La mort subite secondaire à une embolie pulmonaire au Nord de la Tunisie : A propos de 37 cas.

Sudden death due to pulmonary embolism in north Tunisia: 37 cases study.

Shimi Maha[1], Allouche Mohamed[1], Ben Ahmed Habib[2], Zoghlemi Bilel[2], Gloulou Fatma[1], Ben Khelil Mahdi[1], Banasr Ahmed[1], Zhioua Mongi[1], Benzarti Anis[1], Hamdoun Moncef[1], Baccar Hédi[2]

(1) Service de Médecine Légale (2) Service de cardiologie,
Hôpital Charles Nicolle, Université de Tunis el Manar, Faculté de Médecine de Tunis, Tunis-Tunisie.

RÉSUMÉ

But : Déterminer la fréquence de l'embolie pulmonaire comme cause de mort subite et d'étudier les caractéristiques cliniques, épidémiologiques et les facteurs de risque de décès par embolie pulmonaire.

Méthodes : Etude prospective portant sur les cas de mort subite par embolie pulmonaire dont l'autopsie a été effectuée au service de Médecine Légale de l'Hôpital Charles Nicolle de Tunis, entre le mois d'octobre 2009 et de septembre 2011.

Résultats : 37 cas d'embolie pulmonaire ont été recensés ce qui représentait 6,8% de l'ensemble des cas de morts subites d'origine cardio-vasculaires. Les victimes étaient âgées entre 21 et 87 ans avec une moyenne d'âge de l'ordre de 52 ans. Des antécédents pathologiques étaient notés dans 9 cas : trois cas de chirurgie récente, quatre cas de traumatisme du petit bassin et un cas de tumeur ovarienne et un cas dont l'embolie pulmonaire est survenue en postpartum. Concernant les autres facteurs de risque de l'embolie pulmonaire, l'alitement a été noté dans 24 cas (64,8%), l'obésité dans 12 cas (32,4%), une hypertension artérielle dans 4 cas. Des antécédents de pathologie psychiatrique étaient notés dans 5 cas (13,5%). La symptomatologie précédant le décès était dominée par la mort subite avec 13 cas (35%) suivie par la dyspnée avec 11 cas (30%) et les douleurs thoraciques (6 cas) et les douleurs abdominales dans 2 cas. Dans 8 cas, les victimes ont consulté les urgences dans les 48h précédant le décès, pour une symptomatologie variée sans que le diagnostic d'embolie pulmonaire ne soit suspecté. A l' autopsie, 30 cas l'embolie était massive. Dans 29% des cas, une thrombose veineuse profonde a été mise en évidence notamment au niveau des veines iliaques primitives.

Conclusion : L'embolie pulmonaire est une affection qui tue encore beaucoup alors qu'elle peut bénéficier d'une prévention et d'un traitement efficace. Ceci témoigne de l'importance capitale du diagnostic clinique de l'embolie pulmonaire ainsi que celle des moyens techniques d'aide au diagnostic qui revêtent toute leur importance étant donné qu'il s'agit souvent d'un tableau trompeur.

Mots-clés
Embolie pulmonaire ; mort subite ; facteurs de risque ; prévention

SUMMARY

Aim: To determine frequency of pulmonary embolism as the cause of sudden death and to study clinical, epidemiological characteristics and risk factors.

Methods: Prospective study of cases of sudden death secondary to pulmonary embolism, whose autopsy was performed in the forensic department of Tunis, between October 2009 and of September, 2011.

Results: During study period, 37 cases of pulmonary embolism were recorded. They represented 6.8 % of all cases of sudden cardiovascular deaths. Victims were male in most cases (65 %). Victims were aged between 21 and 87 years with an average age of about 52 years. Pathological histories were noted in 9 cases: three cases of recent surgery, four cases of pelvic trauma, a case of ovarian tumor and a case of which the PE arose in post-partum. Concerning other risk factors of pulmonary embolism, confinement to bed was noted in 24 cases (64.8 %), obesity in 12 cases (32.4 %), an arterial high blood pressure in 4 cases. Histories of psychiatric pathology were noted in 5 cases (13.5 %). Symptomatology preceding death was dominated by sudden death (35 %) followed by dyspnoea (30 %) and thoracic pains (16 %). In 8 cases , victims consulted emergencies within 48 hours preceding death, for a varied symptomatology without diagnosis of pulmonary embolism is suspected. At autopsy, in 30 cases embolism was massive. In 29 % of the cases, a deep venous thrombosis was revealing in particular at the primitive iliac veins.

