EPIDEMIOLOGY AND RISK FACTORS OF SUDDEN DEATH DUE TO PULMONARY THROMBOEMBOLISM: A RETROSPECTIVE STUDY

Rokas Šimakauskas[1], **Martinas Baltuonis**[2], **Sigitas Laima**[3], **Sigitas Chmieliauskas**[4], **Dmitrij Fomin**[5], **Algimantas Jasulaitis**[6], **Jurgita Stasiūnienė**[7]

Abstract:

Introduction. Pulmonary thromboembolism (PTE) is not an uncommon cause of sudden, unexpected death. Autopsy is the gold standard for cause of death determination in cases of suspected PTE. Mortality rates due to PTE are not estimated accurately.

Objective. The aim of this study was to analyze distribution patterns and risk factors of sudden deaths due to PTE.

Methods. Retrospective analysis of Lithuanian State Forensic Medicine Service autopsy data, period 2014-2018. A total of 4533 cases were reviewed; 80 cases met the criteria of immediate cause of death being PTE and were included in the study. PTE epidemiology, risk factors, clinical and pathoanatomical characteristics were described by reviewing scientific literature and statistical databases.

Results. PTE as the cause of sudden death was diagnosed in 37(46.25%) men and 43(53.75%) women. Median age at the time of death was 62.8±17.2 years. Death occurred in hospital in 21(26.25%) cases. Trauma was the underlying cause of PTE in 11(13.75%) cases; 9(81.8%) patients were admitted to hospital after a traumatic event. Cardiac hypertrophy was observed in 70(87.5%) autopsies. Abdominal subcutaneous fat thickness was 4.08±2.64 cm in men and 5.35±2.69 cm in women. Deep vein thrombosis (DVT) was confirmed upon microscopic examination in all cases, being the underlying cause of death in 67(83.75%) cases.

Conclusion. Sudden death due to PTE usually occurs at an older age and in absence of medical care. PTE is common after sustaining severe traumatic injuries which, when not immediately lethal, are managed in hospital. Cardiac hypertrophy and obesity may increase risk of death due to PTE. Undiagnosed and untreated DVT is often the underlying cause of sudden death due to PTE.

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Keywords: Pulmonary thromboembolism, sudden death, autopsy, DVT

Introduction

Pulmonary thromboembolism (PTE) or pulmonary artery thromboembolism (PATE) is a possibly lethal component of venous thromboembolism (VTE) (Giordano et al., 2017). VTE is a combination of PTE (ICD-10 code I26) and deep vein thrombosis (DVT; ICD-10 code I80) (Ministry of Health of the Republic of Lithuania, 2015). Autopsy is the gold standard for cause of death determination (Rampatige et al., 2014) and proves to be indispensable when PTE diagnosis relies only on clinical suspicion. However, most of PTE diagnoses are based on clinical findings, partly due to decreasing autopsy rates. In the clinical setting, PTE may present as a sudden and severe circulatory collapse, hindering the application of imaging techniques to confirm the diagnosis (Sweet et al., 2013). The rates of PTE and DVT have been increasing in the last 15 years (Arshad et al., 2017). However, PTE mortality rates are difficult to estimate. Mortality data in official statistics describe the underlying causes of death (Cicėnienė et al., 2011). Since PTE is commonly considered as a complication of DVT, i.e. an intermediate cause of death, PTE mortality rates are not accurate in official data (Smith et al., 1998).

The main objective of this study was to examine epidemiological characteristics and possible risk factors of sudden deaths due to PTE. The objective was achieved by analyzing the data of medicolegal autopsies

[1] Department of Pathology, Forensic Medicine and Pharmacology, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, and State Forensic Medicine Service, Vilnius, Lithuania, rokas.simakauskas@mf.vu.lt
[2] Faculty of Medicine, Vilnius University, Vilnius, Lithuania, lemartinas@gmail.com
[3] Department of Pathology, Forensic Medicine and Pharmacology, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, and State Forensic Medicine Service, Vilnius, Lithuania, sigitas.laima@mf.vu.lt
[4] Department of Pathology, Forensic Medicine and Pharmacology, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, and State Forensic Medicine Service, Vilnius, Lithuania, sigitas.chmieliauskas@mf.vu.lt
[5] Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, and State Forensic Medicine Service, Vilnius, Lithuania, dmitrij.fomin@mf.vu.lt
[6] Faculty of Medicine, Vilnius University, Vilnius, Lithuania, algimantas.jasulaitis@inbox.lt
[7] Department of Pathology, Forensic Medicine and Pharmacology, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, jurgita.stasiuniene@mf.vu.lt

performed in recent years, comparing the results with other authors' findings, and giving scientific explanations based on relevant literature sources.

