the examinations on a standard picture-archiving and communication workstation and were free to modify their window settings as needed.

Clinical, breath, and blood data collection. To minimize missing or biased data and to simulate the knowledge held by decider clinicians, clinical data were obtained in real time at the bedside, as opposed to chart review, including all data in Tables 1 and 2. Each data field had an explicit definition, and coordinators were trained by the principal investigator (JK) according to an explicit set of

Table 2. Predictor variables: comorbidities

	Echo done ($n = 184$)		Echo not done ($n = 247$)			Echo with isolated RV dysfunction or overload ($n = 64$)		Echo with normal RV and LV function ($n = 75$)		
	n	%	*n*	%	*P*	*n*	%	*n*	%	*P*
No prior lung disease	133	72	158	64	.068	47	73	49	65	.303
COPD	20	11	34	14	.369	8	13	11	15	.711
Asthma	32	17	51	21	.396	11	17	14	19	.821
Other nonmalignant lung disease	12	7	18	7	.757	3	5	6	8	.429
Never smoked	118	64	141	57	.140	40	63	47	63	.984
Past smoker, stopped	31	17	54	22	.196	13	20	14	19	.807
Smoker, ≤10 cigarettes/day	21	11	32	13	.630	6	9	10	13	.466
Smoker, >10 cigarettes/day	19	10	25	10	.945	6	9	7	9	.993
Malignancy, prior history	14	8	18	7	.900	5	8	6	8	.967
Malignancy, under treatment	19	10	31	13	.476	11	17	5	7	.053*
Kidney dialysis	3	2	4	2	.993	0	0	2	3	.188
Warfarin in past 7 days	22	12	26	11	.641	5	8	8	11	.565
Recent surgery	17	9	47	19	.005	6	9	8	11	.801
Bed rest or hospitalization, >72 h	25	14	41	17	.390	10	16	8	11	.385
Current trauma	2	1	3	1	.903	0	0	1	1	.354
Recent trauma	0	0	4	2	.083	0	0	0	0	NA
Thrombophilia	1	1	5	2	.194	0	0	0	0	NA
Estrogen replacement therapy	10	5	25	10	.078	3	5	5	7	.618
Pregnancy or post partum	4	2	3	1	.436	3	5	1	1	.238
Immobility>48 h in past 3 days	3	2	6	2	.566	0	0	2	3	.188
Paralysis of one or more limbs	2	1	2	1	.767	1	2	0	0	.277
Stroke	4	2	1	0	.090	1	2	2	3	.655
Left heart failure	22	12	21	9	.237	6	9	6	8	.774
Intravenous drug use	1	1	1	0	.834	1	2	0	0	.277
DVT without PE	3	2	7	3	.412	0	0	2	3	.188
Active connective-tissue disease	10	5	8	3	.260	2	3	4	5	.523
Focal infection	17	9	25	10	.760	8	13	4	5	.134
New onset renal failure	3	2	3	1	.716	0	0	2	3	.188
Neuromuscular disease	1	1	0	0	.246	0	0	1	1	.354
BMI > 36	42	23	65	26	.407	18	28	17	23	.460

Note: BMI: body mass index; COPD: chronic obstructive pulmonary disease; DVT: deep venous thrombosis; Echo: echocardiography; LV: left ventricular; NA: not applicable; PE: pulmonary embolism; RV: right ventricular.

