Endobronchial ultrasound: A novel screening test for pulmonary hypertension prior to major pulmonary surgery

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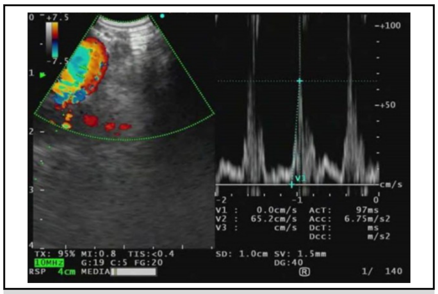
ABSTRACT

Objectives: Pulmonary hypertension (PH) is an important physiologic variable in the assessment of patients undergoing major thoracic operations but all too often neglected because of the need for right heart catheterization (RHC) due to the inaccuracy of transthoracic echocardiography. Patients with lung cancer often require endobronchial ultrasound (EBUS) as part of the staging of the cancer. We sought to investigate whether EBUS can be used to screen these patients for PH.

Methods: Patients undergoing a major thoracic operation requiring EBUS for staging were included prospectively in the study. All patients had also a RHC (gold standard). We aimed to compare the pulmonary artery pressure measurements by EBUS with the RHC values.

Results: A total of 20 patients were enrolled in the study. The prevalence of abnormal pulmonary artery pressure was 65% based on RHC. All patients underwent measurement of the pulmonary vascular acceleration time (PVAT) by EBUS with no adverse events. Linear regression analysis comparing PVAT and RHC showed a correlation ($r = -0.059$, -0.010 to -0.018, $P = .007$). A receiver operator characteristic curve (area under the curve = 0.736) was used to find the optimal PVAT threshold (140 milliseconds) to predict PH; this was used to calculate a positive and negative likelihood ratio following a positive diagnosis of 2.154 and 0.538, respectively.

Conclusions: EBUS interrogation of pulmonary artery hemodynamic is safe and feasible. EBUS may be used as a screening test for PH in high-risk individuals. (JTCVS Techniques 2024;23:146-53)



Endobronchial ultrasound evaluation of the pulmonary artery vascular acceleration time.

CENTRAL MESSAGE

Endobronchial ultrasound (EBUS) can meaningfully provide insight in relation to pulmonary artery hemodynamics and may be considered in the screening armamentarium for pulmonary hypertension.

PERSPECTIVE

Pulmonary hypertension is an underestimated clinical variable in the preoperative assessment of patients undergoing major pulmonary surgery. EBUS is a simple and promissory method with which to investigate pulmonary hypertension when compared with the gold standard RHC, in patients at high risk of PH and in need for EBUS for staging or diagnostic purposes.

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Abbreviations and Acronyms

BSE = British Society of Echocardiography
CI = confidence interval
COPD = chronic obstructive pulmonary disease
EBUS = endobronchial ultrasound
IQR = interquartile range
LMA = laryngeal mask airway
OSA = obstructive sleep apnea
PAP = pulmonary artery pressure
PH = pulmonary hypertension
PVAT = pulmonary artery acceleration time
RHC = right heart catheterization
TTE = transthoracic echocardiogram

Proper risk stratification before major pulmonary surgery is essential to a smooth postoperative outcome. Cardiac hemodynamics evaluation is indispensable in this patient population and can predict postoperative mortality and morbidity depending on the extent of resection[1-3]; however, the impact of pulmonary hypertension (PH) is often overlooked and almost never properly evaluated. The National Emphysema Treatment Trial highlighted the importance of PH in the mortality and morbidity of patients undergoing lung volume–reduction surgery, going as far as establishing PH as a contraindication to surgery.[4] Furthermore, PH could be one of the most important neglected physiologic variables leading to postpneumonectomy pulmonary edema.[5]

With an increased understanding of the effect of PH on intraoperative hemodynamics and outcomes, noninvasive screening approaches using echocardiography have been investigated generating a plethora of formulas.[6-11] Unfortunately, these models remain inaccurate,[12] lack validation,[13,14] and fail to predict patients who might require the gold-standard diagnostic right heart catheterization (RHC) and, therefore, preoperative medical optimization or intraoperative interventions.[15] These limitations in noninvasive testing are further accentuated in patients with obstructive sleep apnea (OSA) and those with underlying lung disease such as chronic obstructive pulmonary disease (COPD) with barrel-chest deformities.[16]

