Current perspectives

The diagnosis of acute pulmonary embolism. A review of the literature and current clinical practice

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The optimal approach to the diagnosis of acute pulmonary embolism is still controversial. The poor sensitivity and specificity of most of the clinical manifestations, the suboptimal accuracy of the majority of the laboratory and instrumental examinations and the highly variable local availability of the diagnostic resources, makes it in fact difficult for a univocal strategy to be adopted. Recently published practical guidelines, however, support the use of lung scanning (either ventilation/perfusion or only perfusion) as a first-line imaging test, since this approach allows for a correct diagnosis in most patients, after careful history taking, physical examination and electrocardiogram, chest X-ray and arterial blood gas analysis performance. When lung scanning is non-diagnostic, either serial non-invasive (i.e. ultrasonographic) evaluation of the lower limbs or pulmonary angiography should follow. Growing evidence is accumulating on the use of spiral computed tomography scanning either as an alternative or as a complement to lung scanning, while echocardiography should be reserved for the bedside evaluation of critically ill patients, when more validated techniques are not readily available. The role of plasma D-dimer measurement has yet to be defined, especially in hospitalized patients.

In current clinical practice, however, these recommendations seem to be only partially followed. Depending in fact on the different characteristics of the populations examined in the seven available studies reporting on this issue, the use of the different diagnostic techniques appears highly variable. Although a standard diagnostic pathway does not seem applicable to all patients with suspected acute pulmonary embolism, further work is nonetheless needed in order to identify in different patient subsets the diagnostic approach capable of minimizing the use of diagnostic resources while obtaining the greatest amount of information.

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Introduction

The diagnosis of acute pulmonary embolism (PE) is based on its clinical suspicion. The occurrence of unexplained sudden onset of dyspnea and/or chest pain and/or fainting, especially in patients with risk factors for venous thromboembolic disease, should in fact prompt physicians to proceed with further testing. Electrocardiogram (ECG), chest X-ray and arterial blood gas analysis should represent the basic examinations, since their usefulness in reinforcing the clinical suspicion and in ruling out diseases to be differentiated from PE has been clearly established.

The ECG changes, which range from ST segment depression to tachycardia, T wave inversion in V_1-V_2, $S_1Q_3T_3$ pattern and right bundle branch block[1,2], are poorly sensitive, since they are also found in diseases other than acute PE. Moreover, these findings are frequently transient and are influenced by the severity of PE and by preexisting cardiopulmonary diseases[3]. The ECG signs of right ventricular overload ($S_1Q_3T_3$ pattern, T wave inversion in V_1-V_2, and transient right bundle branch block), however, have recently been shown to be highly specific[2], so that ECG, also because it allows for the differentiation from acute myocardial infarction, still retains a very important role in the diagnosis of acute PE. Additionally, ECG changes over time (namely, the normalization of inverted T waves in the precordial leads) appear to carry significant prognostic information, in that they are accelerated when the disease regresses spontaneously or pharmacologically[4].

Chest X-ray in acute PE, when carefully performed and interpreted, results abnor-

mal in over 90% of cases, showing anomalies which commonly include elevated hemidiaphragm, oligemia, amputation of the hilar artery, parenchymal consolidation compatible with pulmonary infarction, and pleural effusion[2,5]. Although poorly sensitive, some of these alterations (oligemia, amputation of the hilar artery, and pulmonary infarction) have proven to be highly specific[2], so that chest X-ray, besides helping to rule out diseases, such as pneumothorax, aortic dissection, pulmonary or pleuric infection, which can mimic acute PE, should be considered capable of confirming the diagnosis in the appropriate setting.

Arterial blood gas analysis in patients with acute PE generally shows hypoxemia with hypocarbia, due to the ventilation-perfusion mismatch. This finding, however, is influenced by preexisting cardiopulmonary diseases, and is absent in as many as 20% of cases[5,6]. The evaluation of gas exchanges in the lungs via different tests, such as the determination of oxygen alveolar-arterial gradient, does not seem to increase the diagnostic accuracy[7].

The process of integrating clinical, ECG and chest X-ray data, although not accurate enough to diagnose or rule out with certainty acute PE, is very useful for the estimation of an *a priori* probability to compute the *a posteriori* probability after further diagnostic testing. In the presence of either sudden onset dyspnea or chest pain or fainting, associated with any of the following abnormalities: ECG signs of right ventricular overload, radiographic signs of oligemia, amputation of the hilar artery and pulmonary infarction, the clinical probability of acute PE should be considered high (90%), since the positive predictive value is 96%[2]. The clinical probability should be considered intermediate (50%) in the presence of at least one of the symptoms, not associated with any ECG or chest X-ray abnormalities or associated with ECG changes only, and low (10%) when the symptoms are absent or recognized to be due to alternative diagnoses[2]. Concordantly, a (pre-test) clinical probability of 10, 50 and 90% is associated with a (post-test) probability of 58, 93 and 99%, respectively, when the lung scan results are compatible with PE, and of 2, 13 and 58%, respectively, when the lung scan results are negative for PE[2].