* $P < .1$.

standard operating procedures on how to collect them. Vital signs recorded were those closest in time to when the patient was enrolled, and all pulse oximetry readings were obtained with the patient breathing room air. Blood samples were drawn by qualified phlebotomists within 12 hours of CTPA scanning, and the D-dimer assay and fibrinogen concentrations were analyzed on instruments cleared by the US Food and Drug Administration.[12] For collection of breath data, including end-tidal CO_2 and O_2, and respiratory mechanical values (tidal volume, minute ventilation, inspiratory and expiratory flow rates and times, airway dead space volume, and oxygen and CO_2 volume), patients breathed room air, wore a nose clip, and breathed into a duckbill mouthpiece for 1–2 minutes, as previously described.[24]

CTPA interpretation. Interpretations by the IRR laboratory (Medical Metrics), as well as the site interpretation, were integrated into this analysis. At the site hospitals, images were interpreted by board-certified hospital radiologists who had completed a fellowship in emergency radiology or body imaging. Later, at the IRR laboratory, images that were stripped of protected health information and any added comments or markings were interpreted by 1 of 2 board-certified radiologists who had completed fellowship training in body imaging. The IRR radiologists interpreted images as "no PE," "positive for acute PE", or "positive for chronic PE." Chronic PE was characterized by 3 criteria: indistinct or fuzzy margins of the filling defect, adherence of clot to the vessel wall, and a webbed or "plexiform" appearance of the filling defect.[25,26] "Positive for other finding" was further graded, including a specific code for pulmonary infiltrate suggestive of pneumonia (which had to be read both at the site and by the IRR) or parenchymal lung disease. Parenchymal lung disease was considered present if the IRR indicated findings of emphysema, fibrosis, scarring, or diffuse ground-glass appearance. Radiologists were not asked to systemically grade the severity of these findings. They could, however, make a comment about the finding, and many used the words "mild," "moderate," or "severe." All CTPA scans were also evaluated for evidence of RV dilation, defined as a ratio of the RV diameter to the left ventricular (LV) diameter greater than 0.9 in transverse plane.[27,28] The IRR radiologist also dichotomously recorded a field designated as "signs of pulmonary hypertension," based on findings of enlarged diameter (RV/LV diameter ratio >0.9) with or without contrast reflux into the vena cava, dilated central pulmonary arteries (e.g., diameter of main pulmonary artery greater than that of ascending aorta), tortuous pulmonary arteries, vascular pruning, and/or a mosaic perfusion pattern, defined as sharply demarcated regions of variable attenuation without evidence of destruction or displacement of pulmonary vessels.[29] All parameters were weighed equally, and radiologists were allowed autonomy to put these findings together in making a dichotomous assessment. A normal CTPA scan was defined as having no significant pathological finding. Interpretations of CTPAs at each site were performed as part of standard care, and the final, written interpretation entered into the medical record was abstracted with a standardized approach to determine the site reading.

Echocardiography. Transthoracic echocardiograms were performed within 7 days after CTPA scanning at the discretion of the clinical care team. All echocardiograms were performed in IAC echocardiography-approved laboratories, using contemporaneous equipment, and were interpreted by board-certified cardiologists with specialty training in echocardiography. We included only results of echocardiograms that had adequate acoustic imaging to evaluate RV morphology and function. We abstracted data from the standard echocardiographic clinical report form. RV dysfunction or overload was defined as present with any one of the following: cardiologist qualitative interpretation of RV hypokinesis, dilation (defined as an end-diastolic diameter >35 mm in the apical 4-chamber view), or evidence of PH (peak tricuspid regurgitant jet velocity >2.7 m/s, obtained by continuous-wave spectral sampling from reliable waves).[30] Normal LV function required an ejection fraction greater than 45% and no evidence of diastolic dysfunction.

Clinical follow-up. All patients had telephone follow-up at 90 days. A scripted query was used, and a specific data collection template was designed to discover interval adverse events; diagnostic testing, including CTPA scanning with the results; and any change in treatment status.

Data analysis

The primary patient sample consisted of those with persistent dyspnea and no PE on CTPA. Persistent dyspnea was defined as the patient's statement that he or she had the sensation of shortness of breath while breathing room air at rest.

