How often suspected pulmonary embolism is diagnosed and its main diagnostic characteristics, in an emergency nuclear medicine service? Four years experience

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Abstract

Objective: Acute pulmonary embolism (APE) is an emergency condition and its treatment must be immediate. Nevertheless, the diagnosis of APE is difficult because its symptoms and risk factors are not specific. We present our 4 years experience on this subject. **Subjects and Methods:** We retrospectively studied 2178 lung perfusion scintigraphies (LPS). Of them 1846 were performed to patients suspected for APE admitted to the emergency departments of the University Polyclinic of Bari and examined immediately by our Nuclear Medicine Department. Contingency tables and odds ratio (OR) were used to estimate the relation between symptoms, risk factors, D-dimers dosage, other imaging diagnostic tools and LPS results. **Results:** Lung perfusion scintigraphy was positive for APE in 309/1846 (16.7%) patients which then were treated successfully. In 89.5% of these, 309 patients D-dimer dosage was previously examined and was increased in 97.7% of them, but was not predictive of APE (OR=1.04, P=1). Among all symptoms, a low diagnostic capacity was found for cough (OR=1.25, P=0.066) and for chest pain (OR=0.95, P=649). On the contrary, dyspnea was a significant symptom correlated with positive LPS (OR=1.78, P<0.001). The presence of risk factors was predictive of positive LPS and positively correlated with the number of positive lesions in LPS. x^2_{Poglin}=6.472, P=0.011). Lung perfusion scintigraphy positive for APE were significantly associated with computed tomography pulmonary angiography and/or chest X-ray results (x^2=9.618, P= 0.022). **Conclusion:** Lung perfusion scintigraphy could early diagnose APE in 16.7% of the cases (referred to our Nuclear Medicine Emergency Service) and exclude APE in 83.3% of these cases. Immediate treatment or release of these patients from the emergency department was thus possible. LPS has a key role in the early diagnosis but even more in exclusion of APE, optimizing the management of patients who do not require admission to intensive care. Our four-year and large-scale experience, based on clinical and resource optimization, support the need of Nuclear Medicine Units to perform LPS as emergency in on-call 24 hrs service.

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Introduction

Acute pulmonary embolism (APE) is a relatively common emergency, with a yearly incidence in Western countries of 0.5 per 1000 inhabitants; in Italy there are about 65000 new cases/year [1]. Acute pulmonary embolism is defined as a sudden occlusion of a pulmonary artery mainly caused by thrombus-derived embolus that develops in the veins of the lower extremities venous system, in the presence of deep vein thrombosis (DVT) [2]. Other non-thrombotic conditions, such as cancer and sepsis, can be linked to the development of APE [3].

Thromboembolic risk factors linked to APE are primary and secondary. The primary risk factors are due to coagulation factors deficit; the secondary risk factors are trauma, neurological diseases, age, central venous catheter, venous thrombosis, smoke, pregnancy, surgery, neoplasm, cardiac failure, obesity and drugs (contraception and chemotherapy) [4-6].

Age above 40 years is related to APE onset and risk increases with advancing age. However, it is important to keep into account that APE may also arise in patients without risk factors.

Acute pulmonary embolism is considered one of the most important clinical emergencies because it has a high risk of mortality and morbidity. Its diagnosis is difficult because it may remain asymptomatic or show symptoms not specific [7] thus emerges the need for early diagnosis of APE, preferably during the first hour. Multidetector computed tomography pulmonary angiography (CTPA) is the gold standard for APE diagnosis, but the low patient's compliance reduces its feasibility to perform, especially in emergency

conditions. Lung perfusion scintigraphy (LPS) is a nuclear medicine procedure often used for the diagnosis of APE [8]. Furthermore, LPS is a simple, fast and cheap examination, without contraindications and can be performed in all emergency patients when needed. In particular, the high specificity of LPS has been recognized as a valid criterion for excluding APE [2].

The aim of this study was to describe our experience for using LPS in the diagnosis and management of patients with suspected APE and thus to indicate the importance for having an emergency Nuclear Medicine LPS Service.