The integrated clinical, ECG and chest X-ray evaluation appears therefore also useful in selecting patients to be sent to subsequent examinations, in order to obtain a definitive objective diagnosis. Confirmation of clinically suspected acute PE, however, is still difficult due to the suboptimal accuracy of most of the laboratory and instrumental tests. Moreover, the local availability of the different diagnostic resources is highly variable, thus making it difficult to adopt a standardized diagnostic pathway.

Laboratory and instrumental examinations

The pivotal examination in suspected acute PE has long been established as ventilation/perfusion lung scanning, which, in a suitably sized and designed study, is the only technique until now comparable with the known diagnostic gold standard represented by pulmonary angiography. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) a group of 931 patients (either in-patients or out-patients) suspected of having acute PE and who had previously agreed to undergo pulmonary angiography, had ventilation/perfusion lung scintigraphy according to the standard technique. The results were classified as high probability, intermediate (or indeterminate) probability, low probability and normal pattern and were compared with the angiographic findings (available in 81% of the population)[8]. Ventilation/perfusion lung scanning proved to be highly sensitive (98%), but poorly specific (10%), with high positive and negative predictive values only when the results were classified as high probability (88%) and normal (91%), respectively. These two patterns, however, accounted only for 27% of the total scans, while the remaining 73% included intermediate (39%) and low (34%) probability classifications, which yielded a positive predictive value of 33% and 16%, respectively. In addition, with intermediate and low probability results, the interobserver agreement was only 70-75%, while it was 95% with high probability or normal classifications. Thus, it can be concluded that ventilation/perfusion lung scanning performed in the case of suspected acute PE gives non-diagnostic results, which warrant further investigation, in about two thirds of cases.

This situation improved somewhat when the results of ventilation/perfusion lung scanning were interpreted in the light of the associated clinical probability. The association of both clinical and scintigraphic high probability made the positive predictive value of the latter as high as 96%, similar to the negative predictive value of both low clinical and scintigraphic probability. However, an intermediate scintigraphic probability had once again a highly variable positive predictive value, ranging from 6 to 28 to 66%, depending on whether the associated clinical probability was low, intermediate or high, respectively[8].

Since the PIOPED population included only patients who had previously agreed to undergo pulmonary angiography, the diagnostic accuracy of ventilation/perfusion lung scanning was also examined in a larger group of patients that included those (not enrolled in the PIOPED) who underwent pulmonary angiography on the recommendation of their attending physician. Among the 1487 patients included in this group, it was confirmed that ventilation/perfusion lung scintigraphy had high sensitivity (99%) and low specificity (12%), along with the high positive predictive value (87%) of a high probability result and the high negative predictive value (88%) of a low probability result. In addition, a high interobserver reading agreement was confirmed when the scans were classified as normal or high probability (87-89%), along with a poor interobserver agreement (58-75%) when the scans were classified as intermediate or low probability[9].

Attempts have been made to improve the diagnostic accuracy of ventilation/perfusion lung scanning, by revising the PIOPED criteria[10,11]. Although promising, these modified classification schemes are not yet extensively used in the clinical setting.

Since the ventilation phase is costly, time consuming, not widely available and not applicable to all patients, a simplification of the scintigraphic technique, based on the perfusion phase only, has also been evaluated. In the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) 890 consecutive patients with suspected acute PE underwent perfusion lung scanning, followed by pulmonary angiography in the case of abnormal results[12]. Differently from PIOPED, the scintigraphic results were categorized into only four groups (normal, near-normal, abnormal compatible with PE, abnormal not compatible with PE), according to the presence or the absence of wedge-shaped perfusion defects, regardless of their number and size. With this approach, the sensitivity of lung scanning confirmed to be very high (92%), and also specificity turned out to be elevated (87%). In turn, the positive predictive value of an abnormal perfusion scan compatible with PE and the negative predictive value of an abnormal perfusion scan not compatible with PE were 92 and 88%, respectively. Once again, integrating the scintigraphic data with the clinical, ECG and chest X-ray results, the diagnostic accuracy increased: in the presence of high, intermediate and low clinical probability the likelihood of acute PE was 99, 92 and 55%, respectively when the lung scan results were compatible with PE, and 39, 20 and 3%, respectively when scintigraphy, although abnormal, was not compatible with PE[2].