It could be expected that clinicians selected patients with more severe symptoms for echocardiography; therefore, the first analysis compares frequency and parametric clinical variables with a χ^2 test and an unpaired t test, respectively, between patients with and without echocardiography. Specifically, we compared the 97 clinical vari-

ables in Tables 1–4. To create the prediction rule, all candidate predictor variables were included and screened with univariate analysis that used a χ^2 test for frequency data and an unpaired *t* test for parametric data. Dichotomous variables with $P < .1$ were entered into multivariate logistic regression analysis. Parametric values with $P < .1$ were subjected to receiver operating characteristic (ROC) analysis to determine whether they had significant predictive value (i.e., lower limit of 95% confidence interval [CI] above 0.5). Logistic model fit was assessed by *P* values from the Pearson's goodness-of-fit χ^2, the Hosmer-Lemeshow test, the pseudo-R^2 (McFadden), and the area under the ROC curve in the derivation data set (*C* statistic).[31,32]

RESULTS

Characteristics of the study population and prevalence of RV dysfunction

Patients were enrolled from January 30, 2007, to April 27, 2008. Figure 1 shows a flow diagram of patients, starting with subjects screened for inclusion and ending with repeated CTPA instances. Six hundred seventy-eight patients signed a consent form and underwent CTPA, and 647 had complete data, including a CTPA and clinical, blood, and breath sample data. The criterion standard for any filling defect consistent with PE was found in 120 of the 647 patients (18% [95% CI: 15%–22%]). Ninety-six patients did not have persistent dyspnea, leaving 431 patients with persistent dyspnea. As part of usual care, clinicians ordered transthoracic echocardiography that yielded adequate acoustic images for 186 of these 431 patients (42%), with 2 having images inadequate to assess RV function, leaving 247 who did not undergo echocardiography. Of the 184 patients with usable echocardiography, 64 (35% [95% CI: 28%–42%]) had isolated RV dysfunction or overload, 45 (24%) had LV dysfunction, and 75 (41%) had normal RV and LV function (Fig. 1). Of the 64 patients with an abnormal RV on echo, 20 had RV dilation or hypokinesis, together with an RV systolic pressure higher than 35 mmHg; 24 had only dilation or hypokinesis; and 20 had RV systolic pressure higher than 35 mmHg with normal RV size and contraction. Patients with LV dysfunction were not included in the analysis. On follow-up, 54 of the 647 patients (8%) had a repeat CTPA for recurrent dyspnea.

Tables 1–4 compare predictor variables between patients with (n = 184) and without (n = 247) echocardiography. These tables then compare patients who had echocardiography between those with isolated RV dysfunction (n = 64) and those with normal RV and LV function (n = 75). Table 1 compares demographic data and symptoms, Table 2 compares comorbid conditions, Table 3 compares measured continuous variables (e.g., vital signs and respiratory data), and Table 4 compares bivariate results (e.g., CTPA and electrocardiographic results). Of note, the prevalence of parenchymal lung disease on CTPA was the same (23%) in the group that had echocardiography and in the group that did not, suggesting that this finding did not drive the decision to order or not order an echocardiogram.

Differences between patients with and without echocardiography

Comparisons of patients with and without echocardiography in Tables 1–4 were performed with a χ^2 or unpaired *t* test, yielding $P < .05$ for age, inspiratory and expiratory times, cough, recent surgery, and inpatient status. In particular, patients who underwent echocardiography were more likely to be inpatients or ED patients, were less likely to have substernal chest pain, pleuritic chest pain, or cough, and were less likely to have had recent surgery. Furthermore, they were likely to be older and to have a lower Borg score. They were less likely to have an S1Q3T3 pattern on electrocardiogram, but more likely to have T wave inversions.

Parameters associated with RV dysfunction

In the group undergoing echocardiography (n = 184), 64 (35%) patients exhibited signs of RV dysfunction or overload (Fig. 1). Seventy-five (41%) patients had a normal echocardiogram. Forty-five (24%) patients exhibited isolated LV dysfunction; these patients were not included in the analysis. The probability of isolated RV dysfunction or overload on echocardiography was higher in ED patients (36/86, 42%) than in inpatients/rehabilitation patients (26/98, 27% [95% CI for difference of 15%: 16%–29%], P = .02, exact binomial test). Because radiologists found RV dilation (defined as RV/LV diameter ratio > 0.9) on CTPA in only 7 patients, 4 of whom underwent echocardiography, this variable was not analyzed.