Subjects and Methods

Patients population

We have performed 2178 LPS between 2012-2016 in patients with suspected APE, who were admitted to the University of Bari Polyclinic emergency departments and were then referred to us, to be examined in our emergency LPS Service. From these patients 332 were omitted because were younger than 18 years, or because their clinical condition showed that they were not finally APE suspected patients, as their physicians finally decided. Thus only 1846 patients APE suspected were studied.

The following variables were recorded for each patient: age, gender, pregnancy status, hospitalization department, risk factors, symptoms and previous clinical and instrumental evaluation (D-dimer dosage, Chest X-rays and/ or CTPA).

The suspicion of APE was based on: presence of clinical symptoms such as chest pain, dyspnea and cough; altered D-dimer dosage results; pathological instrumental imaging results (Chest X-rays and/ or CTPA), performed within 24 hours before the LPS [9].

For each patient, an individual informed consensus was obtained allowing us to use all data for research purposes.

Diagnostic exams

The perfusion scintigraphies were acquired using gamma OPTIMA NM/CT 670 and OPTIMA NM/CT 640 camera (GE Medical System, West Milwaukee, WI, USA) after the intravenous injection of 185-370MBq technetium-99m (^{99m}Tc)-labelled macroaggregated albumin particles. Lung perfusion scintigraphy was performed according to the EANM guidelines with planar technique. Anterior, posterior, right and left posterior oblique ad right and left anterior oblique projections were acquired using with 256x256 matrix and 500-700kcounts per projection.

We used the following two criteria recommended by the Prospective Investigative Study of Acute Pulmonary Embolism (PISA-PED) in order to interpret LPS: a) The presence of single or multiple wedge-shaped perfusion defects, b) the size of the lesion which corresponded to that of the lobar, segmental, or subsegmental region of the lung [10]. Two expert nuclear medicine physicians retrospectively revised all patients' data. Difficult cases were reported by consensus. D-dimer testing was performed with MDA D-dimer (bioMérieux Inc., Durham, NC, USA), a quantitative and rapid latex agglutination assay. D-dimer dosage of more than 500 ng/mL was considered suspicious of APE. All CTPA were performed with a multidetector scanner (MX 8000, Philips Medical System, Cleveland, OH, USA). Based on a standard protocol we performed two consecutive acquisitions after injection of contrast medium and during the arterial pulmonary and also later phases. The clinical suspicion of APE was evaluated using validated scales as Wells or Geneva, based on the presence of one or more of the following factors: For the Wells score these factors were: Previous APE and deep venous thrombosis, heart rate >100bpm, surgery or im-mobilization, haemoptysis or active cancer. For the Geneva Score the following factors are also included: The presence of lower limb pain and age > 65 years [11].

Statistical analyses

Patients' demographic data as age, sex, type of exams requested ("emergency call" or "24h person call service") and previous diagnostic examinations were studied using data from the acceptance or hospitalization department (Figure 1) and LPS results. Comparisons among patients' quantitative variables were performed by one-way ANOVA or Student's t-test for unpaired data. For qualitative variables Chi-square test was performed. We evaluated the LPS data in relation to symptoms, risk factors and results of instrumental tests by contingency tables followed by Chi-square test or Odds Ratio (OR). The value $P<0.005$ was considered statistically significant. Chi-square for trend was performed when requested.

Results

On the 1846 examinations performed in our department, 1157 of cases were performed as "24h person call service". Most of these requests came from Emergency Unit (70.1%). The distribution of LPS during "24h person call service" in relation to the department of origin is reported on Figure 1, showing a significantly difference between these departments (χ^2=116.063, $P<0.001$). Distribution of gender and sex for each group of all 1846 patients is described in Table 1.

