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Predictors of Pulmonary Infarction

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Abstract: In the setting of acute pulmonary embolism (PE), pulmonary infarction is deemed to occur primarily in individuals with compromised cardiac function.

The current study was undertaken to establish the prevalence of pulmonary infarction in patients with acute PE, and the relationship between infarction and: age, body height, body mass index (BMI), smoking habits, clot burden, and comorbidities.

The authors studied prospectively 335 patients with acute PE diagnosed by computed tomographic angiography (CT) in 18 hospitals throughout central Italy. The diagnosis of pulmonary infarction on CT was based on Hampton and Castleman's criteria (cushion-like or hemispherical consolidation lying along the visceral pleura). Multivariable logistic regression was used to model the relationship between covariates and the probability of pulmonary infarction.

The prevalence of pulmonary infarction was 31%. Patients with infarction were significantly younger and with significantly lower prevalence of cardiovascular disease than those without ($P < 0.001$). The frequency of infarction increased linearly with increasing height, and decreased with increasing BMI. In logistic regression, the covariates significantly associated with the probability of infarction were age, body height, BMI, and current smoking. The risk of infarction grew with age, peaked at approximately age 40, and decreased afterwards. Increasing body height and current smoking were significant amplifiers of the risk of infarction, whereas increasing BMI appeared to confer some protection.

Our data indicate that pulmonary infarction occurs in nearly one-third of the patients with acute PE. Those with infarction are often young and otherwise healthy. Increasing body height and active smoking are predisposing risk factors.

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Abbreviations: BMI = body mass index, CI = confidence interval, CT = computed tomography, CTEPH = chronic thromboembolic pulmonary hypertension, DVT = deep vein thrombosis, FDG = fluoro-deoxy-glucose, KeV = kilo electron volt, Kv = kilo volt, mAs = milli Ampere per second, MBq = mega Becquerel, PE = pulmonary embolism, PET = positron emission tomography, RV = right ventricle, TAPSE = tricuspid annular plane systolic excursion, VTE = venous thromboembolism.

INTRODUCTION

Hampton and Castleman provided the first accurate description of the radiologic appearance of pulmonary infarction.[1] In their series of 370 patients with autopsy-proven pulmonary embolism (PE), pulmonary infarction was found in nearly 70%. The frequency of infarction was the highest among the patients who came to death with a history of longstanding heart failure.[1] Ever since then, pulmonary venous hypertension, secondary to heart failure, has been regarded as a predisposing risk factor for pulmonary infarction in the setting of acute PE.[2–4] Elevated pulmonary venous pressure is believed to hinder collateral blood flow via broncho-pulmonary anastomoses distal to embolized regions.[2,3]

Kent and Reid, however, described cases of PE, many with infarcts, in active duty servicemen.[5] Most of these individuals were under 40 years of age and all in good health before embolism.[5]

The current study was undertaken to establish the prevalence of pulmonary infarction in a fairly large sample of unselected patients with proven PE, and to investigate on the relationship between infarction and a number of variables including age, body height, body mass index (BMI), smoking habits, extent of PE, and comorbid conditions. Multivariable logistic regression was used to model the relationship between covariates and the probability of pulmonary infarction.

METHODS

Ethical Approval

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), and was approved by the institutional review board (Comitato Etico, Azienda Ospedaliero-Universitaria Careggi). Before entering the study, the subjects provided an informed written consent to let their clinical and radiologic data be used anonymously for the current analysis.

Sample

The study sample included 335 patients (98% white Caucasians) who were diagnosed with and treated for acute PE in 18 hospitals throughout the region of Tuscany (Italy). In all patients, the diagnosis had been established by contrast-enhanced multidetector computed tomography (CT).

Treatment in the acute stage consisted of unfractionated heparin (50%), low-molecular weight heparins (29%), fondaparinux (17%), or thrombolysis (4%), followed by oral anticoagulation. The patients were referred to the outpatient clinic of the Atherothrombotic Disorders Unit, Careggi University Hospital, Florence (Italy) within 2 months after hospital

FIGURE 1. Examples of pulmonary infarction. A, 47-year-old man with infarction in right lower lobe. B, 48-year-old woman with multiple infarcts in right lower lobe. C, 57-year-old man with infarction in right lower lobe. D: 29-year-old woman with bilateral, multiple infarcts in right and left lower lobes. In all images, infarcts are arranged along the visceral pleura and have a cushion-like of hemispherical shape. Focal hyperlucencies within the infarction are evident.

discharge. They were examined for the following reasons: to search for inherited or acquired thrombophilia, to plan the duration of oral anticoagulant therapy, to assess perfusion recovery by lung scintigraphy, and right ventricular function by transthoracic echocardiography within a year of the incident embolic event.

