S_{pO_2}/F_{IO_2} on Presentation as a Predictor for Early Hemodynamic Deterioration in Intermediate Risk Acute Pulmonary Embolism

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BACKGROUND: Patients with intermediate-risk acute pulmonary embolism are at risk of hemodynamic deterioration, and identification of risk factors for decompensation could guide the administration of thrombolytics. We aimed to assess whether S_{pO_2}/F_{IO_2} on presentation is associated with early hemodynamic deterioration in this population. METHODS: A retrospective chart review of subjects admitted between 2006 and 2018 with intermediate-risk pulmonary embolism (hemodynamically stable with right ventricle to left ventricle ratio > 0.9 or tricuspid annular plane systolic excursion < 18 mm). Early hemodynamic deterioration was defined as requirements for vasopressors or rescue thrombolytics within 48 h. Results are presented as median (interquartile range). RESULTS: A total of 178 subjects were included. Early hemodynamic deterioration occurred in 13% of the subjects and was associated with a median (interquartile range) lower S_{pO_2}/F_{IO_2} on presentation in univariate analysis (243 [123–275] versus 438 [335–457], $P < .001$) and in a multivariate analysis, including heart rate and right ventricle to left ventricle ratio as covariates (odds ratio 0.992, 95% CI 0.987–0.996; $P < .001$). The initial S_{pO_2}/F_{IO_2} predicted hemodynamic deterioration with an area under the receiver operating characteristic curve of 0.81 and a threshold of 260 was associated with a sensitivity of 74% and specificity of 88%. Sensitivity analyses restricted to subjects with hypoxemia on presentation and subjects with an elevated troponin level led to similar results. CONCLUSIONS: In intermediate-risk pulmonary embolism, S_{pO_2}/F_{IO_2} on presentation can help predict the risk of early hemodynamic deterioration. *Key words: pulmonary embolism; hypoxia; right ventricular failure; shock; oxygenation; acute respiratory failure.* [Respir Care 2019;64(10):1279–1285. © 2019 Daedalus Enterprises]

Introduction

Venous thromboembolic disease, including deep venous thrombosis and pulmonary embolism, is a frequent disease, with an annual incidence of 100–200 cases per 100,000 people.[1] Patients with acute pulmonary embolism have a 3-month mortality of ~15%[2] but present with a wide variety of disease severity. At one extreme of the spectrum, high-risk or massive pulmonary embolism, defined by the presence of shock or hypotension despite intravenous fluid administration, is associated with a 58% mortality[2] and is a recognized indication for thrombolytic therapy,[1] which decreases the rate of recurrent pulmonary embolism or death.[3] The other side of the spectrum includes patients who are normotensive with no sign of right-ventricular dysfunction and low-risk scores (such as simplified pulmonary embolism severity index (sPESI)[4]), whose mortality is <1%.[5] In between, patients who are normotensive and with signs of right-ventricular dysfunction (intermediate-risk or submassive pulmonary embolism) represent a challenge: their mortality is lower than in patients with hypotension but remains concerning (~8%).[6] There currently is no proven benefit of thrombolytics on survival in these patients and, therefore, no recommendation about their use,

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The authors have disclosed no conflicts of interest.

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which requires a case-by-case evaluation of the benefits/risk ratio.

Arterial hypoxemia is common during acute pulmonary embolism, being observed in 14–43% of unselected patients with acute pulmonary embolism.[7-10] Its mechanisms mainly involve a ventilation/perfusion ratio mismatch,[11] but intrapulmonary shunting[12] or low venous P_{O_2}[13] due to decreased cardiac output may also be contributing in selected patients. The severity of hypoxemia has generally been considered to be related to the degree of arterial obstruction[14] despite the lack of strong evidence and the observation that this may not be true in the presence of shock.[15] Hypoxemia has been associated with the presence of right-ventricular dysfunction,[16,17] and several studies reported more-frequent and/or severe hypoxemia in unselected subjects with pulmonary embolism and with a fatal outcome, although hypoxemia was not an independent predictor of mortality for most of these studies [7,8,10,18]