Multiple societies across the world recently addressed an epidemiologic discrepancy in the diagnosis of abnormal pulmonary artery pressures by decreasing the diagnostic threshold from 25 mm Hg to 20 mm Hg[17-19] mean pressure. This led to an increased incidence of PH,[20] which increased the positive predictive value of existing screening strategies and decreased the negative predictive value.[12]

Considering that patients undergoing major thoracic operations routinely undergo bronchoscopic staging with endobronchial ultrasound (EBUS),[21,22] we sought to investigate the feasibility, value, and accuracy of an EBUS-based method to evaluate pulmonary artery hemodynamics in patients scheduled for major pulmonary resection. We hypothesized that endobronchial evaluation of the pulmonary artery acceleration time (PVAT) by Doppler would feasibly and accurately provide insight regarding pulmonary vascular outflow physiology and hemodynamics.

METHODS

Following approval by the internal review board (PA: 2018-0500), 20 patients were prospectively recruited. All patients were scheduled to undergo a major thoracic operation and suffered from a clinical condition that could affect their pulmonary artery physiology, such as a diagnosis or suspicion of OSA, a diagnosis of COPD, or the need of a pneumonectomy. All patients required a staging EBUS preoperatively.

Endobronchial Ultrasonography

Following consent, patients underwent a staging endobronchial procedure under general anesthesia, with laryngeal mask airway (LMA), and with additional local analgesia obtained with 6 mL of 2% lidocaine applied to the tracheobronchial tree. First, a slim video diagnostic bronchoscope (Olympus BF-Q190; Olympus Surgical Technologies) was introduced through the LMA to examine the tracheobronchial tree of both lungs. Following this, a convex probe EBUS bronchoscope (Olympus UC180F; Olympus Surgical Technologies) was introduced through the LMA and was further used to evaluate the peribronchial anatomy. During the procedure, peribronchial lymph nodes were evaluated, and tissue samples were obtained when appropriate. The endobronchial evaluation of pulmonary artery pressure was via Doppler interrogation of the pulmonary artery through the right mainstem bronchus, in order to generate a PVAT in milliseconds, across 3 time points, regardless of heart rate.[8] The 2 measurements with the least variance were used in this analysis. The PVAT was defined as the time required for the pulmonary artery vascular flow to accelerate from minimal velocity to maximal velocity (V1 and V2, respectively, as calculated in Figure 1). This was performed using the EVIS EXERA III ultrasound processor (Olympus Surgical Technologies). Historically, a transthoracic echocardiogram (TTE) Doppler-generated PVAT of less than 105 milliseconds was characterized as being abnormal, in accordance with the British Society of Echocardiography (BSE) guidelines, where the pulmonary arterial systolic pressure has been estimated on echo by using the simplified Bernoulli equation from the peak tricuspid regurgitant velocity in patients with cardiac disease.[23] All measurements were performed by the same interventional pulmonologists (G.A.P., R.F.C.).

Right Heart Catheterization

All patients underwent cardiac catheterization under intravenous sedation. RHC generated measurements of mean pulmonary artery pressure (PAP), systolic PAP, and diastolic PAP using a standard fluid-filled catheter. All measurements were performed by the same interventional cardiologist (J.B.D.). A mean PAP of 20 mm Hg or greater was considered abnormal.[17-19]

Statistical Methods

The primary analysis aimed to evaluate whether the EBUS-generated PVAT measurements correlated with PAP measurements originating from the RHC procedure. The study was powered (n = 20) to provide a 95% confidence interval (95% CI) of 0.56 should an estimated correlation of 0.7 be discovered. The analysis used the mean of the 2 EBUS PVAT measurements and the RHC mean PAP values. We evaluated the measurements