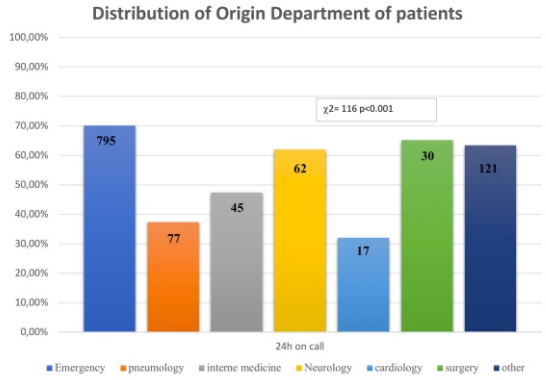

Figure 1. Distribution of all 1157 patients studied as they were submitted to us from different departments of the Hospital that were at 24h on call service.

Table 1. *Demographic characteristics of the 1846 patients studied in relation to the departments of origin.*

			Unit Department							
	n=1846		Pneumonology n=206		Internal Medicine n=116	Neurology n=100	Cardiology n= 53	Surgery n=46	Other Units n=191	Test
Sex	Male, n (%)	765 (41.4%)	434 (38.3%)	107 (51.9%)	51 (44.0%)	47 (47.0%)	20 (37.7%)	27 (58.7%)	79 (41.4%)	χ^2=21.576 P=0.001
	Female, n (%)	1081 (58.6%)	700 (61.7%)	99 (48.1%)	65 (56.0%)	53 (53.0%)	33 (62.3%)	19 (41.3%)	112 (58.6%)	
Mean age (SD)	71 (16)		71 (17)	74 (15)	74 (15)	77 (12)	69 (14)	68 (18)	66 (17)	F=6.692 P<0.001

Table 2. *Previous tests of all 1846 patients performed in the other departments.*

		Unit Department							
n=1846		Emergency n=1134	Pneumonology n=206	Internal Medicine n=116	Neurology n=100	Cardiology n= 53	Surgery n=46	Other Units n=191	Test
Previous CT/Chest X-ray	1721 (93.2%)	1060 (93.5%)	202 (98.1%)	112 (96.6%)	82 (82.0%)	48 (90.6%)	40 (87.0%)	177 (92.7%)	χ^2=33.277 P<0.001
D-dimers dosage	1664 (90.1%)	1063 (93.7%)	184 (89.3%)	106 (91.4%)	86 (86.0%)	48 (90.6%)	30 (65.2%)	147 (77.0%)	χ^2=88.288 P<0.001

Distribution of patients in relation to sex was significantly different among Units of origin. Women more frequently were submitted to us from the departments of Cardiology and the Emergency Unit while men from the department of Surgery (x^2=21.576, P=0.001) (Table 1). Patients' mean age was 71 years (S.D±16) and was significantly different among the different departments of origin, with the oldest patients coming from the Neurology department (F=6.962, P<0.001) (Table 1). Data about the performance of previous instrumental tests (chest X-rays and/or CTPA) and D-dimer dosage in all 1846 patients are reported on Table 2.

Patients had already by 93.2% performed chest X-rays and/or CTPA (Table 2). D-dimer values were increased (>500ng/mL) in 1625 of 1664 patients in which was previously performed (97.7%), (D-dimers mean value was 4448.59±191.84ng/mL).

Lung perfusion scintigraphy was positive for APE in 309/1846 (16.7%) patients [176 female (57%) and 133 male (43%)] that consequently were promptly treated by their clinicians, with hospitalization in intensive care unit, and negative in 1537/1846 (83.3%) patients. Patients with negative LPS were dismissed and advised to return for follow-up within 2-3 weeks.

The frequency of LPS negative was statistically significant for all origin departments (X^2= 20.04, P=0.003). The highest percentage of positivity was found in patients from the Cardiology department (28%), followed by Neurology (22%), with statistically significant differences between the other departments (Table 3).

The number of risk factors positively correlated with the number of positive LPS (x^2_{lin}=6.472, P=0.011) (Table 4 and Figure 2). The most frequent risk factor was "arrhythmia" and/or "heart disease" present in 608/1846 patients followed by previous "surgery" (326/1846), and "deep venous thrombosis" (278/1846). However, the only risk factor predictive of positive LPS was "venous thrombosis" (OR=1.57, P=0.004) (Table 5).