A naturally arising question is whether hypoxemia on presentation is associated with an increased risk of hemodynamic deterioration in intermediate-risk pulmonary embolism. Indeed, in submassive pulmonary embolism not treated with thrombolytics, ~10% of patients develop worsening shock within a few days;[18] these patients may benefit from delayed thrombolytic therapy but mortality in this setting is significant, and tools to predict this clinical deterioration and perhaps guide early administration of thrombolytics are lacking. The objective of this study was to assess the relationship between S_{PO_2}/F_{IO_2} on presentation and early (<48 h) hemodynamic deterioration in subjects with intermediate-risk acute pulmonary embolism.

QUICK LOOK

Current knowledge

In patients with intermediate-risk acute pulmonary embolism, identification of risk factors for early hemodynamic deterioration would help to assess the benefits/risk ratio of thrombolytics. Hypoxemia is common during acute pulmonary embolism and has been assumed to be related to the degree of arterial obstruction, which suggests that the severity of hypoxemia on presentation could be predictive of subsequent hemodynamic deterioration in initially stable patients.

What this paper contributes to our knowledge

In this retrospective study of subjects with intermediate-risk pulmonary embolism, we observed that S_{PO_2}/F_{IO_2} on presentation was significantly associated with hemodynamic deterioration within 48 h, in univariate and multivariate analysis. S_{PO_2}/F_{IO_2} seemed to perform better than heart rate or right ventricle to left ventricle ratio in predicting subsequent hemodynamic deterioration.

Methods

This retrospective study was approved by the Pennsylvania State University Institutional Review Board (8288), and informed consent was waived due to the retrospective design of data collection. All adults (ages > 18 y) admitted as inpatients between January 1, 2006, and March 30, 2018, with (1) an *International Classification of Diseases, 9th Revision* or an *International Classification of Diseases, 10th Revision* diagnosis of acute pulmonary embolism; (2) a systolic blood pressure > 90 mm Hg at the time of pulmonary embolism diagnosis; (3) an echocardiogram performed during their admission; (4) signs of right ventricular dysfunction, as defined by a right ventricle to left ventricle ratio of >0.9 and/or tricuspid annular plane systolic excursion < 18 mm were included.

Data collected included demographics, main comorbidities, cardiac biomarkers when available, results of lower-extremity duplex, computed tomography pulmonary angiography, and echocardiogram. Vital signs and O_2 requirements on presentation were collected as follows: for patients admitted through the emergency department, the first available set of parameters was taken into account; for in-patients, the parameters were recorded at the closest time to diagnostic suspicion and before any intervention. S_{PO_2}/F_{IO_2} on presentation was computed by using a conversion table as follows: for subjects who received O_2 via a nasal cannula, O_2 flows of 1, 2, 3, 4, 5, and 6 L/min were converted to F_{IO_2} of 0.24, 0.28, 0.32, 0.36, 0.40, and 0.44, respectively, as previously published.[19] All the subjects who received O_2 via a non-rebreather mask had a flow of 15 L/min, which was converted to a F_{IO_2} of 0.80 based on available studies.[20] The simplified pulmonary embolism severity index score was calculated.[21] Early hemodynamic deterioration was defined by the requirement for vasopressors or use of rescue thrombolytics within 48 h of diagnosis. Day 30 mortality was collected.

Statistical Analysis

Data were analyzed by using the r statistical package (https://www.R-project.org/. *Accessed April 24, 2019*) and are presented as median (interquartile range [IQR]) for quantitative variables and number (percentage) for categorical variables. Continuous and categorical variables were compared between groups with the Wilcoxon rank-sum test and Fisher exact test, respectively. A multivariate logistic regression model was used to predict the occurrence of early hemodynamic deterioration with covariates selected based on univariate analysis and clinical relevance. We performed a receiver operating characteristic

Table 1. Comparison of Subject Characteristics Based on the Occurrence of Hemodynamic Deterioration Within 48 Hours of Intermediate-Risk Acute Pulmonary Embolism Diagnosis