Collection of Clinical Data

All the patients were evaluated consecutively by one of the authors (MM) between January 2012 and December 2013. Anthropometric data, smoking history, transient or permanent risk factors for PE, and comorbid conditions were recorded. Thrombophilia was rated present if anyone of the following abnormalities were present: deficiency of antithrombin, protein C, or protein S; mutation in the factor V Leiden or prothrombin gene; lupus anticoagulant. Each patient was then invited to complete a self-administered standardized questionnaire, including the description of the symptoms experienced before the diagnosis of PE.[6]

Acquisition and Analysis of Computed Tomography Images

Multidetector-row CT parameters were: 1.25-mm slice thickness with a 1.2-mm reconstruction interval at 120 kV/120 mAs, 60 to 100 mL of nonionic contrast material with an injection speed of 4.0 mL/s and bolus tracking in the common pulmonary artery to get optimal contrast opacification of the pulmonary arteries. Computed tomography images, obtained at the time of PE diagnosis, were retrieved, had the identification data removed, and were given a random code. Images (axial, sagittal, and coronal) were examined by 3 raters (MM, CC, and LR) for the presence of lung consolidations suggestive of

infarction. In doing so, the raters rigorously applied the criteria put forward by Hampton and Castleman,[1] and later by Fleischner.[7] According to these authors, the most common appearance of pulmonary infarction is of a cushion-like or hemispherical consolidation with the base lying along the surface of the visceral pleura (lateral, diaphragmatic, mediastinal, or interlobar pleura). Focal radiolucencies within the infarction (best seen on CT with the mediastinal window) were also recorded.[8,9] Examples of pulmonary infarction are given in Figure 1.

A semiquantitative estimate of the pulmonary clot burden was made by applying the CT obstruction index introduced by Qanadli et al.[10] With this method, the arterial tree of each lung is regarded as having 10 segmental arteries (3 to the upper lobes, 2 to the middle lobe and lingula, and 5 to the lower lobes). An embolus in a segmental artery is scored 1 point, and emboli in the most proximal arteries are given a score n equal to the number of segmental arteries arising distally. A weighing factor d is assigned depending on the degree of vascular obstruction (no obstruction $= 0$; partial obstruction $= 1$; and complete obstruction $= 2$). Thus, the maximum CT obstruction index is 40, and the percentage of vascular obstruction is calculated as $[\sum(n*d)/40]*100$. Pulmonary embolism was categorized as massive if the extent of the embolic obstruction was $\geq 50\%$. Right ventricular overload was rated present if the ratio of the right-to-left ventricular diameter, measured at the valvular plane on the transaxial view, was $\geq$ than 0.9.[11]

Follow-up Studies

The extent of residual perfusion defects was estimated on lung scintigraphy obtained within 12 months of PE diagnosis. Lung scintigraphy was obtained after intravenous injection of human serum albumin microspheres labeled with [99m]Technetium

(70–150 MBq), taking care to inject the radioactive bolus with the patient seated to preserve the effect of gravity on the regional distribution of pulmonary blood flow. Lung scans were acquired by means of a large field gamma camera equipped with a high resolution, parallel-hole collimator, using a 20% symmetric window set over the 140 KeV photopeak. Images consisted of anterior, posterior, both lateral, and both posterior oblique views, with 5 00 000 counts per image. No ventilation imaging was used.

In estimating residual perfusion defects, we applied a method originally validated against pulmonary angiography.[12] Briefly, each lobe is attributed a weight according to regional blood flow (right upper lobe: 0.18; right middle lobe: 0.12; right lower lobe: 0.25; left upper lobe: 0.13; lingula: 0.12; and left lower lobe: 0.20). The perfusion of each lobe is estimated visually by means of a 5-point score (0, 0.25, 0.5, 0.75, and 1) where 0 means "not perfused" and 1 "normally perfused." Visual estimates of perfusion are based on the combined evaluation of 6 scintigraphic views (anterior, posterior, both lateral, and both posterior oblique). Each lobar perfusion score is obtained by multiplying the weight assigned to the lobe by the estimated perfusion of that lobe. The overall perfusion score is the sum of the perfusion scores of the 6 lobes, and the percentage of pulmonary vascular obstruction is calculated as: $(1 -$ overall perfusion score$)^*100$.