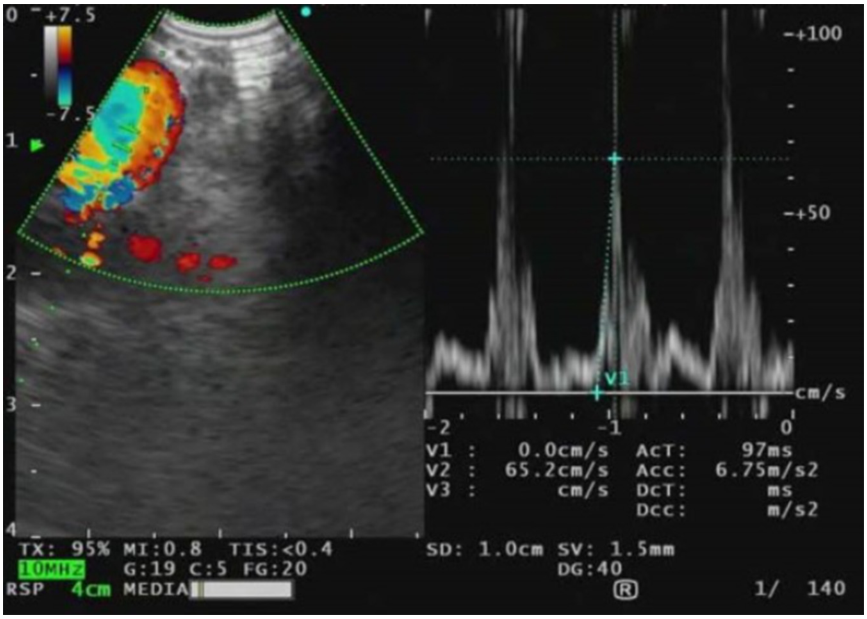

FIGURE 1. Olympus (EVIS EXERA III)-generated endobronchial ultrasound investigation of the pulmonary artery, with velocities graphically represented on an x-y axis. V1 represents a velocity of 0 cm/s, and V2 represents maximal velocity. AcT represents the acceleration time taken between V1 and V2.

from both modalities and their association with a Spearman correlation analysis and a univariate linear regression model in order to measure the strength and direction of the monotonic relationship. Using the equation generated from our regression model, the difference in measurement was evaluated using the Bland–Altman method. An area under the curve analysis of a receiver operator characteristic curve was performed. Data distribution was assessed using the Shapiro–Wilkes test. Lastly, a comparison of varying thresholds according to previously determined diagnostic criteria was also performed. All statistical analyses were performed using GraphPad Prism (version 9.3.1 for Windows; GraphPad Software).

RESULTS

Patient Population

All 20 patients were recruited between November 2018 and April 2023. Patients had a mean age of 69 years (standard deviation: 9 years), were predominantly female (n = 11, 55%), and usually had a history of smoking (n = 11, 55%). Patients underwent surgical evaluation for bronchogenic carcinoma, thymoma requiring en-bloc resection with lung, mesothelioma, and one case for obstructing broncholithiasis (no cancer on final pathology). Many patients had risk factors for PH due to a previous diagnosis or suspicion of OSA (heavy snoring), cardiac disease, or COPD (Table 1). Measurements of PAP occurred at an average of 6 days between one another (range, 1-20).

Endobronchial Ultrasound

All patients underwent endobronchial evaluation of PVAT, with a total of 3 measurements each. The median PVAT calculated using the aforementioned methodology in this cohort was 147.0 milliseconds (interquartile range [IQR], 107.0-183.0), and ranged from 82.5 to 250.0 milliseconds (Table 2). Based on BSE criteria (<105 milliseconds), 5 (25%) patients had abnormal readings that were suggestive of PH. There were no adverse events due to the endobronchial procedure in any of the patients included.

Right Heart Catheterization

All patients also underwent RHC, with mean PAP ($mPAP_{RHC}$) measurement. The median $mPAP_{RHC}$ in this cohort was 20.0 (IQR, 18.0-23.0), and ranged from 12.0 to 32.0. Based on the Sixth World Symposium on PH criteria (≥20 mm Hg), 13 (65.0%) patients had abnormal readings. In this cohort, the median pulmonary vascular resistance was 1.77 (IQR, 1.30-3.18), and the median pulmonary capillary wedge pressure was 11.5 (IQR, 10.0-14.3) (Table 2). There were no adverse events due to the cardiac catheterization procedure in any of the patients included.