Data and Methodology

A retrospective analysis of Lithuanian State Forensic Medicine Service Vilnius Department archive data was performed. A total of 4533 documented cases in the period 2014-2018 were reviewed. Keywords denoting PTE in forensic medical diagnosis were chosen as inclusion criteria: "pulmonary embolism", "thromboembolism". 80 cases met the inclusion criteria and were selected for the study.

The following data were collected: age and sex of the deceased, body length, abdominal subcutaneous fat thickness, heart mass, description of cardiac muscle lesions, neoplastic lesions, presence and location of DVT, blood and urine alcohol concentration, when and where the deceased was found, and underlying cause of death. Results were compared with findings of other similar studies. Descriptive and inferential statistical analysis was performed using R Commander version 2.5-1 and IBM SPSS Statistics version 23. $p<0.05$ showed statistically significant difference.

Results and Discussion

According to Lithuanian legislature, medicolegal autopsies are ordered if death is known or suspected to be violent, the deceased is unidentified, late post-mortem changes are present, improper treatment/care is suspected, and in cases of sudden death, when no information regarding the circumstances and possible causes of a person's death can be obtained from medical records (Prosecutor General's Office of the Republic of Lithuania, 2011). Sudden death is defined as a death which occurs unexpectedly, with or without known conditions, and in up to 24 hours after the onset of symptoms (Mosby's, 2012, p. 1709). Thus, the cases in this study reflected only a part of the population (usually when death was violent or the cause of sudden death could not be determined by antemortem findings).

Epidemiology

According to an epidemiological model by Cohen et al. (2007), 370,012 VTE-related deaths per annum were estimated in 6 EU countries (France, Germany, Spain, Italy, Sweden, UK), with only 26,473 (7%) of them being from VTE diagnosed antemortem. In the Eurostat database of causes of death (including 28 EU countries), VTE is assigned to the category of "Other diseases of the circulatory system", which excludes all forms of ischemic heart disease (I20-I25) and cerebrovascular diseases (I60-I69). 354,041 deaths (1469 in Lithuania) in this category were reported in 2014, and 369,166 deaths (1557 in Lithuania) – in 2015. According to the Hygiene Institute of Lithuania, PTE and DVT accounted for 307 deaths in 2014 and 340 deaths in 2015, or 20.9% and 21.8% of deaths, respectively, in the aforementioned category in the Eurostat database.

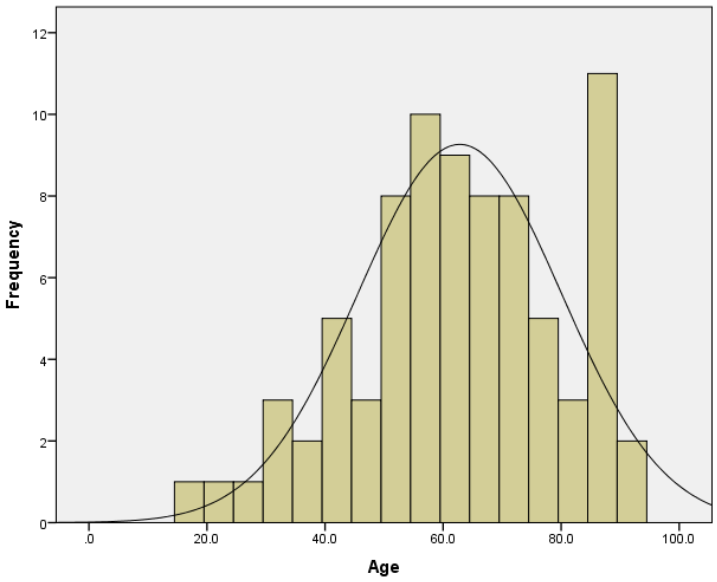
80 cases of PTE constituted 1.8% of all autopsies (4533 cases). Similar PTE rates were observed in other studies: 1.2% in an analogous study by Lucena et al. (2007), and 1.9% in a cardiovascular mortality study by Mesrati et al. (2017). The negligible difference might be explained by the widespread prevalence of cardiovascular diseases (CVDs). According to the WHO, CVDs are the leading cause of death worldwide. Furthermore, CVDs are the most common cause of sudden death diagnosed in medicolegal autopsies (Zanjad & Nanadkar, 2007).