Table 3. *Departments of origin in relation to LPS results.*

Department of origin (n=1846)	LPS positive for APE (n=309)	LPS negative for APE (n=1537)	Test	P
Emergency (n=1134)	178 (15.7%)	956 (84.3%)		
Pneumology (n=206)	43 (20.8%)	163 (79.2%)		
Int. Medicine (n=116)	21 (18.1%)	95 (81.9%)		
Neurology (n=100)	22 (22%)	78 (78%)	χ^2=20.044	
Cardiology (n=53)	15 (28.3%)	38 (71.7%)	P=0.003	
Surgery (n=46)	8 (17.4%)	38 (82.6%)		
Other Units (n=191)	22 (11.5%)	169 (88.5%)		

Table 4. *Number of risk factors in relation to LPS results.*

	n=1846	LPS positive for APE (n=309)	LPS negative for APE (n=1537)	Test	P
Risk factors				χ^2_{lin}=6.472	
none	628	94 (15.0%)	534 (85%)	P=0.011	
1	950	161 (17.0%)	789 (83%)		
2	250	53 (21.2%)	197 (78.8%)		
3 or more	18	6 (33.3%)	12 (66.7%)		

Table 5. *Risk factors in relation to LPS results.*

Risk Factors		LPS positive for APE	LPS negative for APE	Test	P
Arrhythmia/Heart disease	608	114 (18.8%)	494 (81.2%)	χ^2=1.8	0.180
Surgery	326	60 (18.4%)	266 (81.6%)	χ^2=0.488	0.485
Deep venous thrombosis	278	64 (23.1%)	214 (76.9%)	χ^2=8.187	0.004
Trauma/Fractures	155	22 (14.2%)	133 (85.8%)	χ^2=1.004	0.316
Drugs	77	16 (20.8%)	61 (79.2%)	χ^2=0.774	0.379

The most often referred symptoms in our patient were dyspnea (1322/1846), chest pain (726/1846) and cough (420/1846). In 49.2% of patients was present only 1 symptom, in 33.4% 2 symptoms, in 5.9% all 3 symptoms while 11.5% of patients had no symptoms but they presented one or more risk factors.

A significant association was observed between positive LPS and dyspnea (OR=1.78, P<0.001), conversely chest pain and cough were not associated with positive LPS (OR=0.95, P=649 and OR=1.25, P=0.066, respectively). D-dimers mean value was 4448.59ng/mL (S.D. 191.84ng/mL). Even if, the increased D-dimer dosage was not statistically associated with LPS results (OR=1.04, P=0.57), we observed that the D-dimer mean value was higher in patients with positive LPS (6886.615±650,18ng/mL) than in patients with negative LPS (3986,773±189.71ng/mL). This difference was statistically significant (t=-5.58, P<0.0001).

Chest X-rays and/or CTPA were negative for APE in 24.3% out of the 27.4% of patients suspected for APE, in 19.5% of non-specific cases for APE with pleural effusion and in 28.8% of non-specific with inflammatory interstitial diseases. Lung perfusion scintigraphies were positive in 13.6% of patients with negative chest X-rays and/or CTPA and in 21.3% with suspected chest X-rays and/or CT. Furthermore, was positive in 16.4% of cases with pleural effusion, in 15.2% with chronic obstructive pulmonary disease and in 16.6% with pulmonary inflammatory interstitial diseases. The remnant 16.9% of patients with positive lung pulmonary scintigraphy didn't

performed previous diagnostic examination but had presence of severe symptoms and risk factors.