Correlation Between Modalities

Considering the 5 patients with abnormal EBUS readings based on a threshold of 105 milliseconds, 4 also had abnormal RHC readings. Given a parametric distribution in our PVAT and $mPAP_{RHC}$ data, a Spearman correlation analysis was performed and revealed a coefficient of −0.56 (95% CI, −0.80 to −0.16, $P = .010$). The univariate linear regression analysis between $mPAP_{RHC}$ and PVAT

TABLE 1. Clinicopathologic variables of patients who met inclusion criteria and indication for endobronchial PAP evaluation

Patient ID	Age	Sex	Smoking status	Indication for PAP evaluation	Histopathology	TN status
1	70	Female	Never	Hx of snoring	Adenocarcinoma	T2aN0
2	60	Female	Ever	Dx of emphysema	Squamous cell carcinoma	T3N0
3	91	Male	Never	Hx of cardiac disease	Squamous cell carcinoma	T2N0
4	65	Male	Ever	Exercise intolerance	Adenocarcinoma	T2aN1
5	82	Male	Ever	Hx of cardiac disease	Squamous cell carcinoma	T3N0
6	68	Female	Never	Dx of OSA	Adenocarcinoma	T2N0
7	55	Female	Ever	Mass effect upon PA	Adenocarcinoma	T4N1
8	68	Male	Never	Dx of OSA	Sarcoma	T2N1
9	74	Female	Never	Hx of cardiac disease	Adenocarcinoma	T2aN0
10	73	Female	Ever	Hx of snoring	Broncholithiasis	n/a
11	75	Female	Ever	Hx of snoring	Adenocarcinoma	T3N2
12	48	Female	Never	Dx of OSA	Mesothelioma	T1N0
13	68	Female	Never	Dx of OSA	Adenocarcinoma	T2aN2
14	66	Male	Ever	Heavy smoker	Squamous cell carcinoma	T3N0
15	66	Male	Ever	Dx of emphysema	Adenocarcinoma	T2aN1
16	75	Female	Never	Advanced age	Adenocarcinoma	T2bN0
17	67	Male	Ever	Dx of OSA	Adenocarcinoma	T2bN0
18	76	Male	Ever	Dx of OSA	Adenocarcinoma	T2N0
19	65	Male	Ever	Dx of OSA	Adenocarcinoma	T1bN0
20	68	Female	Never	Dx of OSA	Thymoma	n/a

PAP, Pulmonary artery pressure; *TN*, tumor and nodal; *Hx*, history; *Dx*, diagnosis; *OSA*, obstructive sleep apnea; *PA*, pulmonary artery; *n/a*, not available.

(EBUS) revealed a weak but significant correlation (slope = −0.059; 95% CI, −0.010 to −0.018, $P = .007$, Figure 2). The univariate linear regression produced the following equation to generate a calculated mPAP from PVAT ($mPAP_{EBUS}$):

$$mPAP_{EBUS} = -0.059 * PVAT + 30.46$$

The difference between $mPAP_{EBUS}$ and the $mPAP_{RHC}$ was analyzed using the Bland–Altman method, which showed limits of agreement with a mean value of −0.003 and standard deviation of 4.439 (Figure 3).

Next, an area under the receiver-operating characteristic curve analysis was performed and found to be 0.736 when using a PVAT threshold of <140 milliseconds, leading to a sensitivity of 61.5% and specificity of 85.7% and accuracy of 65% (Figure E1). Using this new threshold in our cohort, the prevalence of patients with PH was found to be 45% based on EBUS measurements. This led to a positive likelihood ratio of 2.154 and negative likelihood ratio of 0.538 (Figure 4). In addition, we compared the previously published threshold of 105 milliseconds with the old RHC threshold of 25 mm Hg. Using these 2 values (105 milliseconds and 25 mm Hg), we found that EBUS achieved a sensitivity of 50.0%, specificity of 81.3%, and accuracy of 75.0%.

COMMENT

The medical optimization of patients with comorbidities before surgery is vital to the practice of surgery. PH may be a significant factor associated with perioperative morbidity and it is often neglected in the preoperative assessment. Current echocardiographic screening approaches are lacking in efficacy and accuracy, relying on RHC for accurate diagnosis, which is a step many thoracic surgeons prefer to avoid. The reported models based on TTE measurements continue to be inaccurate and there is real need for a reliable screening or diagnostic test to stratify the perioperative risks based on the PAP.