Distribution by age and sex

37 (46.25%) cases were males and 43 (53.75%) were females. The average age was 62.8±17.2 years (62.4±12.7 years for males and 63.2±20.5 years for females; p=n.s.) ranging from 37 to 87 years for males and from 17 to 91 years for females. In 53 (66.25%) cases, the age was >55 years (26 males, 27 females). Case distribution by age and age groups is represented in Figure 1 and Table 1. PTE risk increases with age (Giordano et al., 2017) (ClinicalKey, n.d.), especially from the 4th decade (Oliveira & Gabriel, 2018). The average age estimated in this study does not differ from earlier, similar studies of PTE and PTE-related deaths, conducted in the last two decades (Carvalho et al., 2013) (Lucena et al., 2009) (Willich et al., 2018).

Autopsy data show that lethal PTE distribution among sexes varies between approximately equal (Carvalho et al., 2013) to male-predominant (Sweet et al., 2013) (Lucena et al., 2009). The male sex is considered as a risk factor for PTE (Oliveira & Gabriel, 2018). 3 (3.75%) young individuals (age <30 years) were observed in this study, all of them – female. An explanation to this finding could be the use of contraceptives containing estrogen, or the first trimester of pregnancy (Giordano et al., 2017).

Figure 1: Distribution of PTE cases according to age



Source: Authors

Table 1: Distribution of PTE cases according to age groups

Gender	Young (<30 y.)	Middle-aged [30-55 y.]	Elderly (>55 y.)
Male	0	11	26
Female	3	13	27
Total	3	24	53

Source: Authors

Season, place and time of death

The majority of deaths occurred in spring – 29 (36.25%); in summer – 18 (22.5%); in autumn – 16 (20%); and finally in winter – 17 (21.25%). Deaths among the elderly were more frequent in autumn ($p=0.0093$), and less common in summer ($p=0.0053$). Increased mobility after winter months, while outdoor temperature is still low, and atmospheric pressure variations in spring and autumn are risk factors for lethal PTE (Törő et al., 2016). Seasonal distribution by age groups is represented in Figure 2.

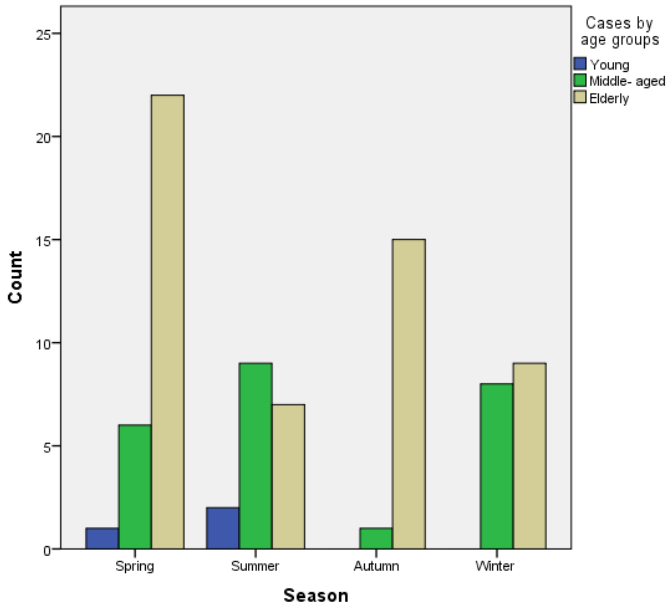
In 21 (26.25%) cases, death occurred at hospital, in 59 (73.75%) cases – elsewhere: 48 – indoors, 11 – outdoors. Hospitalization time varied from 4 hours to 998 hours (41.5 days), median was 182 hours (7.6 days). According to hospital records, in 8 (38.1%) cases, death occurred during the daytime (12–17 h.), in 6 (28.57%) cases – in the evening and at night (18–5 h.), in 7 (33.33%) cases – in the morning (6–11 h.). Immobilization of >3 days, which is not uncommon in hospitalized patients, is an independent risk factor for thromboembolism (Oliveira & Gabriel, 2018).