Parameter	Subjects Without Early Deterioration (n = 155)	Subjects With Early Deterioration (n = 23)	P
Age, median (IQR) y	66 (56–74)	61 (44–69)	.06
Men/women, n	84/71	15/8	.37
BMI, median (IQR) kg/m^2	30 (26–35)	31 (26–40)	.49
Malignancy, n (%)	55 (35)	6 (26)	.48
Previous thromboembolic disease, n (%)	36 (23)	4 (17)	.79
CAD/CHF, n (%)	48 (31)	5 (22)	.47
COPD/OSAS, n (%)	26 (17)	3 (13)	.77
Vital signs on presentation			
Heart rate, median (IQR) beats/min	99 (87–111)	121 (108–129)	<.001
Frequency, median (IQR) breaths/min	20 (18–24)	24 (18–30)	.24
SBP, median (IQR) mm Hg	132 (118–148)	136 (112–146)	.58
S_{pO_2}, median (IQR) %	95 (92–97)	93 (92–97)	.88
O_2 requirement, n (%)	48 (31)	18 (78)	<.001
Laboratory values (first 24 h), median (IQR)			
Troponin I, ng/mL	0.085 (0.027–0.448)	0.28 (0.11–0.56)	.09
Troponin T, ng/mL	0.07 (0.02–0.16)	0.07 (0.03–0.19)	.84
NT-pro BNP, pg/mL	1470 (300–3875)	2100 (540–4395)	.44
Imaging results			
Lobar or saddle pulmonary embolism, n (%)	121 (78)	21 (84)	.17
RV/LV, median (IQR)	1.16 (0.96–1.38)	1.4 (1.2–1.7)	.008
LV ejection fraction, median (IQR) %	65 (60–65)	65 (55–70)	.75
RV basal diastolic diameter, median (IQR) cm	4.4 (3.7–5.0)	5.1 (4.3–5.5)	.02
TAPSE, median (IQR) cm	1.6 (1.3–2.1)	1.3 (1.0–1.9)	.07
Systolic pulmonary arterial pressure, mm Hg	45 (35–55)	49 (45–55)	.46
IVC diameter, median (IQR) cm	2 (1.5–2.4)	2.1 (1.7–2.3)	.75
IVC collapsibility, n (%)	86 (67)	7 (58)	.54
McConnell sign, n (%)	16 (10)	4 (17)	.30
Positive LE duplex, n (%)	39 (80)	7 (78)	>.99
sPESI $\geq$ 1, n (%)	102 (66)	18 (78)	.34
S_{pO_2}/F_{IO_2}, median (IQR)	438 (335–457)	243 (123–275)	<.001
Day 30 mortality, n (%)	22 (14)	7 (30)	.07

IQR = interquartile range
BMI = body mass index
CAD = coronary artery disease
CHF = congestive heart failure
OSAS = obstructive sleep apnea syndrome
SBP = systolic blood pressure
NT-pro BNP = N-terminal pro-brain natriuretic peptide
RV = right ventricle
LV = left ventricle
TAPSE = tricuspid annular plane systolic excursion
IVC = inferior vena cava
LE = lower extremity
sPESI = simplified pulmonary embolism severity index

analysis to assess the performance of S_{pO_2}/F_{IO_2} and heart rate on presentation as predictors of early hemodynamic deterioration. All tests were 2-sided, with $P < .05$ being considered for statistical significance.

Results

We included 178 subjects with intermediate-risk acute pulmonary embolism. Characteristics of the subjects according to the development of early hemodynamic deterioration are detailed in Table 1. Twenty-three subjects (13% of the population) subsequently developed hemodynamic deterioration: on presentation, they had a higher heart rate, right ventricle to left ventricle ratio, right-ventricular basal diastolic diameter, and lower tricuspid annular plane systolic excursion, and were more frequently administered oxygen compared with the subjects who remained stable. No difference in breathing frequency but significantly lower