Transthoracic echocardiography, and postero-anterior and lateral chest radiographs were obtained at the time of perfusion lung scintigraphy. Echocardiographic assessment of the right heart function was based on standardized criteria.[13] Measured variables included the end-diastolic right ventricle (RV) diameter, the thickness of the RV free wall, the tricuspid regurgitation velocity (if measurable), and the tricuspid annular plane systolic excursion. Right ventricle wall motion was assessed qualitatively. End-diastolic RV diameter <26 mm, RV wall thickness <7 mm, tricuspid regurgitation velocity <2.7 m/s, and tricuspid annular plane systolic excursion >18 mm were regarded as normal.

Chest radiographs were examined by one of the authors (MM) for the presence of cardiac, pulmonary, or pleural abnormalities. Attention was paid to identify blunting of costophrenic angles or linear scars in the lung parenchyma, which are expression of healed pulmonary infarcts.[14,15] Dilatation of the pulmonary artery trunk and of the RV with pruning of peripheral pulmonary vessels were regarded as suggestive of chronic thromboembolic pulmonary hypertension (CTEPH).[16]

Right heart catheterization was obtained in those patients in whom CTEPH was suspected on the basis of scintigraphic, echocardiographic, and chest radiographic abnormalities. Hemodynamic criteria for CTEPH included a mean pulmonary artery pressure >25 mm Hg at rest with a mean pulmonary wedge pressure <15 mm Hg.[17]

Statistical Analysis

Patients' baseline characteristics were compared across the 2 groups (infarction versus no infarction) by Fisher's exact test for the categorical variables. For the continuous variables, differences were tested for by Mood's median test.[18] Two-tailed *P*-values less than 0.05 were considered statistically significant throughout.

We modeled the probability of pulmonary infarction as a function of the covariates with logistic regression. We included the following covariates: sex, age (continuous in years), height (continuous in cm), BMI (continuous in kg/m²), current cigarette smoking, use of oral contraceptives, recent trauma or surgery, family history of venous thromboembolism, comorbid conditions, patient location at the time of the incident embolic event (in- or outpatient), thrombophilia, massive PE, and acute right ventricular overload. We first considered univariate associations with the probability of each of the above covariates and the probability of pulmonary infarction. The relationship between the 3 continuous covariates (age, height, and BMI) and the probability of infarct was carefully inspected. Departures from linearity on the logit scale were tested by including 3-knot natural cubic splines, and by visual assessment of regression residuals. The relationship was approximately linear with height and BMI, but markedly nonlinear with age. Therefore, age was introduced with as three-knot natural cubic splines with knots placed at 10, 30, and 60 years. The covariate that showed statistical significance less than 0.20 were later included in a multivariable model. Those that were not significant were removed if the change in the remaining coefficients following their removal was smaller than 10%. Further details are given in the online supplement, http://links.lww.com/MD/A464. The statistical analyses were performed using Stata release 13 (StataCorp LP, College Station, TX, USA).

RESULTS

Sample Characteristics

A diagnosis of pulmonary infarction was established in 105 (31%) of 335 patients. Infarcts were usually multiple and, in 87%, unilateral. Eighty-five percent of them were distributed in the lower lobes with the remaining 15% equally partitioned among the other lobes. Focal hyperlucencies within the infarction were seen in 82% of the cases.

The baseline characteristics of the study sample are reported in Table 1. Patients with pulmonary infarction were significantly younger, taller, and thinner than those without, and featured a significantly lower prevalence of cardiovascular disease. Nearly one-third of them were current smokers at the time of the incident embolic event as opposed to 10% of those without infarction. As shown in Figure 2A, the frequency distribution of pulmonary infarction in relation to age was curvilinear and skewed to the left (mode in the fourth decade). The frequency of infarction increased linearly with increasing body height (Fig. 2B), and decreased with increasing BMI (from 42% for BMI ≤ 20 to 18% for BMI > 35 kg/m²).

With regard to symptoms, pleuritic chest pain prevailed significantly among the patients with infarction, and so did hemoptysis (Table 2). The latter, however, occurred in less than 20% of the cases with radiologic evidence of infarction.