Conclusion: Pulmonary embolism is an affection that still kills a lot. It can benefit from prevention and from an effective treatment. This testifies the major importance of clinical diagnosis of pulmonary embolism as well as the technical means for the diagnosis.

Key-words
Pulmonary embolism ; sudden cardiac death ; risk factors ; prevention

Pulmonary embolism (PE) establishes with deep venous thrombosis, two sides of the same clinical entity that is venous thromboembolism. Although it is a pathology that can benefit from effective treatment and prevention, its mortality rate did not vary and remains high (1).

Diagnosis of PE remains a great challenge for clinicians despite numerous studies that tried to establish decision-making algorithms aiming to make diagnosis easier. Thus, a large number of diagnoses pass unnoticed explaining high mortality rate.

Sudden death represents first and last symptom of PE in approximately 25% of cases (2,3). PE is consequently well known in medical and forensic practice having been the subject of numerous studies (4,5).

The aims of our study were to determine the frequency of PE as cause of sudden death and to explore clinical features, epidemiology and risk factors of deaths secondary to PE.

METHODS

We carried out a prospective study extended over a period of 24 months from October 2009 to September 2011, including all forensic autopsies performed in Department of Forensic Medicine at Charles Nicolle hospital in Tunis.

During this period, we carried out 3211 autopsies including 542 cases of sudden death. Among them, all cases of PE, representing 37 cases, were included.

For each case, collection of information focused on the following parameters:

- Clinical and epidemiological data: age, sex, medical history and symptoms prior to death.
- Risk factors related to PE: history of recent surgery, trauma of the pelvis, bed rest, hypertension, diabetes, intra-pelvic tumors and medication taken in the last two months.
- Results of external examination and autopsy: measurement of waist circumference (WC) in order to identify central or visceral obesity which was, according to WC, defined if 94 cm for men and 80 cm for women. However, central obesity was considered of high cardiovascular risk if >102 cm in men and > 88 cm in women (6)). It included also search for the source of thrombus in the inferior vena cava, deep pelvic venous system, cardiac cavities and deep venous system of lower extremities
- General toxicological analyses of blood and urine as well as histopathological study of all organs.

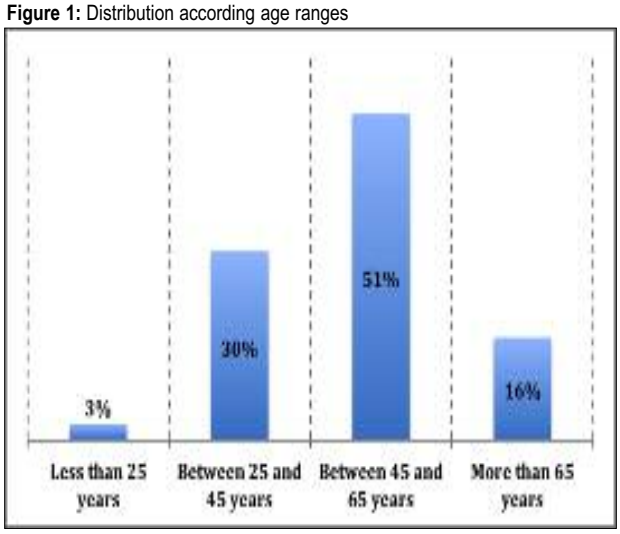
Descriptive statistical analysis of the data was performed using SPSS for Windows version 15.0. Chi-square was performed for group comparisons.

RESULTS

Cases of PE were 37 which represented 1.15 % of all the autopsies and 6.8 % of all the cases of cardiovascular sudden deaths. Most of victims were male (24 cases) with a sex-ratio (M/F) equal to 1.84. Victims were aged between 21 and 87 years old with a mean age of about 51.96 ± 15.53 years. Victims aged less than 45 years represented 33 % of the cases (Figure 1).

We found that 9 cases (24.3 %) presented significant events in their history.

Figure 1: Distribution according age ranges



- Act of recent surgery in 3 cases which all consisted in acts of orthopaedic surgery; the prevention by LMWH was found in two cases among three.
- In four cases, recent trauma (dating less than 15 days) of the pelvis was found. Only one among these four victims had consulted a medical structure and benefited from treatment by LMWH.
- Both remaining cases concerned a state of post-partum which was under LMWH and one case of an ovarian tumor.

