ORIGINAL ARTICLE

Prevalence of Pulmonary Embolism among Patients Hospitalized for Syncope

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ABSTRACT

BACKGROUND

The prevalence of pulmonary embolism among patients hospitalized for syncope is not well documented, and current guidelines pay little attention to a diagnostic workup for pulmonary embolism in these patients.

METHODS

We performed a systematic workup for pulmonary embolism in patients admitted to 11 hospitals in Italy for a first episode of syncope, regardless of whether there were alternative explanations for the syncope. The diagnosis of pulmonary embolism was ruled out in patients who had a low pretest clinical probability, which was defined according to the Wells score, in combination with a negative D-dimer assay. In all other patients, computed tomographic pulmonary angiography or ventilation–perfusion lung scanning was performed.

RESULTS

A total of 560 patients (mean age, 76 years) were included in the study. A diagnosis of pulmonary embolism was ruled out in 330 of the 560 patients (58.9%) on the basis of the combination of a low pretest clinical probability of pulmonary embolism and negative D-dimer assay. Among the remaining 230 patients, pulmonary embolism was identified in 97 (42.2%). In the entire cohort, the prevalence of pulmonary embolism was 17.3% (95% confidence interval, 14.2 to 20.5). Evidence of an embolus in a main pulmonary or lobar artery or evidence of perfusion defects larger than 25% of the total area of both lungs was found in 61 patients. Pulmonary embolism was identified in 45 of the 355 patients (12.7%) who had an alternative explanation for syncope and in 52 of the 205 patients (25.4%) who did not.

CONCLUSIONS

Pulmonary embolism was identified in nearly one of every six patients hospitalized for a first episode of syncope. (Funded by the University of Padua; PESIT ClinicalTrials.gov number, NCT01797289.)

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N Engl J Med 2016;375:1524-31.
DOI: 10.1056/NEJMoa1602172

Syncope is defined as a transient loss of consciousness that has a rapid onset, short duration, and spontaneous resolution and is believed to be caused by temporary cerebral hypoperfusion.[1-3] According to current classifications, syncope can be neurally mediated (i.e., vasovagal, situational, or carotid-sinus syncope), can be caused by orthostatic hypotension (i.e., drug-induced hypotension or hypotension due to primary or secondary autonomic failure or due to volume depletion), or can have a cardiovascular origin (i.e., arrhythmias, structural cardiovascular diseases, or pulmonary embolism).[1]

Although pulmonary embolism is included in the differential diagnosis of syncope in most textbooks, rigorously designed studies to determine the prevalence of pulmonary embolism among patients hospitalized for syncope are lacking. Indeed, current international guidelines, including those from the European Society of Cardiology and the American Heart Association, pay little attention to establishing a diagnostic workup for pulmonary embolism in these patients.[1,2] Hence, when a patient is admitted to a hospital for an episode of syncope, pulmonary embolism — a potentially fatal disease that can be effectively treated — is rarely considered as a possible cause.

In this study, we used a systematic diagnostic workup to assess the prevalence of pulmonary embolism in a large number of patients who were hospitalized for a first episode of syncope, regardless of whether there were potential alternative explanations for the syncope.

METHODS

STUDY DESIGN AND OVERSIGHT

This was a cross-sectional study that was aimed at determining the prevalence of pulmonary embolism among patients older than 18 years of age who were hospitalized for a first episode of syncope. The study was designed by the first and last authors. The first author vouches for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol. The protocol was approved by the institutional review board at each participating hospital.

Syncope was defined as a transient loss of consciousness with rapid onset, short duration (i.e., <1 minute), and spontaneous resolution, with obvious causes such as epileptic seizure, stroke, and head trauma ruled out.[1-3] All patients with syncope who visited the emergency department and were admitted to the medical ward of 1 of 11 participating general hospitals (2 academic and 9 nonacademic hospitals, each serving more than 100,000 inhabitants) were potentially eligible for enrollment in the study. Reasons for hospital admission were trauma related to falls, severe coexisting conditions, failure to identify an explanation for the syncope, or a high probability of cardiac syncope on the basis of the Evaluation of Guidelines in Syncope Study score.[4] Patients were excluded if they had had previous episodes of syncope, if they were receiving anticoagulation therapy, or if they were pregnant. All the patients provided written informed consent.