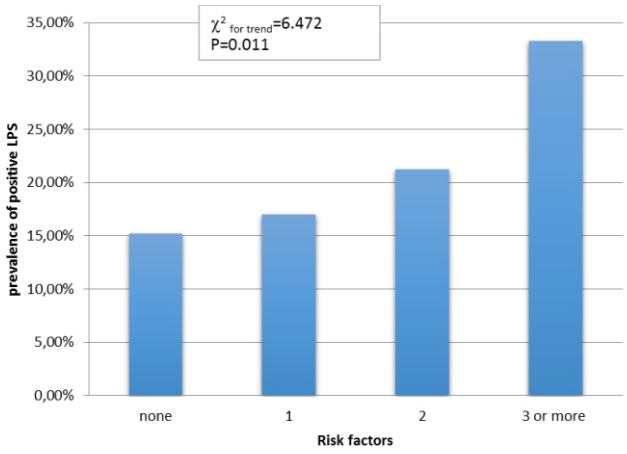

Figure 2. Relationship of positive LPS and the number of risk factors.

Discussion

Since APE may be completely of partly symptomatic, its diagnosis can be incidental and sometimes challenging [12]. Mortality in untreated cases is about 30%. Early diagnosis and adequate antithrombotic therapy reduce mortality to 2%-8% [11].

The high number of examinations performed in our hospital and especially in its Emergency Units reflects the high prevalence of suspicion for APE. Furthermore, our Emergency Nuclear Medicine Service confirmed that APE is more frequently diagnosed in females and older patients, because the presence of comorbidity and risk factors for APE increase with age. In 90% of cases, chest X-rays and/or CTPA and D-dimers dosage were performed before LPS, even if they are not specific tools for APE diagnosis. The distribution of APE suspected patients by Hospital Care Unit in our study confirmed the fundamental role of LPS especially in emergency scenarios.

The high number of negative LPS performed by our LPS Service demonstrated that LPS is a key factor for early diagnosis and for selecting the patients that need emergency treatment.

Our results confirm the observation of Miniati et al. (2010), which report very high specificity of LPS (97.7%) [10].

The presence of one or more risk factors was fundamental in the diagnosis of APE. Our study in fact, shows that LPS positive is statistically correlated with the number of risk factors. Deep venous thrombosis was, as others have found, the major risk factor for APE [11]. In addition, in most patients, dyspnea, chest pain, cough and syncope can supported the diagnosis of APE [12].

Dyspnea is considered the most frequent symptom of APE. It may be paroxysmal or severe in central APE, and mild and transient in small peripheral APE. Worsening dyspnea, in patients with pre-existing heart diseases, may be the only symptom suggestive of APE [13]. In our study population, dyspnea was present in 71.6% of cases and was the only symptom significantly correlated with positivity LPS, confirming the necessity to not underestimate it.

Chest pain is also frequent in patients with suspected APE, caused by pleural irritation, due to distal embolism. In central pulmonary embolism, chest pain may imitate angina, possibly reflecting ventricular dysfunction, eventually associated with ischemia. For this reason, patients with chest pain should be more frequently investigated with LPS.

Tests as chest X-rays and/ or CTPA and D-dimers dosage are usually performed in patients with suspected APE, even if they are not specific to discriminate patients with APE. In fact, increase in D-dimer concentration is seen in several conditions such as DVT, cancer, inflammation, bleeding, trauma, surgery and (tissue) necrosis. Despite the elevated negative predictive value of D-dimers dosage, its positive predictive value is low and elevated D-dimer dosage does not help to confirm APE [14]. Our study confirms that the increased value of D-dimer (>500ng/mL) is not predictive of APE but shows that D-dimers mean values are statistically higher in patients with positive LPS. In fact, as reported in literature, D-dimer levels are related to the simultaneous activation of coagulation and fibrinolysis in the presence of acute thrombosis [15,16].

Chest X-rays allowed recognition of pulmonary embolism in sporadic cases while in most of the cases showed a non-specific pattern specifically in cases of pleural effusion or inflammatory interstitial diseases, so integration with LPS is necessary to confirm the diagnosis of PE [17], as shown in Figure 3.

Currently, multidetector CTPA is the examination of choice for studying pulmonary vasculature in patients with suspected APE, thanks to the improvement of spatial and temporal resolution of the gamma camera and the quality of arterial opacification. Computed tomography pulmonary angiography allows a panoramic view of the whole chest and visualization of different diseases like atelectasis, bronchopulmonary foci, hemorrhagic foci and emphysema [18-19].