Predictors of Pulmonary Infarction

In logistic regression, 4 covariates were significantly associated with the probability of pulmonary infarction: age, body height, BMI, and current cigarette smoking (Table 3). The relationship with age was curvilinear, the probability of infarction being the highest approximately at the age of 40 years (Fig. 3). Current smoking was an amplifier of the risk of infarction (Fig. 3), and so was increasing body height (Fig. 4). By contrast, increasing BMI appeared to have a protective effect against infarction (Table 3).

FOLLOW-UP

By 1 year of PE diagnosis, 90% of the patients with pulmonary infarction at inclusion had residual perfusion defects on lung scintigraphy not exceeding 11% of the pulmonary

TABLE 1. Baseline Characteristics of the Study Sample

	Pulmonary Infarction		
	Yes (n = 105)	No (n = 230)	*P*-Value
Age, years	47 (36–58)	61 (46–71)	<0.001
Male sex	57 (54)	115 (50)	0.482
Outpatient	98 (93)	213 (93)	1.000
Height (cm)	173 (166–180)	170 (162–175)	0.009
BMI (kg/m^2)	25.0 (23.4–27.2)	26.3 (24.2–29.3)	0.018
Bilateral PE	87 (83)	192 (83)	0.876
Massive PE[*]	32 (30)	80 (35)	0.457
Current smoking	36 (34)	22 (10)	<0.001
Recent surgery or trauma	30 (29)	66 (29)	1.000
Oral contraceptives[†]	27 (56)	24 (21)	<0.001
Familial VTE	20 (19)	32 (14)	0.256
Thrombophilia	28 (27)	57 (25)	0.787
Cardiovascular disease	19 (18)	85 (37)	<0.001
Pulmonary disease	4 (4)	17 (7)	0.330
Endocrine/ metabolic disease	8 (8)	22 (10)	0.682
Connective tissue disease	1 (1)	9 (4)	0.181
Active cancer	1 (1)	8 (3)	0.283

BMI = body mass index, PE = pulmonary embolism, VTE = venous thromboembolism. Data are number (percent) or median (interquartile range).

[*] Pulmonary vascular obstruction ≥50% on contrast-enhanced computed tomography.

[†] In 48 women with infarction and 115 without.

FIGURE 2. Prevalence of pulmonary infarction as a function of age (A) and body height (B) in a sample of 335 patients with acute pulmonary embolism.

TABLE 2. Clinical Symptoms and Signs

	Pulmonary Infarction		
	Yes (n = 105)	No (n = 230)	*P*-Value
Sudden onset dyspnea	82 (78)	170 (74)	0.495
Chest pain (pleuritic)	73 (70)	47 (20)	<0.001
Chest pain (precordial)	4 (4)	17 (7)	0.330
Fainting or syncope	14 (13)	53 (23)	0.040
Hemoptysis	19 (18)	7 (3)	<0.001
Cough (as a new symptom)	3 (3)	9 (4)	0.760
Signs of DVT	28 (27)	84 (37)	0.082
Fever >38°C	5 (5)	4 (2)	0.145
Right ventricular overload[*]	29 (28)	80 (35)	0.211

DVT = deep vein thrombosis.

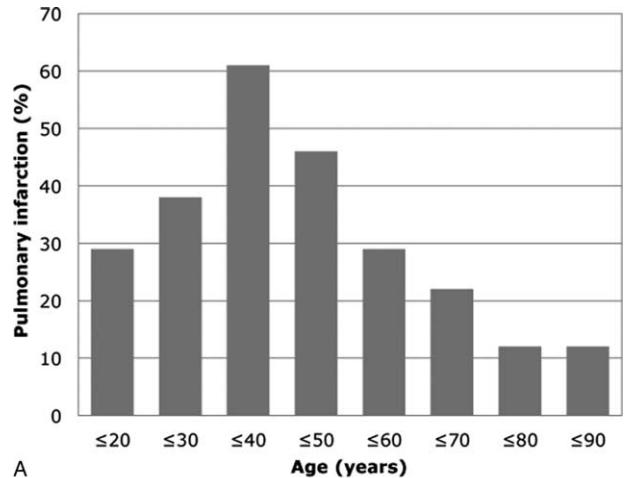[*] On echocardiography or contrast-enhanced computed tomography.

vascular bed. Such figure was not significantly different (*P* = 0.08) from that of patients without infarction (residual defects at the 90th percentile ≤19%). Perfusion lung scans were completely normal in 61% of the patients with infarction and 58% of those without (*P* = 0.633).