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STUDY ASSESSMENTS

All study assessments were completed within 48 hours after a patient was admitted to a hospital, as specified in the study protocol. All the patients were interviewed and evaluated by trained study physicians, who were investigators in the Pulmonary Embolism in Syncope Italian Trial (PESIT). The workup to be performed for each patient was prespecified in the study protocol and was based on the 2014 guidelines of the European Society of Cardiology.[5] A medical history was obtained that included the presence of prodromal symptoms of autonomic activation (sweating, pallor, or nausea), the presence of known cardiac disease, recent bleeding, causes of volume depletion or venous pooling, and recent exposure to new or stronger hypotensive drugs or drugs that could potentially cause bradycardia or tachycardia. In addition, study physicians asked patients about symptoms (pain and swelling) in their legs and recorded the presence of risk factors for venous thromboembolism, including recent surgery, trauma, or infectious disease within the previous 3 months; ongoing hormonal treatment; prolonged immobilization of 1 week or longer; active cancer (i.e., recurrent or metastasized cancer or cancer that had been treated with chemotherapy or radiotherapy in the previous 6 months); and history of venous thromboembolism.

Patients were evaluated for the presence of arrhythmias, tachycardia (i.e., heart rate >100 beats per minute), valvular heart disease, hypotension (i.e., systolic blood pressure <110 mm Hg), autonomic dysfunction (as assessed by measuring blood pressure and pulse rate in the arms

Table 1. Simplified Wells Score for Assessment of the Pretest Clinical Probability of Pulmonary Embolism.*

Variable	Points
Clinical signs or symptoms of deep-vein thrombosis	3.0
Alternative diagnosis less likely than pulmonary embolism	3.0
Heart rate >100 beats/min	1.5
Immobilization or surgery in the previous 4 wk	1.5
Previous venous thromboembolism	1.5
Hemoptysis	1.0
Active cancer	1.0

* A total score of 4.0 or lower indicates that pulmonary embolism is unlikely, and a score higher than 4.0 indicates that pulmonary embolism is likely. This table was adapted with permission from Wells et al.[8]

and legs with the patient in a supine and an upright position), tachypnea (i.e., respiratory rate >20 breaths per minute), and swelling or redness of the legs. All patients underwent chest radiography, electrocardiography, arterial blood gas testing, and routine blood testing that included a D-dimer assay. Further diagnostic workup included carotid sinus massage, tilt testing, echocardiography, and 24-hour electrocardiography recording, if applicable. Soon after hospital admission, patients received prophylaxis for venous thromboembolism, if indicated clinically.[6]

ASCERTAINMENT OF PULMONARY EMBOLISM

The presence or absence of pulmonary embolism was assessed with the use of a validated algorithm that was based on pretest clinical probability and the result of the D-dimer assay.[7] The D-dimer level was measured by the quantitative assay used routinely in each participating center; the cutoff for a positive result versus a negative result ranged between 250 and 500 μg per milliliter, depending on the manufacturer's instructions. The pretest clinical probability of pulmonary embolism was defined according to the simplified Wells score, which classifies pulmonary embolism as being "likely" or "unlikely" (Table 1).[8] In the patients who had a low ("unlikely") pretest clinical probability and a negative D-dimer assay, no further testing was performed and a diagnosis of pulmonary embolism was ruled out. In patients who had a high ("likely") pretest clinical probability, a positive D-dimer assay, or both, computed tomographic pulmonary angiography or ventilation–perfusion lung scanning (in the case of patients with severe renal impairment or allergy to contrast material) was performed.

The criterion for the presence of pulmonary embolism was an intraluminal filling defect on computed tomography or a perfusion defect of at least 75% of a segment with corresponding normal ventilation.[9,10] In the event that a patient died before the completion of this diagnostic algorithm, an autopsy was requested. In patients with pulmonary embolism, the thrombotic burden was assessed by a central adjudication committee through identification of the most proximal location of the embolus on the computed tomographic scan or measurement of the severity of the perfusion defect on the ventilation–perfusion lung scan.[11]

STATISTICAL ANALYSIS

On the basis of pilot data (6 of 50 patients who were admitted to a hospital for syncope had pulmonary embolism), we assumed a prevalence of pulmonary embolism of 10 to 15% among patients with a first episode of syncope. To obtain a two-sided 95% confidence interval of 2.5% for the prevalence of pulmonary embolism, we estimated that a sample size of 550 patients would be required. All participating centers were asked to enroll patients until the estimated sample size was reached.