We present here a feasible test that would not use resources that are not already allocated to preoperative planning in patient population undergoing lung resection. We sought to investigate the feasibility and accuracy of evaluating the hemodynamics of the pulmonary outflow tract during routine preoperative endobronchial ultrasonographical staging. The method developed involved interrogating the acceleration time in the pulmonary artery, by monitoring the velocity curves of the flow of blood and measuring the time between lowest and maximal velocity. Interestingly, using a PVAT threshold of <140 milliseconds had better sensitivity for predicting PH than the current BSE guidelines of <105 milliseconds, which is used for TTE.

TABLE 2. Pulmonary artery hemodynamic readings of all patients

	Endobronchial ultrasound			Cardiac catheterization			
Patient ID	PVAT 1, ms	PVAT 2, ms	mPVAT, ms	mPAP, mm Hg	PVR, mm Hg	PWP, mm Hg	≥20 mPAP
1	134	136	135	21	2.14	12	Yes
2	75	91	83	20	3.2	4	Yes
3	102	118	110	29	3.17	16	Yes
4	172	166	169	21	1.09	11	Yes
5	89	89	89	23	1.25	17	Yes
6	236	250	243	12	0.44	10	No
7	79	86	82.5	32	3.29	15	Yes
8	182	193	187.5	20	15	12	Yes
9	129	122	125.5	31	2.56	18	Yes
10	161	192.5	176.75	22	1.6	14	Yes
11	97	97	97	15	1.3	7	No
12	224	268	246	16	1.4	8	No
13	242	258	250	20	1.7	12	Yes
14	197	206	201.5	18	3.3	10	No
15	140	140	140	19	2.29	9	No
16	152	161	156.5	18	1.68	11	No
17	156	150	153	18	1.2	11	No
18	97	97	97	31	4.3	19	Yes
19	129	129	129	23	1.84	11	Yes
20	177	187	182	20	1.3	13	Yes

PVAT, Pulmonary vascular acceleration time; *mPVAT*, mean pulmonary vascular acceleration time; *mPAP*, mean pulmonary artery pressure; *PVR*, pulmonary vascular resistance; *PWP*, pulmonary wedge pressure.

A screening test in medicine should possess qualities such as a good sensitivity, specificity, and safety. The greater the sensitivity and specificity, the more effective is the screening test. Although there is no universally agreed-upon threshold for what constitutes a good sensitivity and specificity, in general greater values are preferred. Commonly, a sensitivity and specificity of at least 80% or greater are considered reasonable for a screening test.[24]

In comparing the performance of our methodology, with that of other established screening modalities, such as

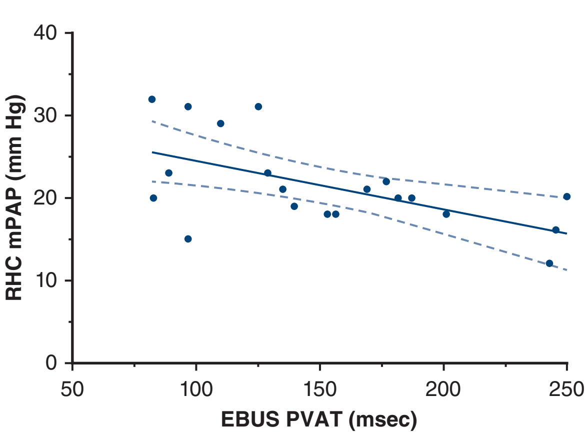

FIGURE 2. Linear regression model with 95% confidence intervals, comparing endobronchial ultrasound–generated pulmonary vascular acceleration time (*EBUS PVAT*) with right heart catheterization–generated median pulmonary artery pressure (*RHC mPAP*).