The overall prevalence of CTEPH was 0.6% (2/335), in close agreement with previous reports.[19–21] Of the 2 patients with CTEPH, one had been first diagnosed with PE 8 years earlier, but was not investigated any further to assess the recovery of pulmonary perfusion. The other had had an episode of pleuritic chest pain and hemoptysis 10 years earlier. At that time, his chest radiograph showed a pleural-based consolidation consistent with infarction, which was mistaken for pneumonia.
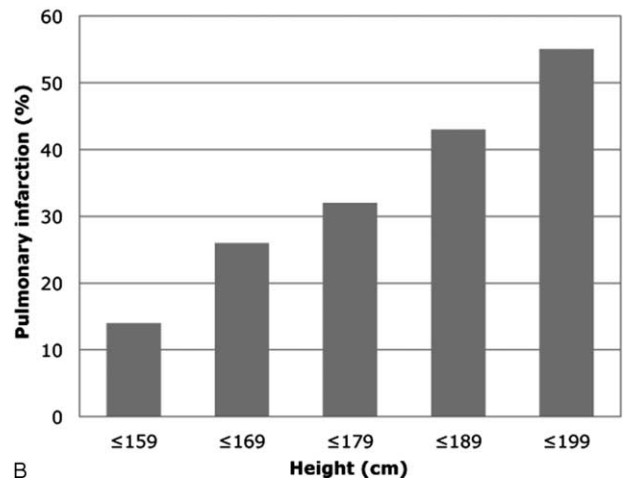
Infarcts were no longer visible on the chest radiographs taken at the time of lung scintigraphy. Remnants of the former infarction, like obliteration of costophrenic angles or linear scars, were seen in 29 (28%) of 105 patients.

DISCUSSION

The lung receives oxygen supply form 3 sources: the pulmonary circulation, the bronchial circulation, and the airways. Accordingly, it is believed to be resistant to an acute ischemic insult.[22]

TABLE 3. Predictors of Pulmonary Infarction

Covariate	Odds Ratio	95% CI	*P*-Value
Age, years	1.16	1.05–1.29	0.005
Spline[*]	0.84	0.76–0.93	0.001
Height, cm	1.04	1.01–1.07	0.008
BMI, kg/m^2	0.90	0.84–0.97	0.004
Current smoking	3.60	1.88–6.91	<0.001

BMI = body mass index, CI = confidence interval.
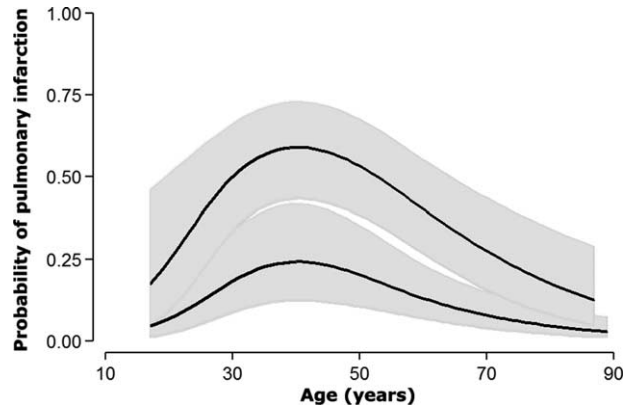[*] Spline = [age − 10]^3/2500 − [age − 30]^3/1500 − [age − 60]^3/3750.

Our data challenge the widely held belief that pulmonary infarction occurs primarily in patients with pulmonary venous hypertension secondary to longstanding heart failure.[1–5] In our sample, patients with infarction were significantly younger than those without, and featured a much lower prevalence of cardiovascular disease. The likelihood of infarction increased with increasing body height and current cigarette smoking. Conversely, increasing BMI appeared to confer some protection. These characteristics are strikingly similar to those of patients with primary spontaneous pneumothorax. In fact, those who experience primary spontaneous pneumothorax are often young, tall and thin, and in good health.[23] Frequently, but not invariably, they are active smokers.[23]