Regarding other risk factors for PE, confinement to bed was noted in 24 cases (64.8%) and it was in relation either with surgery or recent trauma, or with psychiatric or organic affection. Obesity was noted in 12 cases (32.4%) with an average waist circumference measuring 92.84 cm ± 21.11 cm for women and 92.5 ± 18.7 cm for men. Obesity was more frequent in women (statistically significant with p= 0.041).

Hypertension was noted in 4 cases (10.8%) of which only one was under treatment. Diabetes was observed in 5 cases (13.5%), all of which were treated with oral antidiabetics.

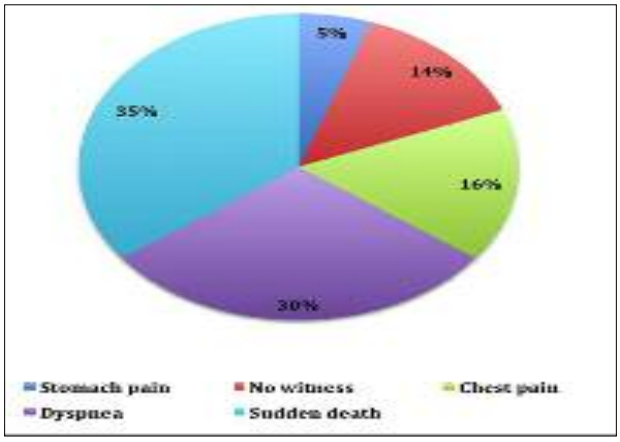
History of psychiatric affections was noted in 5 cases (13.5%): 2 cases of schizophrenia, 2 cases of severe depression and one case of bipolar disorder. All of them were under psychiatric treatment and two cases were hospitalized.

Table 1 : Risk factors of PE

Risk factors	Number of cases (%)
Recent surgery	3 (8.1%)
Recent trauma	4 (10.8)%
Post partum	1 (2.7%)
Ovarian tumor	1 (2.7%)
Obsity	12 (32.4%)
confinement to bed	24 (64.8%)
Hypertension	4 (10.8%)
Diabetes	5 (13.5%)
Psychiatric affection	5 (13.5%)

Symptomatology prior to death (Figure 2) was dominated by syncope with 13 cases (35 %) followed by dyspnea with 11cas (30 %), and then we found chest pain with 6 cases (16 %) and abdominal pain in 2 cases (5 %). In 5 cases (14 %) there were no witnesses having attended the death.

Figure 2: Symptoms before death



It should be noted that in 8 cases (21.6%), victims consulted emergencies within 48 hours prior to death, for variety of symptoms and clinicians did not suspect diagnosis of PE. These victims received only symptomatic treatment.

At autopsy and concerning the seat of thrombus, 30 cases (81 %) were massive embolism in which thrombus blocked both lung arteries from their origins and extended to distal branches in both lung fields (Figure 3 and 4). Thrombus was situated in right lung artery in 3 cases (8 %), in left lung artery in 2 cases (5.4 %) in segmental branches in 3 cases (8 %). In 29 % of cases, a deep venous thrombosis has been found particularly at primitive iliac veins (Figure 5).

Figure 3: A massive thromboembolus overrides between the bifurcations of pulmonary artery

RL: right lung, LL: left lung, PA: pulmonary artery, RV: Right ventricle, LV: left ventricle