On the contrary, CTPA has a significantly higher exposure to ionizing radiation than the LPS. The absorbed dose during CT is always about 10mSv vs 1mSv during LPS [20] and needs the administration of medium contrast, not always possible, especially in emergency conditions as for patients with renal failure and contrast medium allergy. Computed tomography pulmonary angiography allows to diagnose large pulmonary embolism, but has a relatively low sensitivity (<80%) for sub-segmental pulmonary thromboembolism and cannot provide information about the hemodynamic effect of emboli or vascular stenosis, responsible of lung perfusion alterations [21, 22]. Furthermore, the use of CTPA can diagnose a great number of APE cases but does not reduce mortality. It may be that CTPA over-diagnoses APE [23, 24]. Figure 4 indicates the key role of LPS in the noninvasive assessment of APE.

Perfusion scans can be combined with ventilation studies to improve specificity: in APE, ventilation is usually to be normal in hypoperfused segments (mismatch pattern) [25]. Ventilation scan requires a longer preparation and execution time and active patient collaboration. These features do

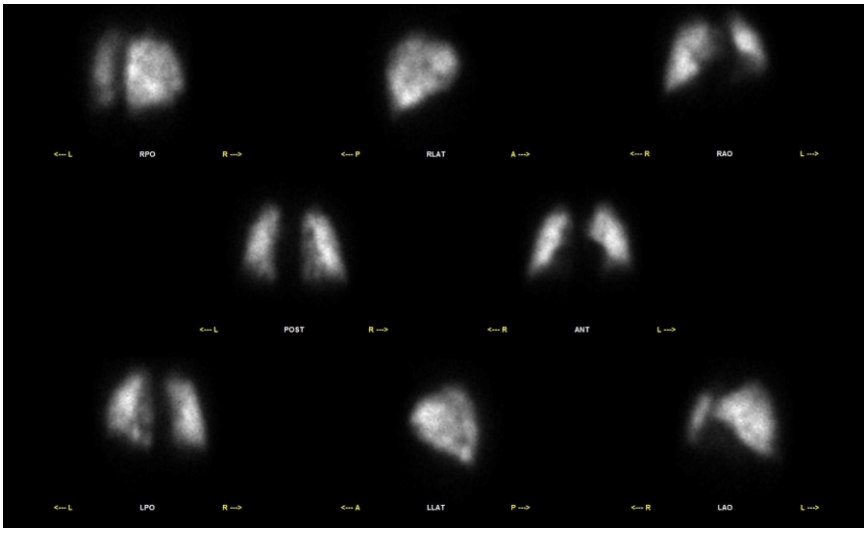

Figure 3. A LPS of a female of 68 years old, with dyspnea, caugh and DVP as a risk factor. The value of D-dimer was 2014μg/L (n.v. <500) and chest CT showed signs of inflammatory intestitial desease. Irregular uptake was detected in both lungs due to chronic parenchymal disease, negative for APE.