The prevalence of pulmonary embolism and the associated 95% confidence interval were calculated for the entire group of patients and for relevant subgroups. To compare the baseline characteristics between patients with and those without pulmonary embolism, we used the chi-square test for categorical variables and Student's t-test for continuous variables. Odds ratios with 95% confidence intervals were calculated with the use of logistic regression. The 95% confidence intervals and P values were calculated according to the normal approximation of the binomial distribution. No adjustments were made for multiple testing. All calculations were performed with the use of SPSS software, version 22.0 (SPSS).

RESULTS

PATIENTS

From March 2012 through October 2014, a total of 2584 patients visited the emergency depart-

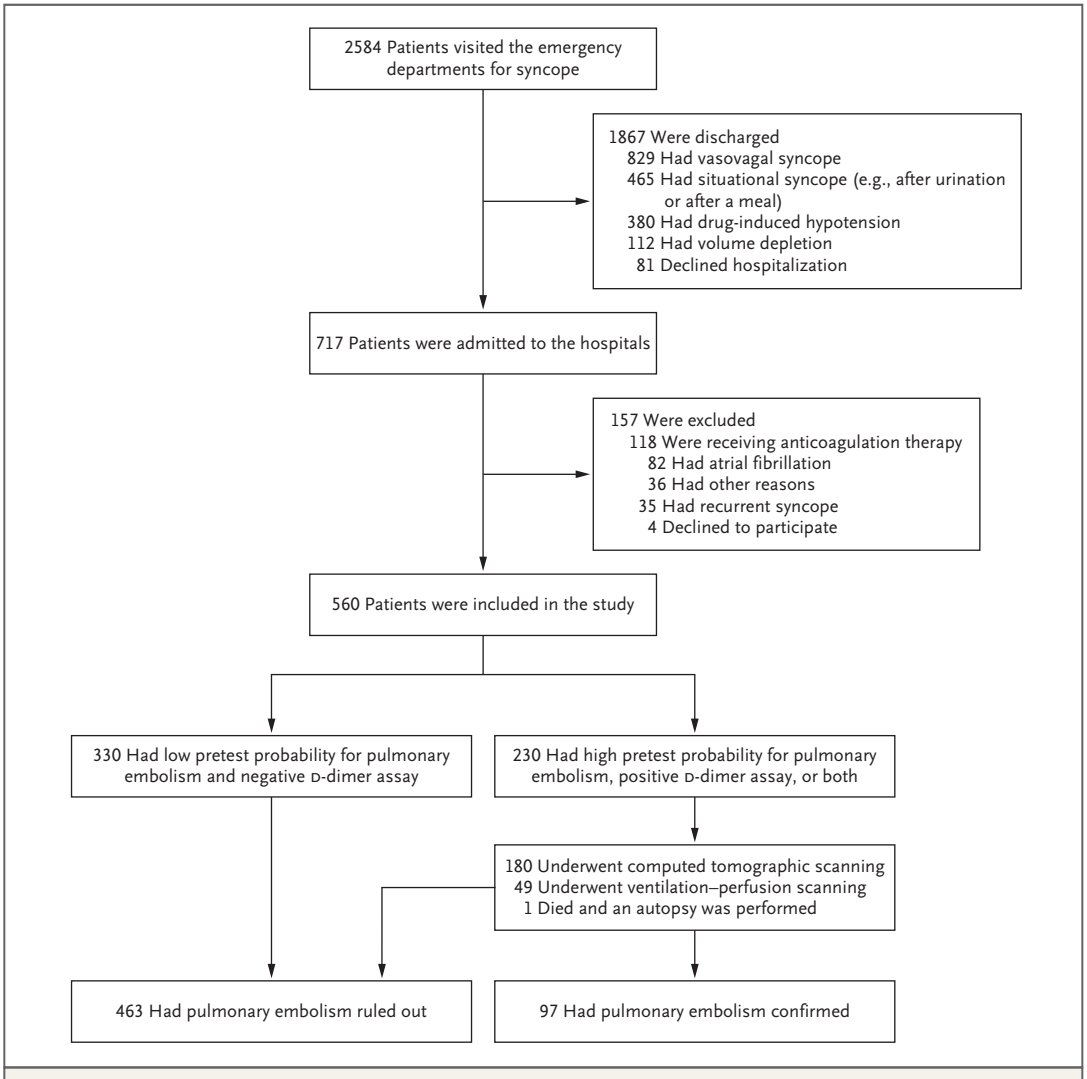

Figure 1. Workup for Pulmonary Embolism among Patients Admitted to the Hospital for Syncope.