To select candidate variables for entry into multivariate regression analysis, we compared data between the patients with isolated RV dysfunction and the patients with normal echocardiograms. Analysis found that the mean values of the parametric variables age and fibrinogen were elevated with isolated RV dysfunction. However, neither value had a significant area under the ROC curve and were subsequently discarded. Dichotomous variables with $P < .1$ positively associated with isolated RV dysfunction included complete right bundle branch block, normal in-

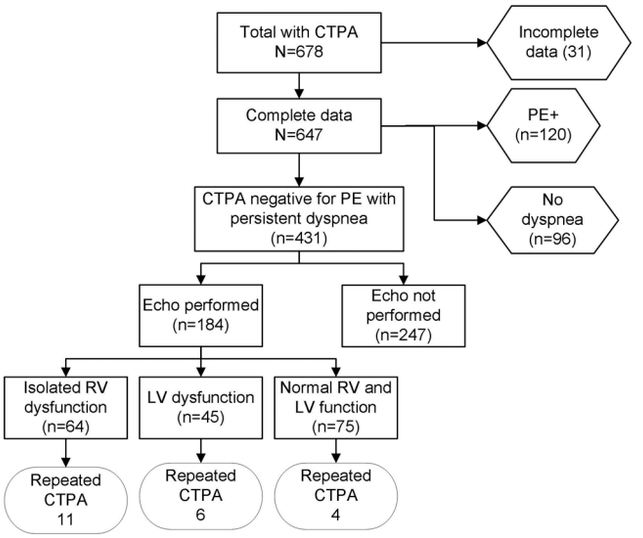

Figure 1. Flow diagram of patients enrolled and results of testing. CTPA: computerized tomographic pulmonary angiography; LV: left ventricular; PE: pulmonary embolism; RV: right ventricular.

dex CTPA scan, and malignancy under treatment. CTPA with infiltrate had a negative association.

Outcome data

Table 5 compares outcome data in a fashion similar to that of the previous tables. Patients with isolated RV dysfunction were more likely to be newly diagnosed with COPD or to have a repeat CTPA scan within 90 days. Interestingly, none of the 36 patients in Table 5 with a repeat CTPA scan had a new, acute pathogenic process discovered that was not present on the index CTPA scan.

The 4 predictor variables retained after univariate and ROC analysis (complete right bundle branch block, normal index CTPA scan, malignancy under treatment, and CTPA with infiltrate) were entered into a logistic regression analysis. Table 6 shows the equation coefficients and the corresponding P values for these variables. The model had good fit, demonstrated by a Pearson's goodness-of-fit χ^2 result of $P = .52$, a McFadden pseudo-R^2 of 0.92, and a Hosmer-Lomeshow test result of $P = .95$. This analysis showed that only one variable, normal index CTPA scan, had significance. Thus, we constructed a final rule consisting of persistent dyspnea plus a normal CTPA scan as the CDR to predict a high probability of isolated RV dysfunction on echocardiography. This rule was positive in 41 patients who underwent echocardiography, of whom 22 (53%) had isolated RV dysfunction (positive predictive value: 53% [95% CI: 37%–69%]). Five of the 22 rule-positive (CDR+) patients had a repeat CTPA scan within 90 days.