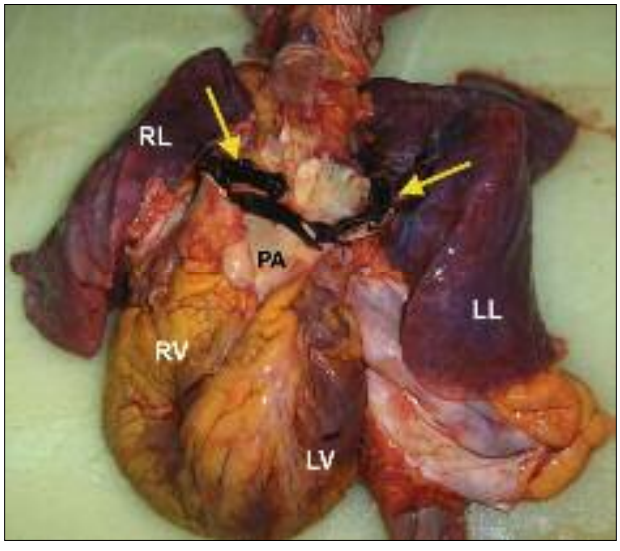


Figure 4 : Fresh thrombi (arrows), in the origin of both pulmonary arteries

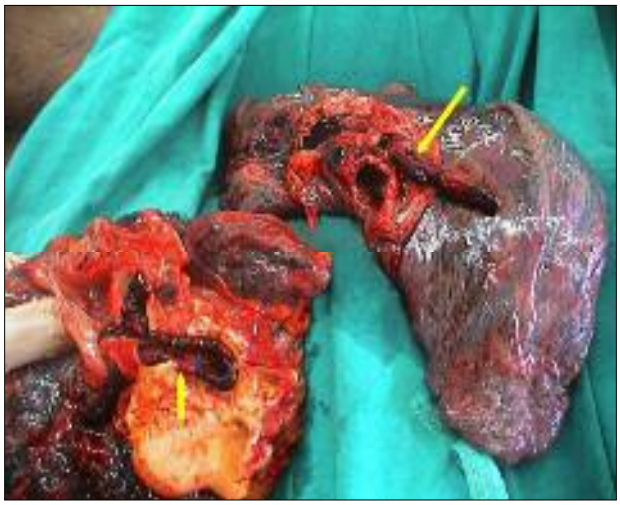
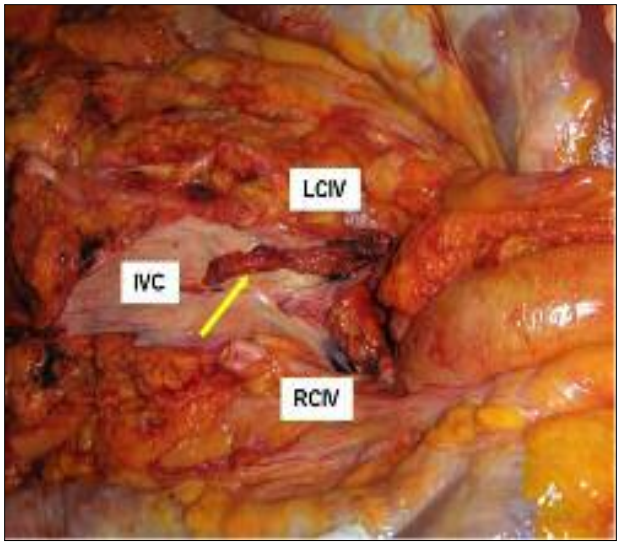


Figure 5: Fresh thrombi (arrow) in the origin of left Common Iliac Vein

IVC : Inferior Vena Cava, RCIV : Right Common Iliac Vein, LCIV : Left Common Iliac Vein



DISCUSSION

During the study period, PE was responsible for 1.15 % of all deaths, what establishes the same order of frequencies found in different published studies including Seville in Spain with 1.2 % (5), New York with 0,8 % (7) and Kitasato in Japan with 2.5 % (8). On the other hand, PE is the fourth aetiology of sudden cardiac deaths behind ischemic heart disease, hypertensive and valvular heart disease. In United States of America (USA), PE is the third leading cause of sudden death of cardiovascular origin after coronary heart disease and stroke (9).

Generally speaking, different studies considered that incidence of PE had not decreased over the last three decades and they explained this by a diagnostic failure. In fact, longitudinal necropsy studies showed that in 70% of deaths by PE, diagnosis was not found out when the patient was still alive (10,11).
In all cases of our study, diagnosis was established only at autopsy, it has been neither suspected nor diagnosed before death. There are even eight cases among the victims, who had visited emergencies department during the forty-eight hours preceding death for symptoms dominated by dyspnea and diagnosis of PE has never been suspected. Moreover, typical symptoms of PE that are dyspnea, chest pain and sometimes hemoptysis are only present in about 25% of cases (10).