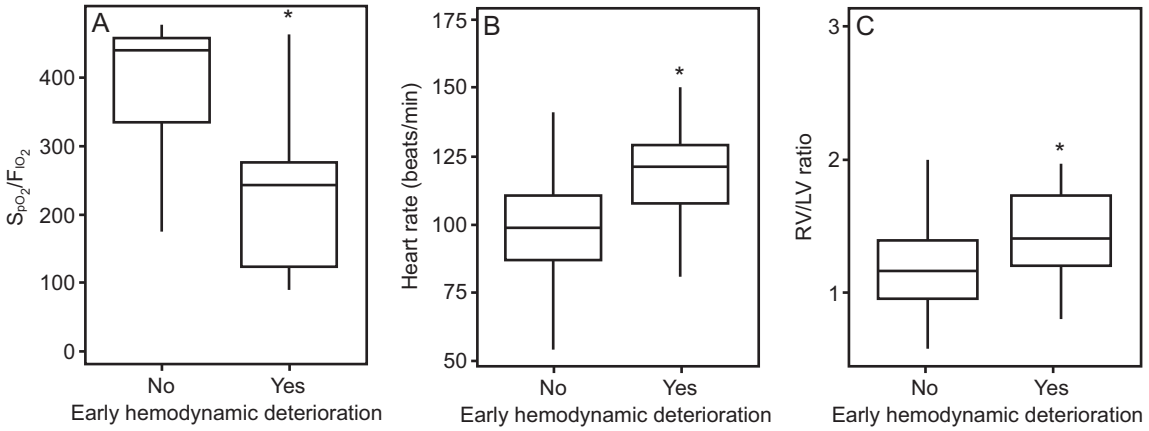

Fig. 1. Comparison of the distribution of S_{pO_2}/F_{IO_2} (A), heart rate (B), and right ventricle to left ventricle (RV/LV) ratio (C) on admission in subjects with intermediate-risk acute pulmonary embolism according to the development of hemodynamic deterioration within 48 h of diagnosis. *Heart rate and RV/LV were significantly higher and S_{pO_2}/F_{IO_2} was significantly lower in subjects with early hemodynamic deterioration.

Table 2. Multivariate Logistic Regression Predicting the Development of Hemodynamic Deterioration Within 48 Hours of Diagnosis in 178 Subjects With Acute Pulmonary Embolism

Variable	*P*	Odds Ratio	95% CI
Heart rate on presentation	.02	1.032	1.007–1.061
S_{pO_2}/F_{IO_2} on presentation	<.001	0.992	0.987–0.996
Right ventricle to left ventricle ratio	.07	3.157	0.908–11.564

S_{pO_2}/F_{IO_2} was observed in the subjects who later deteriorated (median [IQR] 243 [123–275] versus 438 [335–457], $P < .001$). Their 30-d mortality tended to be higher (30% versus 14%, $P = .07$). The subjects who remained stable and those who deteriorated had similar proportion of saddle or lobar pulmonary embolism, and no difference in S_{pO_2}/F_{IO_2} was observed among the subjects with saddle, lobar, segmental, or subsegmental pulmonary embolism. The distribution of S_{pO_2}/F_{IO_2}, heart rate, and right ventricle to left ventricle ratio in subjects with and without early hemodynamic deterioration are summarized in Figure 1. In multivariate analysis, significant predictors of early hemodynamic deterioration were heart rate (odds ratio 1.032, 95% CI 1.007–1.061; $P = .02$) and S_{pO_2}/F_{IO_2} (odds ratio 0.992, 95% CI 0.987–0.996; $P < .001$) on presentation (Table 2).

In Figure 2, receiver operating characteristic curves display the performance of S_{pO_2}/F_{IO_2} and the heart rate as predictors of hemodynamic deterioration within 48 h of diagnosis: the area under the receiver operating characteristic curve was 0.81 for S_{pO_2}/F_{IO_2} and 0.75 for heart rate ($P = .45$). A threshold of $S_{pO_2}/F_{IO_2} < 260$ predicted early hemodynamic deterioration, with a specificity of 88%, sensitivity of 74%, positive predictive value of 47%, and negative predictive value of 96%, whereas these values were 66%, 78%, 74% and 95%, respectively, for a heart rate of >107 beats/min. When combining the 2 parameters in a score defined by (S_{pO_2}/F_{IO_2})/heart rate, the area under the receiver operating characteristic curve increased to 0.85 but the performance of the combined score was not significantly different from S_{pO_2}/F_{IO_2} alone ($P = .12$), and the sensitivity and specificity achieved were similar.