DISCUSSION

We found that 64 of 184 (35% [95% CI: 28%–42%]) patients who had persistent dyspnea after CTPA and a clinical picture that caused clinicians to order echocardiography had isolated RV dysfunction or overload. Hypothetically, had echocardiography been ordered for all 431 patients with dyspnea after CTPA and all other patients had a normal echocardiogram, the prevalence of isolated RV dysfunction or overload would still have been 64 of 431, or 15% (95% CI: 12%–18%). However, it is likely that the performance of echocardiographic studies in the patients who did not undergo echocardiography would have revealed at least a few additional cases of RV dysfunction, thus likely increasing that number. Restricting the sample to patients with dyspnea and a normal CTPA scan (i.e., CDR+) increased the prevalence of RV dysfunction or overload to 53% (95% CI: 37%–69%). Had the derived CDR been applied to the entire 647-patient population, the rule would have been positive and therefore suggests that 103 (16%) of patients should have been referred for echocardiography.

Isolated RV dysfunction on echocardiography was defined as a composite of RV hypokinesis and/or evidence of pathological tricuspid regurgitation, and it excluded patients with systolic or diastolic LV dysfunction. Our 35% prevalence of isolated RV dysfunction or overload appears to lie within the 95% CI for RV dysfunction from the PRIDE study (Chen et al.[23]), which found a 30% (95% CI: 22%–39%) prevalence of moderate or severe tricuspid regurgitation. The two studies cannot be directly compared because our patients all had negative CTPA scanning before echocardiography, and the study by Chen et al.[23] was not intended to discover the rate of isolated RV dysfunction and therefore did not report this variable explicitly. In a large sample of Veterans Affairs patients (n = 10,471, 97% male) who underwent transthoracic echocardiography, Maron and colleagues[18] found that 14% (95% CI: 13.0%–14.4%) had estimated pulmonary artery systolic pressures of at least 40 mmHg. However, this study included any echocardiography that was not done to evaluate a specific cardiovascular disease (e.g., cardiac tamponade).

The prevalence of isolated RV dysfunction in our sample was significantly higher in patients from the ED setting (42% [95% CI 31%–52%]). This is important, because at most hospitals, more than half of all CTPA scans are ordered from the ED, and most show no significant pathology.[11,33] At present, no clinical guideline exists to suggest a next step for the persistently dyspneic patient with

Table 3. Predictor variables measured on day of enrollment (continuous data)

	Echo done (n = 184)		Echo not done (n = 247)			Echo with isolated RV dysfunction or overload (n = 64)		Echo with normal RV and LV function (n = 75)		
Parameter	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
General findings and vital signs[a]										
Age, years	57.2	15.2	52.2	15.7	.001	59.8	15.5	54.7	14.4	.044*
Heart rate, beats/min	83.9	19.4	85.9	17.5	.279	81.3	19.9	84.0	18.0	.395
Respiratory rate, breaths/min	19.6	3.4	19.6	5.9	.934	19.6	3.3	19.6	3.9	.955
Systolic blood pressure, mmHg	130.6	20.2	127.0	21.3	.081	131.6	20.1	131.0	21.2	.859
Diastolic blood pressure, mmHg	74.9	16.3	73.7	12.6	.398	75.4	19.2	73.7	14.8	.558
SaO_2, %	97.0	2.4	97.3	2.5	.337	96.9	2.4	97.1	2.4	.778
Temperature, °F	97.9	1.1	98.1	1.1	.028	97.9	1.0	97.9	1.1	.780
BMI	31.1	9.2	31.1	8.8	.982	32.4	9.8	30.5	8.7	.241
Borg score	3.0	2.5	3.6	2.4	.030	3.2	2.6	2.9	2.4	.490
Test results										
D-dimer, ng/mL	1,393	2,196	1,222	1,692	.362	1,248	2,243	1,204	1,116	.881
Fibrinogen, mg/dL	586	733	582	628	.944	777	1,091	462	398	.022*
Respiratory parameters[b]										
Respiratory rate, breaths/min	18.1	6.5	17.0	6.2	.074	17.5	5.8	17.8	6.8	.801
Maximum breath temperature, °F	36.0	0.7	35.9	0.7	.084	36.0	0.6	36.1	0.7	.155
Minimum etO_2, mmHg	102.6	8.3	103.5	8.3	.303	102.7	9.0	102.2	7.4	.758
Median etO_2, mmHg	106.8	8.4	107.4	8.2	.396	106.5	8.5	106.2	7.8	.831
Maximum $etCO_2$, mmHg	37.5	5.9	37.8	6.2	.541	37.6	5.4	38.0	5.4	.669
Median $etCO_2$, mmHg	35.7	5.9	36.3	6.0	.353	36.1	5.3	36.3	5.4	.788
Minute V_{O_2}, mL	653	221	658	242	.800	659	213	627	233	.395
Minute V_{CO_2}, mL	497	168	513	194	.372	506	159	480	177	.366
Respiratory quotient	0.77	0.08	0.79	0.11	.058	0.77	0.09	0.77	0.09	.941
Inspiratory flow rate, L/min	−51.9	20.9	−51.1	18.8	.680	−51	20.9	−52.5	22.8	.719
Expiratory flow rate, L/min	52.8	24.0	51.0	22.4	.416	51	23.8	52.3	23.9	.803
Tidal volume, median, mL	691	266	728	285	.169	703	266	695	298	.875
Airway dead space, mL	231	38	228	37	.334	233	42	228	37	.482
Total minute ventilation, mL	11,751	3,675	11,644	4,111	.779	11,612	3,716	11,429	3,376	.761
Alveolar minute ventilation, mL	7,620	2,824	7,806	3,286	.538	7,608	2,872	7,427	2,799	.707
Inspiratory time, median, s	1.53	0.55	1.65	0.63	.035	1.53	0.55	1.57	0.59	.723
Expiratory time, median, s	2.16	0.77	2.35	0.98	.031	2.23	0.79	2.20	0.76	.863