This situation, although it is very serious, is not unique to our study. Indeed, during various published studies, the fact that diagnosis of PE is clinically difficult to establish and that most cases go unnoticed was an almost unanimous conclusion. Japanese study conducted in 2007 by Masahito et al (12) showed that although the rate of ante-mortem diagnosis of PE has improved, it was only 22% in 1998. Walden et al (13) showed that in 425 autopsy cases with PE, only 14% were diagnosed before death, 30% had been written on the death certificate, and 56% had been revealed only at autopsy. Paul Stein and col in the USA, conducted a study on pooled data over 20 years (11), they found that the PE was unsuspected or undiagnosed ante-mortem in 84% of all cases. In the most recent studies only 20% of PE cases found at autopsy were clinically suspected (14,15). Thus, all these results taken together indicate that fatal pulmonary embolism is very difficult to diagnose ante-mortem.
Regarding risk factors, although recent surgery has always been considered as the main state promoting PE; in our study, history of recent surgery have been identified in only three cases (8.1%) which is consistent with several studies where nearly 80% of PE occurred among patients who didn't undergo any surgery (10, 16).
Obesity is a well-established risk factor for PE and DVT especially in women (17,18) which corroborate our results. Its prevalence in our study was 32%, while the one found in different studies was much higher (6,19). The risk associated with obesity is strongly entangled with that associated with diabetes, hypertension and physical inactivity. Thus, there are many controversies about considering obesity as an independent risk factor or not (20,21).
Other risk factors that were strongly charged in other studies, had not been found in our as hormonal contraception and substitutive hormonal therapy (22).
This is probably explained by the fact that hormonal contraception is not the most used means of contraception in our country for socioeconomic reasons. Journeys by air with long-distance flights of more than 5000 km were also evoked by some authors (23).
Another risk factor could possibly be discussed; it's about PE that occurred in patients under psychiatric treatment and whose were not necessarily confined to bed. Indeed, in our study, we identified 5 cases. This problem was also pointed in a study carried out in Seville (5) where a rather important percentage of cases (32 %) presented psychiatric diseases under treatment and succumbed to a fatal PE.

Some authors have even attempted to establish probable link between antipsychotic drugs and higher risk of PE; such an association was found especially in female patients (8, 24,25). Although the cause of this high proportion of deaths by PE in patients with psychotic disorders is unknown, many assumptions had try to explain it like reduced mobility of such patients, complications related to antipsychotic drugs such as lupus-like syndrome induced by conventional antipsychotics and increase of platelet aggregability induced by serotonin (25).

In addition to these risk factors classically discussed, we must mention some inherited conditions that predispose to venous thromboembolism, such as factor V deficiency, protein S and C deficiency (26,27). These diseases have not been researched in our study. Moreover, systematic post-mortem search is not systematically indicated, according to different studies but only for cases where there is personal or family history of thromboembolic episodes (28,29).
Regarding autopsy, presence of a large thrombus completely blocking the light of pulmonary artery at its origin is often reported, and thrombus extend most often to segmental branches (9,30,31). It should be noted that signs of chronic right heart failure as hypertrophy and dilatation of the right ventricle are classically found at autopsy (32,33). Regarding the source of thrombus, although theoretically it can come from any systemic vein, it is found in the deep veins of the lower limbs in 90% of cases (9).
Existence of an associated pulmonary infarction has been rarely observed which is not surprising because even fatal PE rarely progresses to pulmonary infarction since pulmonary parenchyma benefits from double vascularization due to the presence of bronchial one (5). Usually, presence of lung infarction is favoured by existence of an associated heart or lung disease.

Our study has some limits. First, it involves only judicial autopsies that make the extrapolation of our results to general population a little difficult. Second, genetic examination searching for thrombophilia which, although would not change our overall results, could provide additional information for some cases.

CONCLUSION

It seems evident through this study that PE still be frequently fatal although it can benefit, in theory, from efficient prevention and treatment. This reflects importance of clinical diagnosis of PE as well as technical assistance, since it is often a misleading clinical presentation.

References

1 Cohen AT, Agnelli G, Anderson FA et al. Venous thrombo-embolism (VTE) in Europe: the number of VTE events and associated morbidity and mortality. Thromb Haemost 2007;98:756–764.

2 Ermenc B. Minimizing mistakes in clinical diagnosis. J Forensic Sci 1999;44: 810–3.

3 Goldhaber SZ. Pulmonary embolism. Lancet 2004;363:1295–305.

4 Miller EJ, Marques MB, Simmons GT. Etiology of pulmonary thromboembolism in the absence of commonly recognized risk factors. Am J Forensic Med Pathol 2003;24:329–33.

5 Lucena J, Rico A, Vázquez R et al. Pulmonary embolism and sudden–unexpected death: Prospective study on 2477 forensic autopsies performed at the Institute of Legal Medicine in Seville. J Forensic Leg Med 2009;16:196-201.

6 Clinical Guidelines on the identification, evaluation and treatment of overweight and obesity in adults. The evidence report, National Institutes of Health. Obes Res. 1998;6:51-209.