What makes young and healthy subjects more prone to develop pulmonary infarction is still unclear, but it may be related to the efficiency of the collateral circulation in peripheral lung regions. In fact, the status of the collaterals determines whether a pulmonary infarction will develop, how large it will become, and how far it will proceed to complete necrosis.[1]

The observed positive association between pulmonary infarction and body height is novel and intriguing for lung size is directly related to body height. This does not imply that larger lungs are frailer than smaller ones. Body height is a highly heritable polygenic trait,[24] so it may be hypothesized that some of the genes implicated in determining adult height may control the ontogenesis of relevant structures, such as the microvessels

FIGURE 4. Predicted probability of pulmonary infarction as a function of age for 2 different levels of body height: 190 cm (upper curve) and 150 cm (lower curve). Shaded areas are 95% confidence intervals. Both subjects have a body mass index of 26.1 kg/m^2 and are nonsmokers.

or the elastic scaffolding of the lung. In connection to this, a recent study provided important clues as to the known inverse association between body height and risk of coronary artery disease.[25] In that study, the relative risk of coronary artery disease increased by 13.5% per one-standard deviation decrease in genetically determined height. Such link was partly explained by the association between shorter height and an adverse lipid profile.[25]

Cigarette smoking is a major risk factor for chronic obstructive lung disease as it triggers an inflammatory response, which ultimately leads to narrowing of small airways and pulmonary emphysema.[26] Smoking is also known to increase the permeability of the alveolar-capillary barrier in otherwise normal smokers.[27] So, it is plausible that it may amplify the risk of pulmonary infarction.

Clinical Implications

Correct recognition of pulmonary infarction during life is of paramount importance for lung consolidations suggestive of infarction may be the first manifestation of acute PE.[7] A cushion-like or hemispherical consolidation arranged along the pleura indicates with strong probability pulmonary infarction, but other conditions, such as pneumonia or lung cancer, must be considered in differential diagnosis. Infarcts are always arranged peripherally along the pleural surface, whereas pneumonic consolidations in the early stage, or during resolution, may appear as a more central consolidation some distance from the pleura.[28] Similarly, tumor masses are also often some distance from the pleura.[28]

Unfortunately, pulmonary infarcts are still often mistaken for pneumonia, granulomatous disease, or neoplasia because of the deeply rooted belief that infarction ought to be triangular in shape with the apex pointing toward the lung hilum.[29–31] As pointed out by Hampton and Castleman[1] and later by Fleischner,[7] this is a misconception because the apical portion of an embolized lung region is spared from infarction thanks to sufficient collateral blood flow.

The last decade witnessed an exponential growth in the use of CT in the emergency departments.[32] Computed tomography permits a clear visualization of lung densities, and helps differentiating them from pleural effusion. With the mediastinal

FIGURE 3. Predicted probability of pulmonary infarction as a function of age for a current smoker (upper curve) and a nonsmoker (lower curve). For both subjects, body mass index and height are set equal to the sample's median value (26.1 kg/m^2 and 170 cm, respectively). Shaded areas are 95% confidence intervals. The upper curve is truncated at 74 years because there were no current smokers beyond that age.

window, focal areas of hyperlucency within the lung consolidation are readily seen. They are common in pulmonary infarcts, and are expression of the geographic distribution of hemorrhage with residual islands of intact parenchyma.[29] Thus, the finding on CT of pleural-based consolidations with sharp, rounded margins, and central hyperlucencies should make the clinician entertain the possibility of PE with infarction, even more so if the patient, no matter if young and otherwise healthy, presents with unexplained pleuritic chest pain or hemoptysis.

In some circumstances, positron emission tomography with[18] Fluorine labeled fluoro-deoxy-glucose may assist in differential diagnosis of pleural-based lung consolidations.[33] As opposed to neoplasm, pulmonary infarction features a characteristic tracer uptake along the periphery of the lesion with no uptake within the consolidation (rim sign).[33]

Study Limitations

In the current study, no sequential radiologic imaging was obtained shortly after PE diagnosis, so we could not tell with absolute certainty whether the lung consolidations we described represented complete or incomplete (fleeting) infarcts. Second, the vast majority of our patients were white Caucasians. Therefore, our findings may not apply to subjects of other ethnic origin.

CONCLUSIONS

In sum, our data indicate that pulmonary infarction occurs in nearly of third of the patients with acute PE. Patients with infarction are often young and otherwise healthy. Increasing body height and active smoking are predisposing risk factors.

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