Note: BMI: body mass index; Echo: echocardiography; etO_2: end-tidal oxygen; $etCO_2$: end-tidal carbon dioxide; LV: left ventricular; RV: right ventricular; SaO_2: saturation level of oxygen; V_{O_2}: volume of oxygen; V_{CO_2}: volume of carbon dioxide.

[a] Vital signs measured in emergency department triage.

[b] Measured with mouthpiece and noseclips in place (see "Methods").

* $P < .1$.

no diagnosis after CTPA. Patients with isolated RV dysfunction or overload had a significantly higher rate of negative CTPA recidivism, suggesting continued symptoms and unwise use of healthcare resources. This is in line with data from the PAH literature that indicate that patients frequently are undiagnosed for 2 years or more, after being subjected to myriad diagnostic tests, before they are ultimately diagnosed with PAH.[34,35] These find-

Table 4. Predictor variables measured on day of enrollment (bivariate data)

	Echo done ($n = 184$)		Echo not done ($n = 247$)			Echo with isolated RV dysfunction or overload ($n = 64$)		Echo with normal RV and LV function ($n = 75$)		
Parameter	*n*	%	*n*	%	*P*	*n*	%	*n*	%	*P*
Elevated serum creatinine (>1.5 mg/dL)	10	5	11	4	.762	3	5	4	5	.882
Elevated serum troponin I (>99th percentile)	27	15	15	6	.080	6	9	5	7	.500
Index CTPA normal	41	22	62	24	.50	22	34	14	19	.035*
Index CTPA infiltrate[a]	9	5	25	10	<.001	0	0	6	8	.021*
Index CTPA with signs of PH[b]	7	4	1	0	.01	4	6	1	1	.120
Index CTPA parenchymal disease[a,c]	42	23	66	23	.28	18	28	13	17	.120
Electrocardiogram findings										
Normal sinus rhythm	141	77	175	71	.180	51	80	62	83	.653
Sinus tachycardia	36	20	47	19	.889	11	17	10	13	.527
Incomplete RBBB	8	4	7	3	.396	1	2	5	7	.140
Complete RBBB	8	4	9	4	.710	5	8	0	0	.014*
ST depression	2	1	4	2	.641	0	0	0	0	NA
S1Q3T3	3	2	13	5	.048	1	2	1	1	.910
T wave inversion > 1 mm in V1–V4	8	4	3	1	.041	2	3	3	4	.782

Note: CTPA: computerized tomographic pulmonary angiography; Echo: echocardiography; LV: left ventricular; NA: not applicable; PH: pulmonary hypertension; RBBB: right bundle branch block; RV: right ventricular.