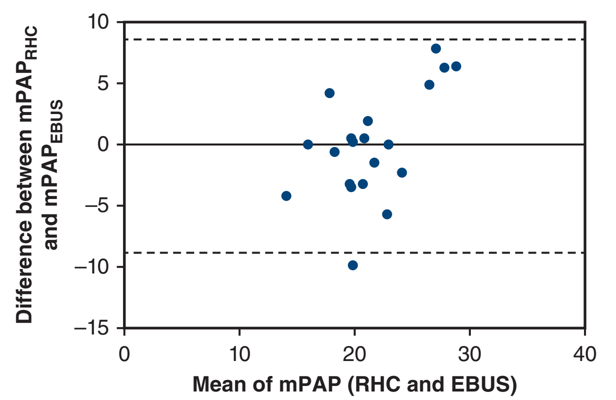

FIGURE 3. Limits of agreement between right heart catheterization (*RHC*)-generated mean pulmonary artery pressure ($mPAP_{RHC}$) and calculated mean pulmonary artery pressure from endobronchial ultrasound (*EBUS*)-generated pulmonary vascular acceleration time ($mPAP_{EBUS}$) originating from the Bland–Altman analysis (*solid line*: median = 0.000, *dotted lines*: 95% confidence interval).

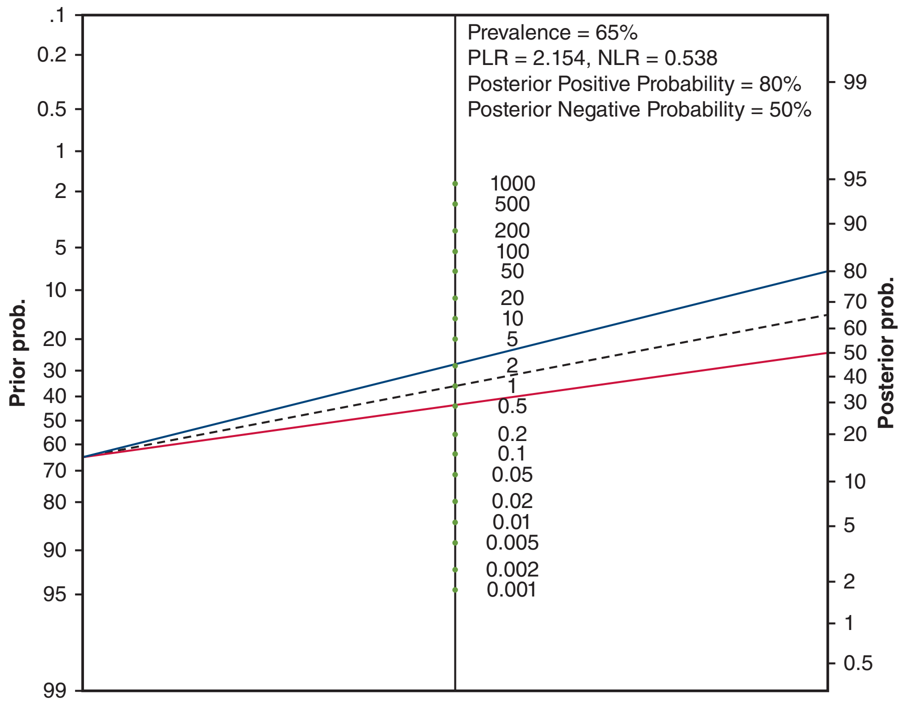

FIGURE 4. Fagan nomogram with pulmonary vascular acceleration time threshold set at 140 milliseconds revealing a positive likelihood ratio (*PLR*) and negative likelihood ratio (*NLR*) of 2.154 and 0.538, respectively, in our sample of patients with a pulmonary hypertension prevalence of 65% (prior prob). The positive probability (*blue line*) and negative probability (*red line*) are 80% and 50%, respectively.

low-dose computed tomography or breast mammography, our approach may be appropriate in patients with a high pretest probability based on clinical characteristics.[25] For example, sensitivity of low-dose computed tomography in detecting lung cancer ranged between 59% and 100% with a specificity ranging from 26.4% and 99.7%.[26] Breast digital mammography achieved a sensitivity of 97% and specificity of 64.5% in the detection of breast cancer.[27]

TTE and Doppler echocardiography have been reported to have a reasonable sensitivity and specificity in detecting PH. Pooled sensitivity values in the range of 85% and specificity of 74%, with a PLR of 3.2 and NLR of 0.2 have been reported in some studies, but only in patients in whom the PAP could be calculated. In patients with underlying lung disease, TTE can be unreliable to measure PAP.[16]