In the light of these results, along with the demonstration of a superior interobserver agreement with the simplified perfusion approach[2] and the only slightly higher (not significant) number of indeterminate results compared to the ventilation/perfusion technique[13], a diagnostic strategy based on the perfusion phase only is currently proposed as the screening imaging test for suspected acute PE[14].

Pulmonary angiography has long been recognized as the diagnostic gold standard for PE. Historically, the test has been recommended to follow a non-diagnostic ventilation/perfusion lung scan. In the PIOPED, 1111 patients underwent pulmonary angiography according to the standard technique within 24 hours of symptom onset, with an overall mortality of 0.5% and a rate of non-fatal major complications (acute respiratory insufficiency requiring cardiopulmonary resuscitation maneuvers or intubation) of 1%[15]. Furthermore, minor complications, such as allergic skin reactions or transient renal failure, occurred in 5% of patients. Interestingly, the complications, although more frequent in sicker patients, were not related to age, sex, presence or absence of PE or average mean pulmonary pressure. In 3 out of 5 deaths, a clear relationship with the angiographic procedure could not be demonstrated. The interobserver agreement was 81% and directly related to the quality of the film, along with the location of the thromboemboli, being 98% for lobar, 90% for segmental, and 66% for sub-segmental locations. The safety of pulmonary angiography was also confirmed in a retrospective analysis of 697 patients with suspected acute PE where mortality and morbidity were reported to be 0 and 0.4%, respectively[16]. Although proven to be very safe, pulmonary angiography continues to be underutilized, being performed in only 12-14% of non-diagnostic ventilation/perfusion lung scans[17], probably due to its high cost and frequent lack of availability in many hospitals. The recent introduction of intravenous digital subtraction angiography (along with non-ionic contrast media) has further increased the safety of this test, without significantly decreasing its diagnostic accuracy. The improved image quality associated with digital subtraction angiography was accompanied by an interobserver agreement of 90% compared to 64-80% with the traditional technique[18].

Due to the high cost, the limited availability and the invasive nature of pulmonary angiography, alternative techniques have been developed to complement a non-diagnostic lung scan. The understanding that PE and deep vein thrombosis (DVT) are just two aspects of the same venous thromboembolic disease, has led to the suggestion that DVT may serve as a diagnostic surrogate for PE. Autopsy studies have in fact shown that most pulmonary emboli originate from the deep venous system of the inferior limbs. In 70% of patients with PE, DVT is present on flebography, and in about 50% of patients with DVT, the ventilation/perfusion scan results are compatible with PE[19,20]. In clinical practice, ultrasonography (either compression B-mode or duplex) of the lower extremities, has replaced flebography, which represents the accepted diagnostic gold standard for DVT. Compared to flebography, this technique has a sensitivity and specificity of 90 and 95% respectively, in symptomatic patients with proximal DVT[21]. On the contrary, ultrasonography of the lower limbs has poor sensitivity in detecting isolated DVT of the muscular veins of the calf and in diagnosing DVT in asymptomatic subjects[21,22].

Since proximal DVT is found on ultrasonography in about 50% of patients with ventilation/perfusion scan abnormalities and angiographic evidence of PE[19,23], serial non-invasive tests (three over a week) of the lower limbs are currently recommended for the diagnosis or exclusion of DVT in patients with a non-diagnostic ventilation/perfusion scan[24,25]. A negative first test could result in fact from a different origin of thromboemboli (i.e. the pelvic, renal or superior limb veins) or from the partial or total detachment of the thrombus from a proximal deep vein of the inferior limbs with no residual thrombus detectable in this system. The efficacy of the above-mentioned strategy has recently been confirmed in a prospective study[26] in which 1564 patients with suspected acute PE and non-diagnostic ventilation/perfusion

lung scan (observed in 53% of the cases) had six serial impedance plethysmographies over a period of 2 weeks. DVT was diagnosed in 12% of patients with a non-diagnostic ventilation/perfusion scan (75% on admission and 25% on serial tests). The patients with negative non-invasive serial tests showed a low incidence of events at 3 months of follow-up, comparable to that of patients where PE was excluded by a ventilation/perfusion lung scan at the time of the initial study (2 vs 0.7%, p = NS).