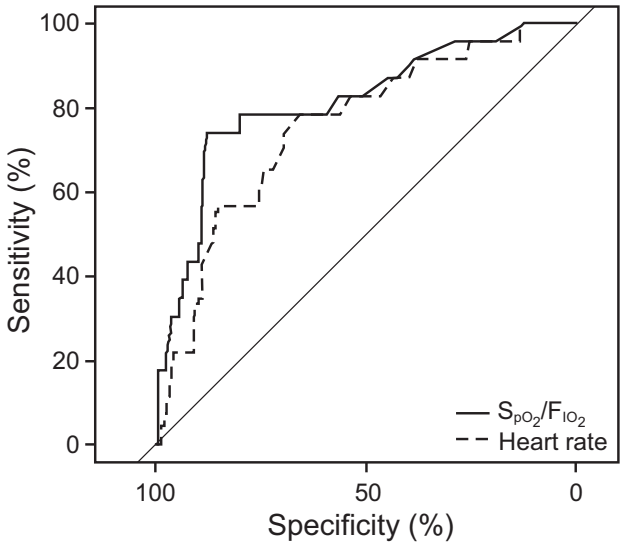

Fig. 2. Receiver operating characteristic curves, describing the performance of S_{pO_2}/F_{IO_2} and heart rate as predictors of hemodynamic deterioration within 48 h of the diagnosis of acute intermediate-risk pulmonary embolism. Areas under the receiver operating characteristic curve were 0.81 and 0.75 for S_{pO_2}/F_{IO_2} and heart rate, respectively ($P = .12$).

In a sensitivity analysis, we included only the subjects with hypoxemia on presentation, as defined by $F_{IO_2} \geq 0.40$ and/or $S_{pO_2} \leq 90\%$ ($n = 59$). Fourteen of these subjects

developed early hemodynamic deterioration compared with 3 of 75 subjects with initial O_2 requirements < 28% (2 L/min via nasal cannula) and $S_{pO_2} \geq 94\%$ ($P = .001$). When compared with the hypoxemic subjects who remained stable, the subjects who subsequently decompensated had a higher heart rate (116 [107–134] beats/min versus 100 [82–116] beats/min, $P = .01$) and right ventricle to left ventricle ratio (1.55 [1.33–1.90] versus 1.10 [0.92–1.36], $P = .008$) and lower S_{pO_2}/F_{IO_2} (128 [104–217] versus 343 [180–405], $P = .002$) on presentation, as in the analysis on the whole population. In multivariate analysis, S_{pO_2}/F_{IO_2} remained significantly associated with early hemodynamic deterioration (odds ratio 0.988, 95% CI 0.975–0.996; $P = .01$), whereas the other covariates were not.

Another sensitivity analysis excluded, among subjects with troponin available ($n = 112$), those with normal levels (intermediate-low risk pulmonary embolism as per recent European Society of Cardiology guidelines,[1] $n = 46$), who had a median (IQR) S_{pO_2}/F_{IO_2} of 436 [314–452] versus 398 [265–451] for subjects with elevated troponin (intermediate-high risk, $n = 66$) ($P = .17$). Indeed, only 9% of these subjects at intermediate-low risk developed early hemodynamic deterioration versus 24% for subjects with intermediate-high risk ($P = .03$). Again, subjects with intermediate-high risk who subsequently deteriorated had significantly lower S_{pO_2}/F_{IO_2} on presentation compared with subjects who remained stable (median [IQR] 234 [122–417] versus 410 [338–452], $P = .003$). S_{pO_2}/F_{IO_2} remained an independent predictor of early hemodynamic deterioration in this subgroup in multivariate analysis (odds ratio 0.992, 95% CI 0.985–0.997; $P = .008$).