ments of the 11 study hospitals (see the Supplementary Appendix, available with the full text of this article at NEJM.org) because of syncope. A total of 1867 of the 2584 patients (mean age, 54 years; range, 16 to 79) were either not admitted to the hospital or declined hospitalization (Fig. 1). Of the 717 patients (27.7%) who were admitted, 157 (21.9%) were excluded from the study because they were receiving ongoing anticoagulation therapy (118 patients, 82 of whom were receiving it for atrial fibrillation and 36 for other reasons), had had previous episodes of syncope (35 patients), or did not provide informed consent (4 patients). Hence, 560 patients with a first episode of syncope were included in the study. The main demographic and clinical characteristics of the patients are provided in Table 2. Most of the patients were elderly (>75% were ≥70 years of age). Clinical evidence suggested an explanation for syncope other than pulmonary embolism in 355 of the 560 patients (63.4%).

PREVALENCE OF PULMONARY EMBOLISM

In 330 of the 560 patients (58.9%), a diagnosis of pulmonary embolism was ruled out on the basis of the combination of low pretest clinical probability of pulmonary embolism and a negative D-dimer assay. Of the remaining 230 patients, 135 (58.7%) had a positive D-dimer assay only, 3 (1.3%) had a high pretest clinical probability

Table 2. Demographic and Clinical Characteristics of the Study Patients.*

Characteristic	All Patients (N=560)	Pulmonary Embolism Confirmed (N=97)	Pulmonary Embolism Ruled Out (N=463)	Odds Ratio (95% CI)	P Value
Age					
Mean — yr	76±14	77±13	76±14		0.84
Median (interquartile range) — yr	80 (72–85)	78 (73–85)	80 (72–85)		0.68
≥70 yr — no. (%)	435 (77.7)	78 (80.4)	357 (77.1)	1.22 (0.71–2.11)	0.48
≥80 yr — no. (%)	294 (52.5)	45 (46.4)	249 (53.8)	0.74 (0.48–1.15)	0.19
Male sex — no. (%)	223 (39.8)	37 (38.1)	186 (40.2)	1.09 (0.69–1.71)	0.71
Obese — no. (%)	34 (6.1)	6 (6.2)	28 (6.0)	1.02 (0.41–2.55)	0.96
Previous venous thromboembolism — no. (%)	31 (5.5)	11 (11.3)	20 (4.3)	2.83 (1.31–6.13)	0.006
Potential explanations for syncope — no. (%)					
Neurally mediated†	149 (26.6)	20 (20.6)	129 (27.9)	0.67 (0.39–1.15)	0.14
Orthostatic hypotension‡	112 (20.0)	14 (14.4)	98 (21.2)	0.63 (0.34–1.15)	0.13
Cardiac disorders§	94 (16.8)	11 (11.3)	83 (17.9)	0.59 (0.30–1.15)	0.12
Undetermined	205 (36.6)	52 (53.6)	153 (33.0)	2.34 (1.50–3.65)	<0.001
Clinical features — no. (%)					
Prodromal symptoms	227 (40.5)	41 (42.3)	186 (40.2)	1.09 (0.70–1.69)	0.70
Respiratory rate >20 breaths/min	77 (13.8)	44 (45.4)	33 (7.1)	10.80 (6.34–18.45)	<0.001
Heart rate >100 beats/min	107 (19.1)	32 (33.0)	75 (16.2)	2.55 (1.56–4.19)	<0.001
Systolic blood pressure <110 mm Hg	141 (25.2)	35 (36.1)	106 (22.9)	1.90 (1.19–3.04)	0.006
Clinical signs of deep-vein thrombosis	60 (10.7)	39 (40.2)	21 (4.5)	14.20 (7.79–25.71)	<0.001
Risk factors for venous thrombosis — no. (%)					
Prolonged immobility	38 (6.8)	10 (10.3)	28 (6.0)	1.79 (0.84–3.81)	0.13
Recent trauma or surgery	27 (4.8)	7 (7.2)	20 (4.3)	1.72 (0.71–4.20)	0.23
Active cancer	65 (11.6)	19 (19.6)	46 (9.9)	2.21 (1.23–3.97)	0.007
Infectious disease	49 (8.8)	12 (12.4)	37 (8.0)	1.63 (0.81–3.25)	0.17