In the last several years, spiral computed tomography (CT) scanning has been proposed as an alternative method for non-invasive evaluation of the pulmonary bed[27,28]. It is based on the capability of visualizing the pulmonary tree (and therefore possible thromboemboli inside it) in a non-invasive way, since a small amount of contrast medium is injected through a peripheral vein, giving excellent image quality obtained by a fast acquisition during a single breath hold. Several early studies, although small in size and non-randomized, were concordant in showing sensitivity and specificity of the technique (about 95 and 97%, respectively) comparable to traditional pulmonary angiography[29-32]. The only exception was thromboemboli exclusively located in the sub-segmental arteries[32], where false negative results were frequently obtained[16,29-32]. However, traditional pulmonary angiography also has a significant incidence of false negative results when thromboemboli are located in sub-segmental arteries[33]. Since pulmonary emboli usually split into an average of 6 to 8 fragments[32] and only in about 6% of cases they are exclusively located in the sub-segmental vessels[33], spiral CT scanning has been proposed as a first-line investigation in place of ventilation/perfusion lung scintigraphy[27,28]. Comparison studies, both retrospective and prospective (although small in size), have demonstrated that spiral CT scanning, compared to ventilation/perfusion lung scanning, has significantly higher sensitivity and specificity (75-95% and 90-97% vs 49-65% and 74-95%, respectively)[34-36]. In addition, spiral CT scanning is associated with a superior interobserver agreement[34] and more frequently can be used to obtain a definitive diagnosis (92 vs 72%, $p < 0.001$) or to find alternative diagnoses (93 vs 51%, $p < 0.001$)[35]. Spiral CT scanning is also considerably less expensive than ventilation/perfusion lung scintigraphy[36]. More recent experience with a small population of patients with suspected acute PE, undergoing both pulmonary angiography and spiral CT, showed however sensitivity of only 53% and specificity of 97% for spiral CT[37], which therefore could be more suitable as a confirmatory study than as a screening study. Indeed, an initial report of 164 patients with possible acute PE, non-diagnostic ventilation/perfusion scan and negative duplex ultrasound of the legs, demonstrated an incidence of subsequent events after negative spiral CT scan comparable to that of patients with negative pulmonary angiograms[38]. Even more recently, the high negative predictive value for subsequent PE of a negative spiral CT has been confirmed in a large study conducted on 548 patients with suspected acute PE and negative/low probability ventilation/perfusion scan or negative spiral CT[39]. During a 3-month follow-up period the incidence of subsequent PE was not significantly different among patients with negative CT scan (1%) and negative (0%) or low probability (3.1%) ventilation/perfusion lung scintigraphy[39]. Therefore, while most clinicians already accept a diagnosis of acute PE based on spiral CT, it now appears that also when the disease is ruled out by means of this technique, the result can be relied upon and the anticoagulation treatment safely withheld. Further work, however, is needed in order to determine whether and when spiral CT scanning should be included in the diagnostic algorithm of acute PE, although the possibility of also performing a CT scanning of the pelvic and leg veins to investigate for DVT in the same thoracic session, clearly represents an advantage which will probably further expand the use of this technique.

In addition to the imaging modalities mentioned above, more modern techniques, such as magnetic resonance[40], are being evaluated and have shown favorable results in preliminary studies. However, for the time being, there is insufficient data to recommend their widespread application in the diagnosis of acute PE.

The role of echocardiography is not well defined in the diagnostic approach to acute PE. Although transthoracic echocardiography is useful for the visualization of the indirect signs of right ventricular pressure overload (dilation and hypokinesia, leftward displacement of the interventricular septum), this technique allows for the direct visualization of thromboemboli in the pulmonary vessels or right heart cavities only in about 4-5% of the cases[41]. Changes in right ventricular morphology and/or function that can be identified by echocardiography are quite sensitive for PE, but lack specificity, with the possible exception of a pattern, recently identified in a small retrospective study and characterized by akinesia of the right ventricular free wall with normal motility of the apex, which has shown 77% sensitivity and 94% specificity for PE[42]. Also retrospectively, it has recently been shown in a large multicenter international registry that the presence of echocardiographic right ventricular hypokinesia in patients with PE carries significant prognostic information, being associated with the doubling of the risk of death within the ensuing 3 months[43]. For the time being, however, transthoracic echocardiography is currently recommended[44] for the bedside evaluation of hemodynamically unstable patients, when more validated diagnostic techniques are not available. Echocardiography is also useful to differentiate PE from other potentially lethal diseases such as aortic dissection, cardiac tamponade and rupture of the interventricular septum. The application of the transesophageal approach has not modified the role of echocardiography in acute PE, although this may be particularly useful for the detection (apparently as accurate as spiral CT) of proximal throm-

boemboli[45,46] and for the exclusion of concomitant aortic diseases.