7 Giuntini C, Di Ricco G, Marini C et al. Pulmonary embolism: epidemiology. Chest 1995;107:3-9.

8 Hamanaka S, Kamijo Y, Nagai T et al. Massive pulmonary thromboembolism demonstrated at necropsy in Japanese psychiatric patients treated with neuroleptics including atypical antipsychotics. Circ J 2004;68:850–2.

9 Ro A, Kageyama N, Tanifuji T, Fukunaga T. Pulmonary thromboembolism: overview and update from medicolegal aspects. Leg Med 2008;10:57-71.

10 Kokturk N, Oguzulgen IK, Demir N, Demirel K, Ekim N. Differences in clinical presentation of pulmonary embolism in older vs. younger patients. Circ J 2005;69:981–6.

11 Stein PD, Kayali F, Olson RE. Estimated case fatality rate of pulmonary embolism, 1979 to 1998. Am J Cardiol 2004;93:1197-9.

12 Masahito S, Mashio N, Tohru T. Pulmonary embolism is an important cause of death in young adults. Circ J 2007;71:1765-70.

13 Walden R, Bass A, Modan R, Adar R. Pulmonary embolism in post-mortam material with clinical correlation in 425 cases. Int Angiol 1985;4:469-93.

14 Attems J, Arbes S, Bohm G et al. The clinical diagnostic accuracy rate regarding the immediate cause of death in a hospitalized geriatric population: an autopsy study of 1594 patients. Wien Med Wochenschr 2004;154:159-62.

15 Aalten CM, Samson MM, Jansen PA. Diagnostic errors: the need to have autopsies. Neth J Med 2006;64:186-90.

16 Alikhan R, Peters F, Wilmott R, Cohen AT. Fatal pulmonary embolism in hospitalised patients: a necropsy review. J Clin Pathol 2004;57:254–1257.

17 Blaszyck H, Wollan PC, Witkiewicz AK, Björnsson J. Death from pulmonary thromboembolism in severe obesity: lack of association with established genetic and clinical risk factors. Virchows Arch 1999;434:529–32.

18 Tsai AW, Cushman M, Rosamond WD, Heckert SR, Polar JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Int Med 2002;162:1182–9.

19 Dekker JM, Girman C, Rhodes T et al. Metabolic Syndrome and 10-year cardiovascular disease risk in the Hoorn Study. Circulation 2005;112:666–73.

20 Hansson PO, Ericsson H, Welin L, Svärdsudd K, Wilhelmsem L. Smoking and abdominal obesity. Risk factors for venous thromboembolism among middle-aged men. The study of men born in 1913. Arch Int Med 1999;159:1886–90.

21 Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Int Med 2000;160:809–15.

22 Vandenbroucke JP, Rosing J, Bloemenkamp KW et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med 2001;344:1527-35.

23 Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. JAMA 1997;277:642-45.

24 Kamijo Y, Soma K, Nagai T, Kurihara K, Ohwada T. Acute massive pulmonary thromboembolism associated with risperidone and conventional phenothiazines. Circ J 2003;67:46–8.

25 Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case–control study. Lancet 2000;356:1219–23.

26 Emmerich J, Aiach M. Facteurs génétiques de risque de thrombose. Ann Cardiol Angeiol 2002;51:129-34.

27 Ely SF, Gill JR. Fatal pulmonary thromboembolism and hereditary Thrombophilias. J Forensic Sci 2005;50:1–8.

28 Rulon JJ, Cho CG, Guerra LL, Bux RC, Gulley ML. Activated protein C resistance is uncommon in sudden death due to pulmonary embolism. J Forensic Sci 1999;44:1111–3.

29 Kuismanen K, Savontaus ML, Kozlov A, Vuorio AF, Sajantila A. Coagulation factor V Leiden mutation in sudden fatal pulmonary embolism and in a general northern European population sample. Forensic Sci Int 1999;106: 71–5.

30 Porter JM, Moneta GL. Reporting standards in venous disease: an update. J Vasc Surg 1995;21:635–45.

31 Wagenvoort CA. Pathology of pulmonary thromboembolism. Chest 1995;107:10-17.

32 Grifoni S, Vanni S, Magazzini S et al. Association of persistent right ventricular dysfunction at hospital discharge after acute pulmonary embolism with recurrent thromboembolic events. Arch Intern Med 2006;23:2151–6.

33 Kjaergaard J, Schaadt BK, Lund JO, Hassager C. Quantitative measures of right ventricular dysfunction by echocardiography in the diagnosis of acute nonmassive pulmonary embolism. J Am Soc Echocardiogr 2006;19:1264–71.