* Plus–minus values are means ±SD. There were no missing data.
† Vasovagal syncope was identified in 86 patients, situational syncope in 51 patients, and carotid-sinus syncope in 12 patients.
‡ Hypotension due to autonomic failure was identified in 46 patients, drug-induced hypotension in 35 patients, and hypotension due to volume depletion in 31 patients.
§ Arrhythmias were identified in 49 patients, and structural disease in 45 patients.

of pulmonary embolism only, and 92 (40.0%) had both. In 229 of these patients, either computed tomography or ventilation–perfusion lung scanning was performed; in the case of 1 patient who died before objective testing could be performed, an autopsy was performed after permission had been obtained. Pulmonary embolism was diagnosed in 72 of the 180 patients (40.0%) who underwent computed tomography and in 24 of the 49 patients (49.0%) who underwent ventilation–perfusion scanning (see the Supplementary Appendix) and was the cause of death of the 1 patient in whom an autopsy was performed. Hence, pulmonary embolism was confirmed in 97 of the patients who had a positive D-dimer assay, a high pretest clinical probability, or both (42.2%; 95% confidence interval [CI], 35.8 to 48.6). In the entire cohort, the prevalence of pulmonary embolism was 17.3% (95% CI, 14.2 to 20.5).

THROMBOTIC BURDEN

Among the 72 patients in whom pulmonary embolism was detected by computed tomography, the most proximal location of the embolus was a main pulmonary artery in 30 patients (41.7%),

a lobar artery in 18 patients (25.0%), a segmental artery in 19 patients (26.4%), and a subsegmental artery in 5 patients (6.9%). Among the 24 patients in whom pulmonary embolism was detected by ventilation–perfusion lung scanning, the perfusion defect involved more than 50% of the area of both lungs in 4 patients (16.7%), 26 to 50% of the area of both lungs in 8 patients (33.3%), and 1 to 25% of the area of both lungs in the remaining 12 patients (50.0%). In the 1 patient who died, pulmonary embolism involved both main pulmonary arteries.

ADDITIONAL OBSERVATIONS

Pulmonary embolism was detected in 52 of the 205 patients who had syncope of undetermined origin (25.4%; 95% CI, 19.4 to 31.3) and in 45 of the 355 patients who were regarded as having a potential alternative explanation for syncope (12.7%; 95% CI, 9.2 to 16.1). Of the latter 45 patients, 31 (68.9%) had a lobar or more proximal location of the thrombus on computed tomography or a perfusion defect of more than 25% of the area of both lungs on ventilation–perfusion scanning.

The prevalence of tachypnea was higher among the patients with pulmonary embolism than among the patients without pulmonary embolism (occurring in 45.4% vs. 7.1% of the patients), as were the prevalences of tachycardia (in 33.0% vs. 16.2%), hypotension (in 36.1% vs. 22.9%), clinical signs or symptoms of deep-vein thrombosis (in 40.2% vs. 4.5%), previous venous thromboembolism (in 11.3% vs. 4.3%), and active cancer (in 19.6% vs. 9.9%). Of the 97 patients with pulmonary embolism, 24 (24.7%) had no clinical manifestations of the diagnosis, including tachypnea, tachycardia, hypotension, or clinical signs or symptoms of deep-vein thrombosis.

DISCUSSION

Our study used a systematic workup for pulmonary embolism in a large series of patients who were hospitalized for a first episode of syncope and showed a high prevalence of pulmonary embolism among these patients; pulmonary embolism was confirmed in approximately one of every six patients (17.3%). Although the prevalence of pulmonary embolism was highest among patients who presented with syncope of undetermined origin (25% of patients), almost 13% of patients with potential alternative explanations for syncope had pulmonary embolism. Not surprisingly, patients with dyspnea, tachycardia, hypotension, or clinical signs or symptoms of deep-vein thrombosis were more likely to have pulmonary embolism, as were those with active cancer. However, the proportion of patients who did not have these features yet had an objective confirmation of pulmonary embolism was not negligible.