Several laboratory tests have been proposed to help in the diagnosis of acute PE, but few of them have proven to be useful. Neither the triad (previously considered pathognomonic) of lactic dehydrogenase and bilirubin elevation with normal serum glutamic oxalacetic transaminase, nor leukocytosis or elevation of creatine kinase has adequate sensitivity or specificity to aid the diagnosis. The only promising laboratory test is the plasma determination of D-dimer, which is a specific product of the degradation of fibrin released into the circulation as a result of endogenous fibrinolysis. The test shows 93-97% sensitivity and 25-45% specificity[47,48], when plasma levels are above a critical threshold value (usually 500 ng/ml). The high sensitivity of this test results in a high negative predictive value (higher than 95% in most of the studies), so that it has been claimed that no further investigation is required when the D-dimer test is negative in patients with non-diagnostic ventilation/perfusion scan[49]. On the contrary, due to the low specificity (lower than 60% in most studies), a positive result always warrants further investigation, especially in hospitalized patients where the inclusion of D-dimer measurement into a non-invasive diagnostic algorithm has proven to be useless[50]. Beside the problem of the suboptimal specificity of the test, the results may vary due to different methods used to perform the assay. The ELISA assay, in fact, appears to be the most accurate (and the most studied), but it is expensive and slow, while the latex absorption tests (more rapid and less costly) are often only qualitative (or semi-quantitative) and frequently yield false negative results[51]. Due to these limitations, the role of D-dimer measurement in acute PE has yet to be defined, although its use as a part of a diagnostic algorithm has already been proposed and tested[52].

Current clinical practice

Based on the evidence accumulated from several studies designed to identify the optimal diagnostic strategy in the suspicion of acute PE, various diagnostic pathways have recently been proposed[14,24,53,54], some also being endorsed by associations such as the British Thoracic Society[53] and the American Thoracic Society[54]. Very little, however, is known about what is actually done in current clinical practice. By means of a Medline search carried out between 1998-1999, using "pulmonary embolism, diagnosis" as key words, only seven papers reporting on the diagnostic approach to acute PE in the routine clinical setting, were retrieved (Tables I and II)[43,55-60].

Ferrari et al.[55] (Table I) conducted a prospective registry in 16 French hospitals over a 30-month period, in order to identify the diagnostic methods used to assess patients with acute PE and/or DVT. A total of 387 patients with PE and 446 with DVT were included. In the 387 patients with PE, ECG and chest X-ray were performed in 100% of cases and lung scintigraphy in 41% (ventilation/perfusion in 61%). In 65% of the patients undergoing lung scanning, however, angiographic confirmation was required. Pulmonary angiography was

Table I. Use of the different diagnostic techniques in the various studies.

	Ferrari et al.[55] (n=387)	Kasper et al.[56] (n=1001)	Rubboli et al.[57] (n=127)	Goldhaber et al.[43] (n=2454)	Roncon et al.[58] (n=880)	Saro et al.[59] (n=251)
ECG (%)	100	98	96	90	100	NR
Chest X-ray (%)	100	NR	95	95	100	NR
Blood gas analysis (%)	NR	NR	90	NR	100	NR
Lung scan (%)	41	57	83	84	35	73
Pulmonary angiography (%)	80	17	4	19	28	7
Spiral CT (%)	1	NR	16	NR	39	NR*
Echocardiography (%)	64	72	48	47	70	NR
D-dimer ELISA (%)	NR	NR	NR	18	NR	NR
Lower limb US (%)	83	71**	73	84	78	36

CT = computed tomography; NR = not reported; US = ultrasonography. * technique not available; ** and/or phlebography.

Table II. Average number of investigations undertaken per hospital designation per year[60].

	General	Teaching	Specialist	All units
Lung scan	271	353	97	274
Spiral CT	15	53	200	26
Pulmonary angiography	3.1	8	15	4.6

CT = computed tomography.

performed in 80% of patients and echocardiography in 64%, the latter yielding results estimated sufficient to allow for a definitive diagnosis in 23%. Finally, in 16% of patients, the diagnosis was established using only clinical and radiological data without the use of scintigraphic, echocardiographic or angiographic examination. In all of these cases, however, a recent DVT was identified. A CT scan of the chest, performed for other reasons (investigation of the pericardium or the aorta), was able to identify clots in the pulmonary bed in only 1% of patients. Among the 446 patients with DVT, venous ultrasonography was performed in 83% of cases and flebography in 50% of patients. Both of these techniques were effective in identifying the venous clot in 96% of the population.