[a] Subset of "other findings" described in "Methods"; infiltrate required agreement by the site and the independent reading radiologist.

[b] At radiologist's discretion, based on findings of enlarged right ventricle with or without contrast reflux into the vena cava, dilated central pulmonary arteries, tortuous arteries, vascular pruning, and/or a mosaic perfusion pattern.

[c] Emphysema, fibrosis, scarring, ground-glass appearance.

* $P < .1$.

ings triggered a national early-diagnosis campaign for PH (http://www.sometimesitsph.org).[20,36] Our findings suggest that the ED would be an important setting to be included in such efforts. Data in Table 2 indicate that patients with isolated RV dysfunction or overload seldom had other severe associated comorbidities, such as COPD or end-stage cancer. We believe that, taken together, the data suggest that the isolated RV dysfunction or overload had a causative role in persistent symptoms. These data support a theoretical construct to develop an organized clinical protocol that would include echocardiography as an initial follow-up test for selected patients after negative CTPA scanning, followed by referral to a specialty clinic that can carry out a structured algorithm to evaluate for treatable causes of PH and/or RV dysfunction.[37]

We therefore derived a CDR as an initial step. Using the univariate-multivariate approach, the final rule consisted of 2 independent criteria: a negative CTPA scan and persistent dyspnea. More than half (53%) of the patients with echocardiography and a positive CDR had isolated RV dysfunction. In a companion paper[38] we found that in a validation sample of persistently dyspneic ED patients with negative CTPA scanning and with echocardiography, 33% (95% CI: 25%–42%) had isolated RV dysfunction. Next steps will be to devise a clinical pathway that refers CDR+ patients for transthoracic echocardiography, followed by appropriate referral.[37] Such a structured diagnostic approach will likely allow for identifying causes of RV dysfunction or overload and for initiating appropriate additional diagnostic and therapeutic mea-

Table 5. Outcomes based on echocardiography status

	Echo done ($n = 184$)		Echo not done ($n = 247$)			Isolated RV dysfunction or overload ($n = 64$)		Echo with normal RV and LV function ($n = 75$)		
Diagnosis/outcome	*n*	%	*n*	%	*P*	*n*	%	*n*	%	*P*
Sepsis	1	1	2	1	.74	0	0	0	0	NA
Deep venous thrombosis	1	1	3	1	.47	0	0	1	1	.35
Anxiety	2	1	2	1	.77	0	0	1	1	.35
Pneumonia	20	11	25	10	.80	8	13	5	7	.24
Coronary artery disease	4	2	2	1	.23	0	0	2	3	.19
Cardiomyopathy	2	1	1	0	.40	0	0	0	0	NA
Pericarditis	2	1	0	0	.10	0	0	2	3	.19
Rib fracture	0	0	1	0	.39	0	0	0	0	NA
Newly diagnosed COPD	7	4	4	2	.15	4	6	0	0	.03*
Heart failure	12	7	2	1	.00	3	5	1	1	.24
Pulmonary embolism	0	0	0	0	NA	0	0	0	0	NA
Chest pain, NOS	37	20	54	22	.66	0	0	0	0	NA
Pneumothorax	0	0	1	0	.39	0	0	0	0	NA
Asthma	1	1	5	2	.19	0	0	0	0	NA
Myocardial infarction	3	2	1	0	.19	0	0	0	0	NA
New solid tumor	1	1	2	1	.74	0	0	0	0	NA
New hematologic malignancy	2	1	0	0	.10	0	0	0	0	NA
Pulmonary arterial hypertension	0	0	0	0	NA	0	0	0	0	NA
Death	1	1	2	1	.74	0	0	0	0	NA
Other diagnosis	162	88	233	94	.08	40	63	55	73	.17
Any serious adverse event	36	20	68	28	.01	18	28	16	21	.35
No adverse events	109	59	167	68	.07	40	63	47	63	.98
Repeat CTPA within 90 days	22	12	14	6	.02	11	17	4	5	.03*