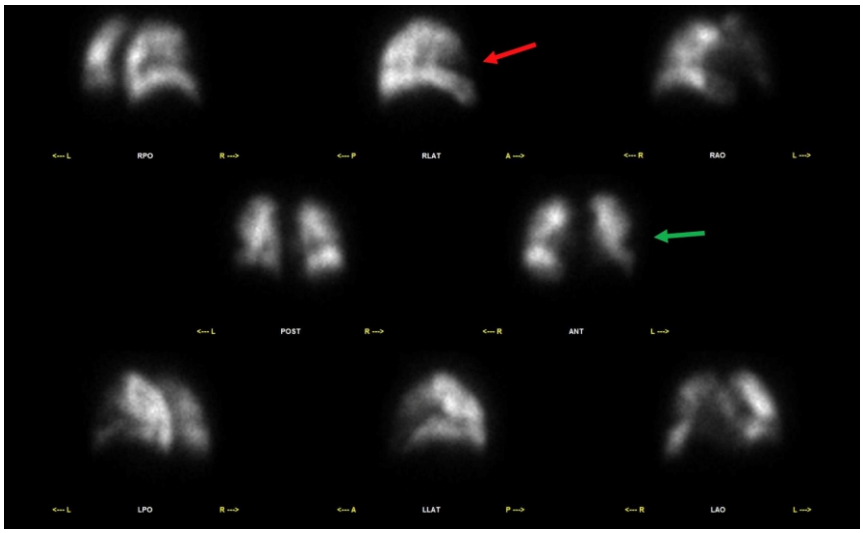

Figure 4. A 70 years old patient affected by multiple myeloma with dyspnea and chest pain, 18 hours after orthopedic surgery for femur trauma. Emergency LPS performed in on-call 24hrs service, showed a perfusion defect on the anterior segment of the right upper lobe (red arrow) and superior lingular division (green arrow), positive for APE.

not make it suitable to be performed in emergency. Both planar and tomographic acquisitions can be performed for a better case evaluation (of the perfusion scans) without further administration of a radiopharmaceutical and thus without ionizing radiation exposure. The availability of modern SPET/CT technology allows to obtain acquisition of tomographic images associated with morphology, thus increasing diagnostic accuracy of APE but has a longer application time and greater exposure to radiation that makes it suitable only in more complicated cases [26].

Currently, no diagnostic imaging protocol has been universally adopted for the diagnosis of APE in emergency conditions. Lung perfusion scintigraphy can be preferably used in young or pregnant females or in renal diseases [27, 28]. According to the Italian legislation, considering the diagnostic levels of reference, LPS has a very low irradiation exposure and so it can also be performed in pregnancy. It does not have side effects, it is well tolerated and it takes about 15 minutes to be performed, so movement artifacts do not occur and sedation of the patient is not necessary [29, 30]. Based on these advantages, we use LPS in the Emergency Nuclear Medicine Service of our hospital.

In our opinion, it is important that high-qualification hospitals have a nuclear medicine emergency unit to provide LPS timely [31].

In conclusion, LPS has many advantages such as to be a simple, quick and inexpensive examination; it does not require preparation and has no side effect so it can be performed in all types of patients including pregnant women, polytraumatized and complicated patients (renal failure and contrast allergy). All these advantages make LPS suitable to be performed as Emergency Nuclear Medicine Service.

Our four year and large-scale experience related to a metropolitan area suggests that in patients with suspected APE, LPS has a key role in the early diagnosis, permitting to select a very low percentage of pts that need adequate

but even more in the exclusion of APE, optimizing the management of pts who do not require admission to intensive care unit with high costs and limited availability.

Based on high incidence of APE, the difficulty of its clinical diagnosis (non-specific symptoms, numerous risk factors) and given the great demand and relevance of LPS, our study highlights how it's strongly recommended for Nuclear Medicine Units to perform LPS as emergency in on-call 24 hrs service.