Kasper et al.[56] (Table I) prospectively evaluated 1001 consecutive patients from 204 centers throughout Germany over a period of 16 months in order to identify the current management strategies as well as the clinical course of acute PE. In the four previously defined groups with increasing clinical and hemodynamic instability, a progressive decrease in the number of tests performed was observed (Table III). Overall, ECG was performed in 98% of cases (ranging from 100 to 92%), while lung scintigraphy (ventilation/perfusion or perfusion) was used in 52% of patients (ranging from 68 to 24%). Pulmonary angiography was performed in 17% of patients (from 23 to 14%) and right heart catheterization in 26% (from 29 to 23%). An echocardiogram was obtained in 72% of cases (from 80 to 66%) and lower limb ultrasonography or phlebography in 71% (from 88 to 40%).

Rubboli et al.[57] (Table I) reported a 2-year retrospective analysis of the diagnostic strategy followed in 127 patients in an Italian general hospital, where multiple diagnostic facilities were available. An ECG, chest X-ray and blood gas analysis were performed in 96, 95 and 90% of cases, respectively. In 68% of patients, the initial evaluation included a D-dimer latex agglutination test. Among the 102 patients who survived the initial phase, lung scintigraphy was performed in 81% (ventilation/perfusion in 93%), spiral CT scanning in 10%, and pulmonary angiography in 2% of the cases. Although only 60% of lung scans yielded high probability results, further testing was performed in only 10% of these patients, spiral CT in 6 cases and pulmonary angiography in 2. The global utilization of the different imaging techniques was therefore 83% for lung scanning, 16% for spiral CT, and 4% for pulmonary angiography. In 7% of patients, the initial evaluation was followed immediately by therapy with no subsequent diagnostic imaging, except for echocardiography and/or ultrasonography of the lower limbs. These latter two tests were employed, however, as second-line tests in 48 and 73% of patients, respectively. Echocardiography showed signs of right ventricular pressure overload in 84% of cases, while thromboemboli in the right heart cavities and/or the pulmonary tree were not detected in any of the patients. Clot visualization in the veins of the lower extremities was obtained by compression/duplex ultrasonography in 80% of patients.

Goldhaber et al.[43] (Table I) prospectively registered 2454 consecutive patients with PE at 52 participating hospitals in 7 American and European countries over a period of 22 months. The principal objectives of this registry, named ICOPER, were to obtain epidemiological and clinical data to identify factors associated with death, along with information about diagnostic and therapeutic strategies. In 86% of the population, autopsy, high probability lung scan, pulmonary angiogram or venous ultrasound of the deep leg veins plus high clinical suspicion confirmed the diagnosis. Among the usual basic investigations, ECG and chest X-ray were performed in 90 and 95% of patients, respectively, while plasma D-dimer ELISA determination was employed in 18% of cases. Perfusion lung scanning was performed in 84% of cases (ventilation/perfusion in 47%) and yielded high probability results in 77%. Pulmonary angiography was used in 19% of patients and echocardiography in 47%. Echocardiography showed signs of right ventricular pressure overload in 40% of the patients examined, while in 4% intracardiac thrombi were seen. Finally, 49% of the population had concomitant DVT, diagnosed in 84% of cases with venous ultrasound and in 6% with flebography.

Table III. Use of the different diagnostic techniques in the groups of patients with progressive hemodynamic impairment[56].

	Group 1	Group 2	Group 3	Group 4
ECG (%)	99.5	99	100	92
Echocardiography (%)	80	73	68	66
Lung scan (%)	68	60	57	24
Pulmonary angiography (%)	23	15	14	14
Lower limb US and/or phlebography (%)	88	79	75	40
Right heart catheterization (%)	29	23	26	24

US = ultrasonography. Group 1 = right ventricular pressure overload or pulmonary hypertension, in the absence of arterial hypotension; Group 2 = arterial hypotension (systolic blood pressure < 90 mmHg), with no clinical signs of cardiogenic shock or catecholamine need for pressure support; Group 3 = cardiogenic shock or need for catecholamines; Group 4 = circulatory collapse with cardiopulmonary resuscitation at presentation.