Based on the present data, the measurement of PAP by EBUS in patients in need of EBUS for staging or diagnostic purposes may be more suitable in individuals considered to be at high risk of suffering from PH than TTE. High-risk individuals include those with OSA, diagnosed or suspected based on sleep behavior, obesity, and the magnitude of the surgery to reduce the vascular bed of the right heart such as in individuals requiring pneumonectomy. In the future, EBUS may play a role in screening all patients who undergo an extensive intrathoracic operation and who are categorized as being high risk in order to physiologically optimize patients before resection.

Those with PH on EBUS can then be guided to have a RHC (still the gold standard), or potentially to measurement of the PAP by direct puncture of the PA, which has been shown to be safe in human and animal models with normal pulmonary pressures.[28,29] Ideally, in the context of patients undergoing EBUS for oncologic staging, pulmonary artery puncture and direct measurement of pulmonary artery pressure may be performed during the preoperative assessment period. This could provide additional data to surgeons that might inform which patients would benefit most from ongoing perioperative physiologic optimization; however, the safety of pulmonary artery puncture and direct measurement of pulmonary artery pressure in patients with significant PH requires additional study. In patients with a confirmation of PH, pharmacologic (pulmonary vasodilators) or physiological intervention (continuous positive airway pressure) to reduce the PAP before surgery may be helpful to reduce the morbidity and the mortality of the planned surgery.

In this clinical trial, despite consistency in approach and methodology, and with paired comparison with the current gold standard for PH diagnosis, a few limitations were encountered. First, although we aimed to develop a robust model, able to reliably predict PH with high sensitivity and specificity, our sample size limited our ability to do so and thus the correlation obtained is weak. Slow accrual may have been secondary to the number of patients requiring RHC as a part of their pre-operative workup. We felt that confirmation of our results with a gold standard was mandatory in order to generate meaningful results. Second, this trial was performed in a single-center, and thus, may have limited dissemination to other patient populations who present at other centers. Lastly, although we identified a cutoff PVAT value that is relevant in the current cohort, a larger multi-institutional study may reveal a different cutoff that may be more sensitive and or specific. In conclusion, the use of EBUS, an already routine test to stage patients with pulmonary malignancies, may be a useful tool to screen for PH in high-risk patients undergoing major pulmonary surgery.

Conflict of Interest Statement

R.F.C. has received research grants from Siemens and Olympus, and he is paid consultant for Intuitive Surgical, Siemens, and Olympus. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: endobronchial ultrasound, high risk lung resection, preoperative screening, pulmonary hypertension

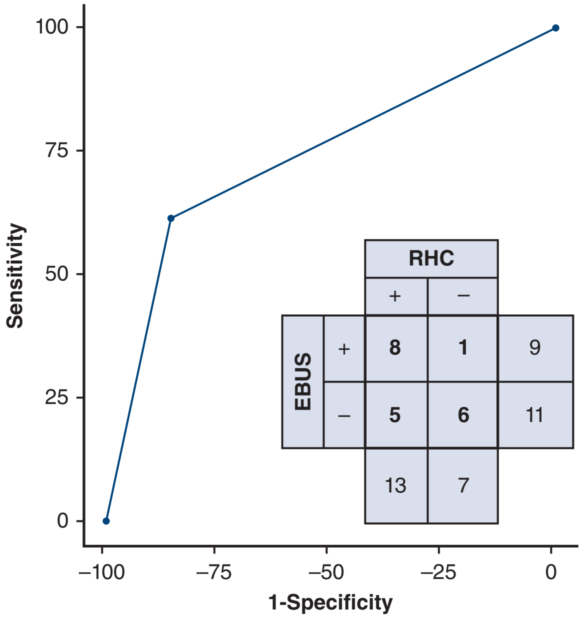

FIGURE E1. Receiver operator curve, with 2 × 2 table representing the results of RHC (threshold of 20 mm Hg), as well as EBUS (threshold of 140 milliseconds). *RHC*, Right heart catheterization; *EBUS*, endobronchial ultrasound.