Discussion

The main findings of this study were that hypoxemia on presentation, as measured by S_{pO_2}/F_{IO_2}, is associated with an increased risk of early hemodynamic deterioration in subjects with intermediate-risk acute pulmonary embolism and that S_{pO_2}/F_{IO_2} could be a better predictor of clinical deterioration compared with initial heat rate or echocardiographic parameters. In our population of 178 subjects with intermediate-risk acute pulmonary embolism, 13% developed hemodynamic deterioration within 48 h. This proportion is consistent with published data: a recent study reported that 9% of 298 subjects with all-risk pulmonary embolism had severe clinical deterioration within 5 d,[9] and other investigators reported 10% of shock developing during the acute phase among 65 subjects who were normotensive and with right-ventricular dysfunction.[18] Although intermediate-risk pulmonary embolism is associated with an overall hospital mortality of ~8%,[6] data on mortality for the subset of subjects initially stable and who subsequently deteriorate is scarce: we observed a 30% mortality among 23 subjects, whereas, in the study by Grifoni et al,[18] 3 of 6 subjects died.

What is the rationale for investigating hypoxemia on presentation as a predictor for subsequent hemodynamic deterioration? Given the uncertainty about indications for thrombolytics and the significant mortality associated with intermediate-risk pulmonary embolism, identifying predictors of clinical deterioration is essential to administer thrombolytics on time in patients likely to deteriorate while preventing bleeding complications associated with thrombolytics (up to 22% of major bleeding in the study by Konstantinides et al[22]) in patients likely to remain stable. The hypothesis that hypoxemia on presentation may be predictive of secondary hemodynamic decompensation is based on pathophysiologic and indirect clinical evidence: the mechanisms of hypoxemia during acute pulmonary embolism involve mainly ventilation/perfusion ratio mismatch and low venous P_{O_2}[11,13,23] secondary to decreased cardiac output. One, therefore, would expect acute pulmonary embolism to proportionally affect cardiac output and oxygenation, even when systolic arterial pressure is maintained. In a series of 20 subjects free of previous cardiopulmonary disease and diagnosed with acute pulmonary embolism, McIntyre and Sasahara[14] observed a good correlation between P_{aO_2} and both cardiac index and the degree of pulmonary vascular obstruction measured by pulmonary angiography. Clinical studies also showed an association between hypoxemia and right-ventricular dysfunction[16,18] or elevated troponin levels,[10] both markers of the hemodynamic impact of acute pulmonary embolism.

Clinical studies that investigated the relationship between hypoxemia on presentation and outcome during acute pulmonary embolism brought mixed results: most studies reported lower P_{aO_2} in subjects with worse outcomes in all-risk[8,16] or intermediate-risk acute pulmonary embolism[24]; however, hypoxemia was not an independent predictor of mortality in multivariate analyses.[18] In a study that focused on factors associated with early (5 d) clinical deterioration in 298 subjects with all-risk acute pulmonary embolism, factors independently associated with a severe outcome (as defined by the occurrence of either death, advanced cardiac life support, ventricular tachycardia or fibrillation, mechanical ventilation, vasopressors, thrombolysis, or thrombectomy) were systolic blood pressure < 90 mm Hg in the emergency department, elevated N-terminal pro-brain natriuretic peptide and right-ventricular strain on echocardiogram.[9] Hypoxemia, as defined by a lowest S_{pO_2} of <95% in the emergency department, was more frequent in the subjects who subsequently developed severe outcome within 5 d but was not associated with severe outcome in multivariate analysis.[9]

However, this study included subjects with all-risk pulmonary embolism (only 20% had echocardiogram), and a lowest S_{pO_2} of <95% in the emergency department was

the only marker of hypoxemia used, which may have affected the conclusions. In another study on 201 subjects with low- or intermediate-risk pulmonary embolism, initial hypoxemia ($P_{aO_2} < 60$ mm Hg on room air) was associated with in-hospital and 3-month all-cause mortality in univariate analysis; however, it was not significantly associated with all-cause mortality in multivariate analysis and was not predictive of specifically pulmonary embolism–related death or clinical deterioration (rescue thrombolysis, vasopressors, mechanical ventilation, or cardiopulmonary resuscitation).[8] None of the variables investigated (troponin, N-terminal pro-brain natriuretic peptide, D-dimer, right-ventricular dysfunction) was actually associated with clinical deterioration or death due to pulmonary embolism.[8]