Roncon et al.[58] (Table I) prospectively evaluated both the diagnostic and therapeutic strategy followed in 1993 in the Italian Veneto Region for patients with acute PE. This survey included 880 cases of acute PE and involved 191 Divisions of Cardiology, Geriatrics, Internal Medicine, Respiratory Medicine and Intensive Care Units (60% provided data). ECG, chest X-ray and blood gas analysis were all performed in 100% of cases. Perfusion lung scanning was performed in 35% of cases, accompanied by ventilation scanning in 20% of patients. Pulmonary angiography was performed in 28% of cases, spiral CT scanning was done in 39%, and echocardiography in 70%. The evaluation of the deep veins of the inferior limbs was carried out by compression ultrasonography in 48% of patients, by duplex ultrasonography in 30%, by impedance plethysmography in 14% and by phlebography in 40%.

Saro et al.[59] (Table I) retrospectively evaluated 251 patients, either admitted to the Emergency Department or with the diagnosis of PE in the discharge clinical report, hospitalized over a 2-year period at a University tertiary center in Spain. The aim of the study was to evaluate the approach to the diagnosis of acute PE in a routine clinical setting. The diagnostic facilities included ultrasonography of the lower limbs and phlebography, available at any time, and pulmonary angiography and isotopic lung scan, accessible on the other hand only during regular working hours. Spiral CT scanning was not available. Lung scanning resulted in being the most commonly used diagnostic technique, having been performed in 73% of patients, although in 64% of cases it yielded non-diagnostic results, warranting therefore further testing (performed however only in two thirds of cases). Pulmonary angiography was employed only in 7% of patients, while lower limb ultrasonography and phlebography were performed in 36 and 31% of cases, respectively. Ultrasonography of the lower limbs allowed for the detection of DVT in 52% of patients.

Burkill et al.[60] (Table II) conducted a survey in the British Islands on the use of lung scintigraphy, spiral CT scanning and pulmonary angiography to diagnose acute PE. By means of a questionnaire sent to 327 hospitals (66% returned the information) the use of the different techniques was investigated, according to hospital designation (general, teaching or specialist) and access to diagnostic facilities (on-site or off-site). The designation of the hospital influenced the availability of the diagnostic resources, since the teaching hospitals had more choice, mainly on-site, compared to others. Overall, 96% of centers had the possibility of access, either on-site or off-site, to lung scanning, 52% to spiral CT and 66% to pulmonary angiography. When both lung scan and spiral CT were available, the former was performed 15 times more often than the latter, while the possibility of all the three techniques evaluated, for every pulmonary angiogram, 6 spiral CT and 85 lung scans were performed.

From the studies described above, it would appear that there is a wide variation in the utilization rates of the different diagnostic techniques in patients with acute PE. While an ECG, chest X-ray and arterial blood gas analysis were performed, as expected, in the majority of patients, the use of subsequent tests showed less consistency (Tables I, II and III). Perfusion lung scanning ranged from 35 to 84%, and was not always accompanied by ventilation scanning. Pulmonary angiography was performed in 4 to 80% of cases, while spiral CT scanning ranged from 1 to 39%. Echocardiography and ultrasonography of the lower limbs, on the other hand, ranged from 47 to 74% and 36 to 84%, respectively. It is possible that the different populations included in each study could have influenced the variability in the use of the different tests. For example, in the study by Ferrari et al.[55] a high prevalence of patients from cardiology sections may well have accounted for the frequent use of echocardiography and pulmonary angiography. Similarly, the study by Kasper et al.[56] was designed to evaluate patients with "major" acute PE (that is, with significant hemodynamic impairment), who represented in fact 59% of the global population of PE patients. The high prevalence of very ill patients, therefore, could explain the extensive use of echocardiography (currently accepted as the best imaging technique for bedside evaluation) (Table III). In addition, the population of Roncon et al.[58] included only patients from Cardiology, Geriatrics, Internal and Respiratory Medicine Divisions and Intensive Care Units, with no patients from either Emergency Departments or Surgery Divisions, where often acute PE occurs and is diagnosed before the patient is transferred to medical wards. Furthermore, patients were included from both large and small hospitals from one region, which may have imposed some restrictions on what diagnostic resources were available.

A more balanced patient population appears to have been analyzed by Goldhaber et al.[43], Rubboli et al.[57] and Saro et al.[59], as well as by Burkill et al.[60]. Indeed, these studies showed much less variability in the utilization of the diagnostic techniques and, not surprisingly, much more adherence to the current recommendations of the literature[14,24,53,54]. Lung scintigraphy, although confirming its suboptimal accuracy, in fact resulted in being the imaging technique most frequently used in the populations of Goldhaber et al.[43], Rubboli et al.[57] and Saro et al.[59] (Tables I and II), having been employed in 84, 83 and 73% of cases, respectively. Pulmonary angiography on the other hand was limited to 19, 4 and 7% of patients, respectively. With the availability of both these techniques, also Burkill et al.[60] showed a much higher use of lung scintigraphy compared to pulmonary angiography (ratio 85:1). While not reported by Saro et al.[59], the use of echocardiography appeared to be comparable in the studies by Goldhaber et al.[43] and Rubboli et al.[57], having been performed in 47 and 48% of cases, respectively. Also ultrasonography of the lower limbs