The unexpectedly high prevalence of pulmonary embolism among our patients with syncope contrasts with that reported elsewhere.[12-17] It should be noted, however, that in the few contemporary studies that involved patients presenting with syncope, diagnostic testing for pulmonary embolism was performed only in selected subgroups, which may have resulted in a potential underestimation of the prevalence of this vascular disorder. In contrast, our study involved consecutive patients, all of whom underwent a guidelines-based workup for pulmonary embolism,[5] regardless of whether another explanation was suggested clinically. Our study also involved multiple centers, and the results across the centers were consistent, with the prevalence of pulmonary embolism ranging from 15 to 20% across centers.

Some methodologic issues in our study require comment. First, patients were included in the study if they were admitted to a medical ward after being examined in the emergency department for syncope, which was defined as full loss of consciousness for less than 1 minute, followed by spontaneous, complete resolution. As a consequence, this study did not include patients who were cared for on an ambulatory basis or patients who visited the emergency department but for whom hospitalization was not considered necessary. Second, syncope is a diagnostic challenge, because the diagnosis is based largely on the history of the patient, which could be supported by observations of bystanders who are usually not medically trained. In addition, there is often uncertainty about the causal relationship between an identified disorder (such as a self-terminating arrhythmia) and the episode of syncope. Third, all participating hospitals used a standardized protocol for the diagnostic workup of syncope that was based on international guidelines,[1,2] but a specific workup was not mandated by the study protocol. In addition, the study

protocol specified that a diagnosis of pulmonary embolism should not affect the usual workup for syncope. Fourth, diagnostic imaging for pulmonary embolism was performed only in patients who had an elevated D-dimer level or a high pretest clinical probability of pulmonary embolism. Nevertheless, well-conducted clinical studies have shown conclusively that pulmonary embolism is highly unlikely in patients who have a low pretest clinical probability and a negative D-dimer assay.[7,8,18-22] Fifth, the study protocol did not mandate objective confirmation of deep-vein thrombosis in symptomatic patients; thus, we are not aware of the rate of this complication among patients who reported pain or swelling in their legs. However, none of the patients who were included in the study spontaneously reported these symptoms or visited the emergency department because of these symptoms. Sixth, the search for other causes of syncope was left to the discretion of the attending physicians. Hence, other causes of syncope may have been underreported. This may have been partly responsible for the fact that a definite cause of the syncope could not be determined in 205 patients. Seventh, pulmonary embolism is unlikely in patients who have had multiple episodes of syncope and in patients who are receiving anticoagulation therapy; therefore, these patients were excluded from our study, and accordingly, our study results are not applicable to such patients. Finally, we did not collect information on treatment decisions and patient follow-up after completion of the diagnostic algorithm for pulmonary embolism because this was not a study objective.

Syncope is generally expected to occur in patients with pulmonary embolism if they have a sudden obstruction of the most proximal pulmonary arteries that leads to a transient depression in cardiac output.[23-25] In 49 of the 73 patients (67.1%) in our cohort who had pulmonary embolism that was diagnosed according to findings from computed tomography or autopsy, the most proximal location of the embolus was a main pulmonary artery or a lobar artery. Similarly, among the 24 patients who were assessed with ventilation–perfusion scanning, the perfusion defect was larger than 25% of the total lung area in 12 patients (50.0%). These findings suggest that, in at least half of the patients with pulmonary embolism in our study, the extent of thrombosis was large enough to produce an abrupt obstruction of the blood flow that would be likely to result in a sudden loss of consciousness.

However, in approximately 40% of the patients, the extent of pulmonary vascular obstruction was smaller. Because there was no standard approach to the evaluation of syncope, a number of patients with small pulmonary emboli may have had syncope that was associated with another condition that was missed. However, other mechanisms may be involved in the occurrence of syncope once a pulmonary embolism has developed, such as vasodepressor or cardioinhibitory mechanisms.[26-28] In addition, when a clot dislodges from the venous system and lodges in the pulmonary circulation, it may induce arrhythmias when it passes through the heart. Hence, even smaller clots could be a potential cause of syncope. Studies addressing the mechanisms that trigger syncope in patients who have limited obstruction of the pulmonary arteries are warranted.

In conclusion, among patients who were hospitalized for a first episode of syncope and who were not receiving anticoagulation therapy, pulmonary embolism was confirmed in 17.3% (approximately one of every six patients). The rate of pulmonary embolism was highest among those who did not have an alternative explanation for syncope.

Supported by institutional research funding from the University of Padua.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Mr. John Suárez for his help in reviewing an earlier version of the manuscript.

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