Whether hypoxemia on presentation can more specifically predict early hemodynamic deterioration in submassive pulmonary embolism remained unclear. A study that addressed the association between hypoxemia and outcome in 124 subjects with acute intermediate-risk pulmonary embolism showed that alveolar-arterial oxygen gradient was a good predictor of 90-d mortality[24]; however, the investigators did not specifically address early clinical deterioration; moreover, hypoxemia was not really diagnosed on presentation, as arterial blood gases were collected within 24 h, and one cannot exclude that some subjects had arterial blood gases collected while they were already deteriorating.

Analysis of our results indicated that hypoxemia on presentation was associated with requirements for vasopressors or rescue thrombolytics within 48 h in subjects with intermediate-risk pulmonary embolism; S_{pO_2}/F_{IO_2} was associated with early deterioration in our population, including in multivariate and sensitivity analyses, and seemed to be a reliable predictor of hemodynamic deterioration. Mortality as the outcome was not the focus of this study, but the fact that hypoxemia on presentation seemed associated with hemodynamic deterioration, whereas the literature does not definitely support its association with mortality, deserves further consideration. First, although acute pulmonary embolism is directly the main cause of death in this setting, studies reported other causes of early death in pulmonary embolism (sepsis, cancer, heart failure),[8,18] so that an impact of hypoxemia on early hemodynamic deterioration would not necessarily translate into mortality. Second, potentially strong interactions between hypoxemia and other covariates, such as right-ventricular dysfunction or cardiac biomarkers, make it difficult to isolate the effect of hypoxemia on mortality, even with sophisticated multivariate analyses.

Limitations of our study are mostly related to its retrospective design. Data collection based on chart review, the lack of protocol to administer thrombolytics or vasopressors, and the arbitrary time window of 48 h used to define hemodynamic deterioration are potential sources of bias. The lack of arterial blood gases to corroborate the degree of hypoxemia and to assess the predictive value of other blood gas parameters (pH, P_{CO_2}, HCO_3^-) is another limitation. At our institution, arterial blood gases are not routinely performed in patients with acute pulmonary embolism, one reason being to avoid arterial puncture before potential thrombolytics administration; results were available for only 78 of the 178 subjects analyzed, with various timing of collection, which made their interpretation with respect to clinical deterioration difficult. We, therefore, chose not to present these results and rather investigated the value of S_{pO_2}/F_{IO_2}, a noninvasive parameter readily available for all the subjects. S_{pO_2}/F_{IO_2} has been used and validated in several studies to assess the severity of hypoxemia as a surrogate for P_{aO_2}/F_{IO_2} in subjects on mechanical ventilation[25,26] and has also been used in subjects not on mechanical ventilation who were on wards to predict the development of ARDS[27] or ICU transfer.[28,29] Finally, one could argue about the use of an estimated F_{IO_2} to compute S_{pO_2}/F_{IO_2} in subjects not on mechanical ventilation; indeed, our retrospective design only allowed us to collect O_2 flow, and several factors related to subjects' respiratory pattern may have affected the O_2 flow/F_{IO_2} relationship. However, we used conversion tables based on published studies,[19,20] and several other investigators used similar conversions[30,31] due to the difficulty in accurately measuring F_{IO_2} in subjects who are spontaneously breathing.

Conclusions

In 178 subjects with intermediate-risk acute pulmonary embolism, S_{pO_2}/F_{IO_2} on presentation was significantly associated with hemodynamic deterioration within 48 h, which occurred in 13% of the subjects; an S_{pO_2}/F_{IO_2} threshold of 260 was the best predictor of decompensation and might be used to help assess the benefits-risk balance of thrombolytics in this setting. Prospective observational studies would be warranted to confirm these results.

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