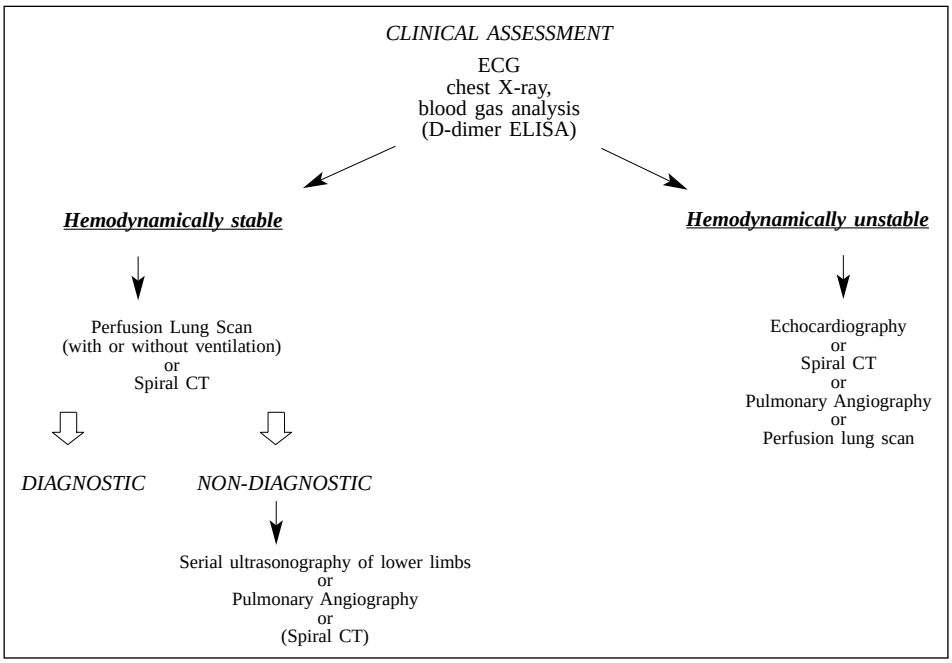

Figure 1. *Diagnostic algorithms in patients with suspected acute pulmonary embolism. CT = computed tomography.*

was similarly used in the populations of Goldhaber et al.[43] and Rubboli et al.[57] (84 and 73%, respectively), while it was performed in only 36% of patients studied by Saro et al.[59].

Conclusions

In the case of suspected acute PE, the fundamental diagnostic step is to carry out a thorough clinical evaluation (history, signs and symptoms), combined with ECG and chest X-ray, followed by perfusion lung scanning, either with or without ventilation. The pattern arising from the integrated clinical, ECG and chest X-ray evaluation will allow an *a priori* probability of PE to be established in the light of which the results of lung scanning (or other diagnostic examinations) are interpreted. This approach has been shown to lead to the correct diagnosis in the majority of cases[2,61], but if this is not the case, a definitive objective diagnosis has to be obtained by subsequent serial compressive/duplex ultrasonography of the lower limbs or by pulmonary angiography. Growing evidence is accumulating on the accuracy of spiral CT scanning, which therefore appears applicable either as an alternative to lung scanning as a first-line examination or as a complement to an inconclusive lung scan. Echocardiography (either transthoracic or transesophageal) should be used as first-line test for the bedside evaluation of critically ill patients who are hemodynamically unstable and for whom more validated diagnostic techniques are not available. Although at present the role of plasma D-dimer determination appears limited, when this test is performed, an immunoenzymatic assay should be used to maximize the reliability of the test results.

In current clinical practice, patient selection seems to greatly influence the diagnostic strategy followed[39,51-56]. Additional work needs to be done to assess test performance and refine diagnostic strategies in various patient populations. Since a standard diagnostic pathway does not seem applicable to all patients suspected of having acute PE at the present time, the clinician should strive to minimize the use of diagnostic resources while obtaining the greatest amount of information that will help establish a definitive diagnosis. In general, the optimal diagnostic strategy should probably be the combination of some type of "central" and "peripheral" imaging technique, although in patients with hemodynamic impairment the most readily available technique (commonly represented by echocardiography) is warranted in order to promptly initiate the most efficacious treatment (Fig. 1).

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