Bibliography

1. Rubini G, Niccoli Asabella A, Stabile Ianora AA et al. Acute pulmonary embolism: comparison and integration of perfusion lung scintigraphy with multislice spiral CT. *Radiol Med* 2007; 112: 174-84.
2. Pelletier-Galarneau M, Zannier E, Zuckier LS, Le Gal G. Referral Patterns and Diagnostic Yield of Lung Scintigraphy in the Diagnosis of Acute Pulmonary Embolism. *Thrombosis* 2017; 2017: 1623868.
3. Heit JA, Silverstein MD, Mohr D et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population- based case-control study. *Arch Intern Med* 2000; 160: 809-15.
4. Anderson FA, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003; 107: I9-I16.
5. Rogers MA, Levine DA, Blumberg N et al. Triggers of hospitalization for venous thromboembolism, *Circulation* 2012; 125: 2092-9.
6. Lane DA, Mannucci PM, Bauer KA. Inherited thrombophilia: Part 2. *Thromb Hamost* 1996; 76: 824-34.
7. Cohen AT, Agnelli G, Anderson FA et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007; 98: 756-64.
8. Costa AF, Basseri H, Sheikh A et al. The yield of CT pulmonary angiograms to exclude acute pulmonary embolism. *Emergency Radiol* 2014; 21: 133-41.
9. Wells PS, Anderson DR, Rodger M et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med* 2001; 135: 98-107.
10. Miniati M, Pistolesi M, Marini C. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). *Am J Respir Crit Care Med* 1996; 154(5): 1387-93.
11. Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2008; 29: 2276-315.
12. Miniati M, Prediletto R, Formichi B. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. *Am J Respir Crit Care Med* 1999; 159: 864-71.
13. Wells PS, Ginsberg JS, Anderson DR et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998; 129: 997-1005.
14. Di Nisio M, Squizzato A, Rutjes AW et al. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. *J Thromb Haemost* 2007; 5: 296-304.
15. Stein PD, Hull RD, Patel KC et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med* 2004; 140: 589-602.
16. Righini M, Aujesky D, Roy PM. Clinical usefulness of D-dimer depending on clinical probability and cutoff value in outpatients with suspected pulmonary embolism. *Arch Intern Med* 2004; 164: 2483-7.
17. Daftary A, Gregory M, Daftary A. Chest radiograph as a triage tool in the imaging-based diagnosis of pulmonary embolism. *Am J Roentgenol* 2005; 185: 132-4.
18. Lake DR, Kavanagh JJ, Ravenel JG. Computed tomography and pulmonary embolus: a review. *Semin Ultrasound CT MR* 2005; 26: 270-80.
19. Scialpi M, Rebonato A, Cagini L et al. Split-Bolus Single-Pass Multidetector-Row CT Protocol for Diagnosis of Acute Pulmonary Embolism. *Iran J Radiolog* 2016; 13(1): e19844.
20. Raja AS, Greenberg JO, Qaseem A et al. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Annals of Internal Med* 2015; 163: 701-11.
21. Van Strijen MJ, De Monye W, Kieft GJ. Diagnosis of pulmonary embolism with spiral CT as a second procedure following scintigraphy. *Eur Radiol* 2003; 13: 1501-7.
22. Members ATF, Konstantinides S, Torbicki A. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014; 35: 3033-69.
23. Anderson DR, Kahn SR, Rodger MA. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. *J Amer Med Assoc* 2007; 298(23): 2743-53.
24. Molaee S, Ghanaati H, Safavi E et al. Computed Tomography Pulmonary Angiography for Evaluation of Patients With Suspected Pulmonary Embolism: Use or Overuse. *Iran J Radiol* 2015; 12(3): e22383.
25. Alderson PO. Scintigraphic evaluation of pulmonary embolism. *Eur J Nucl Med* 1987; 13: S6-10.
26. Perrier A, Desmarais S, Miron MJ. Noninvasive diagnosis of venous thromboembolism. *Lancet* 1999; 352: 190-5.
27. Washington L, Goodman LR, Gonyo MB. CT for thromboembolic disease. *Radiol Clin North Am* 2002; 40: 751-71.
28. Burge AJ, Freeman KD, Klapper PJ, Haramati LB. Increased diagnosis of pulmonary embolism without a corresponding decline in mortality during the CT era. *Clin Radiol* 2008; 63: 381-6.
29. Niccoli Asabella A, Cimino A, Altini C et al. Lung Perfusion Imaging in Tetralogy of Fallot: A Case Report. *Mol Imaging Radionucl Ther* 2018; 27: 146-8.
30. Niccoli Asabella A, Stabile Ianora AA, Di Palo A et al. Lung scintigraphy in pediatric patients with congenital malformations. *Recenti Prog Med* 2013; 104: 442-5.
31. Ferrari C, Cimino A, Bianco G et al. The impact of lung perfusion scintigraphy in the emergency management of patients with suspected pulmonary embolism. *Hell J Nucl Med* 2017; 20 Suppl: 166.