Note: All diagnoses were newly established. COPD: chronic obstructive pulmonary disease; CTPA: computerized tomographic pulmonary angiography; Echo: echocardiography; NA: not applicable; NOS: not otherwise specified.

* $P < .1$.

sures, with the ultimate goal of improving outcomes and decreasing unnecessary use of healthcare resources.

Limitations

In this derivation, the final rule was restricted to patients with a normal CTPA, which excluded patients with radiographic evidence of chronic diseases, such as cardiomegaly, emphysema, or scarring. In a secondary analysis, we created a variable with a broader definition, named "CTPA without acute process" (i.e., no PE, infiltrate, aortic dissection or aneurysm, pneumothorax, mediastinal mass, or lung mass). Substitution of that variable instead of the requirement for a normal CTPA in the CDR would have led to a predictive value positive of 64/179, or 36% (95% CI: 29%–43%). Other limitations to the work include our inability to determine whether patients with our definition of isolated RV dysfunction have treatable causes. For example, the potential contribution of World Health Organization group 3 PH is difficult to assess, because radiologists were not asked to systematically grade the severity of parenchymal abnormalities. However, most of our cases of parenchymal scarring were mild. This does not change our key message, however, that patients with persistent dyspnea and evidence of RV dysfunction need to undergo

Table 6. Results of logistic regression

Component	*B* coefficient	*P* value
Y-axis intercept	−0.519	.0222
Malignancy under treatment	1.129	.0517
Index CTPA normal	0.815	.0474*
Index CTPA infiltrate	−19.164	.998
Complete RBBB on ECG	19.353	.9974

Note: Analysis used variables with $P < .1$ for prediction of right ventricular dysfunction versus normal echocardiography in Tables 1–4. CTPA: computerized tomographic pulmonary angiography; ECG: electrocardiogram; RBBB: right bundle branch block.

* $P < .05$.

expert referral for identification of potentially treatable causes of dyspnea. Second, our echocardiographic basis for RV dysfunction includes heterogenous and controversial criteria, and we recognize that tricuspid regurgitation–derived indexes both over- and underestimate pulmonary arterial pressures.[39] We recognize that tricuspid regurgitation may occur with normal RV contractility, but in the setting of PH, moderate-to-severe tricuspid regurgitation worsens prognosis and is therefore considered to define RV dysfunction.[40] We emphasize the intent to use echocardiography as a screening criterion to move the patient on to a specialty clinic for more definitive diagnosis. Third, RV dysfunction can be caused by many pathologies.[20,36] The current data do not allow for any conclusions regarding the etiology of RV dysfunction. Fourth, although this CDR is intended to align patients at high risk for repeated CTPAs and repeated ED visits with treatment to reduce symptoms, the proposed protocol could unintentionally increase resource use and cost of care. Finally, the relationship between echocardiographic findings of RV dysfunction or overload and persistent symptoms are only associative; these abnormalities may signify pathology that drove patients back to the ED for repeat testing, or the findings, if known by clinicians, may have lowered their threshold to order a repeat CTPA. We do not have specific data to understand the decision-making process that clinicians used when they ordered repeat CTPA scans.

Conclusions

A simple clinical decision rule, consisting of a normal computerized tomographic pulmonary angiography scan and persistent dyspnea, predicts a high probability of isolated RV dysfunction or overload on echocardiography. Patients with these features may benefit from referral for echocardiography to evaluate for signs of pulmonary hypertension and/or RV dysfunction, with subsequent referral for specialty evaluation for identification of potentially treatable causes.

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