Antemortem vs postmortem diagnosis

Antemortem diagnosis of DVT and PTE is difficult, as clinical symptoms are non-specific. Algorithms have been adapted for clinical diagnosis of both DVT and PTE, involving: objective scoring of clinical findings and risk factors (Wells criteria), D-dimer test and medical imaging techniques (usually ultrasound and computed tomography for DVT and PTE, respectively) (Ministry of Health of the Republic of Lithuania, 2015).

PTE is diagnosed postmortem by finding thromboemboli upon routine sectioning of pulmonary arteries and their branches. Thromboemboli must be distinguished from postmortem blood clots: the latter are either homogenously dark-red or with a yellowish component due to plasma separation, their surface is smooth and glossy, and no attachment to the vascular wall is observed. Old emboli and pulmonary thrombi, if present in pulmonary vascular tree, are noted, and the possibility of chronic thromboembolic pulmonary hypertension is considered. Deep veins of the pelvis and limbs are the most common source of thromboemboli and are routinely examined for the presence of DVT if PTE is diagnosed.

Figure 2: Distribution of PTE cases according to season by age groups



Source: Authors

Out of 21 hospital deaths, PTE was diagnosed clinically only in 2 (9.5%) cases and suspected in another 2 (9.5%) cases. This could be explained by the sudden onset of PTE episodes, previously undiagnosed DVT, and an inability to use medical imaging to confirm diagnosis before death. During the autopsy, bilateral occluding emboli were found in 79 (98.75%) cases and embolus in the right pulmonary artery in 1 (1.25%) case. 79 (98.75%) cases had thrombi in popliteal deep veins and 1 (1.25%) – in pelvic veins. There was one case of DVT in the left subclavian vein concomitant with popliteal DVT in an 81 years old female who was found indoors. DVT and PTE were confirmed by histopathological examination in all cases. DVT was the underlying cause of death in 67 (83.75%) cases.

Recent traumatic event

In 11 (13.75%) cases, a recent traumatic event, manifesting as a bone fracture(s), was the cause of lethal PTE. In 9 of these cases (81.8%), death occurred in hospital. Lethal PTE after a recent traumatic event was more common in hospital ($p<0.0001$). Trauma is a risk factor for developing PTE (Oliveira & Gabriel, 2018) (ClinicalKey, n.d.). In a study of trauma-related deaths by Echeverria et al. (2010), the prevalence of PTE confirmed by autopsy was 2.75%. PTE development after trauma is explained by prolonged immobilization and inflammatory response causing hypercoagulation. Significant variation of trauma-related PTE among medicolegal autopsy studies is observed: 11.75% in this study, 12.5% by Lucena et al. (2009), and 45% by Yakar et al. (2016). This could be explained by the diverse legislations of medicolegal examinations in different countries.

Tumors

Non-specified tumor masses were noted in 9 (11.25%) cases. 3 of them were confirmed as malignant by histopathological techniques: lung carcinoma, colon cancer and bilateral glioblastoma. The majority of malignant tumors and associated treatment methods cause hypercoagulation (De Cicco, 2004). Certain malignant tumors increase PTE risk by up to five times compared to the general population: gallbladder, biliary tree, pancreatic, pulmonary, tracheal, ovarian (SIR=10.5), Hodgkin's lymphoma (Sørensen, et al., 2012). A study by Svendsen & Karwinski (1989) showed that tumors of ovaries, biliary tree, stomach, large intestine, pancreas, body of uterus and the brain were most commonly diagnosed neoplasms (11-34%) among palliative care patients.

Abdominal subcutaneous fat

The average subcutaneous abdominal fat thickness at visually the thickest area of vertical section in the abdominal wall was 4.76±2.73 cm (4.08±2.64 cm in males and 5.35±2.69 cm in females; p=n.s.). Nadeem et al. (2018) suggested a formula to calculate body mass index (BMI=16.99+0.39*x, where x – abdominal subcutaneous fat thickness), however, the study used ultrasound measurements. The

estimated BMI varied between 18.94-67.69 kg/m^2, with an average of 35.56±10.63 kg/m^2. BMI in females was higher than in males (p=0.01). A more accurate approach should be used to evaluate obesity as a risk factor for PTE.

Obesity (BMI>30) is up to 3 times more frequent among individuals with lethal PTE, when compared to the general population (Tang et al., 2011). Obesity increases PTE risk (Rosenfeld et al., 2012). A study by Saab & Salvatore (2015) revealed that PTE is one of the leading causes of death among obese persons. Goldhaber et al. (1983) found obesity to be more related to lethal PTE in females.

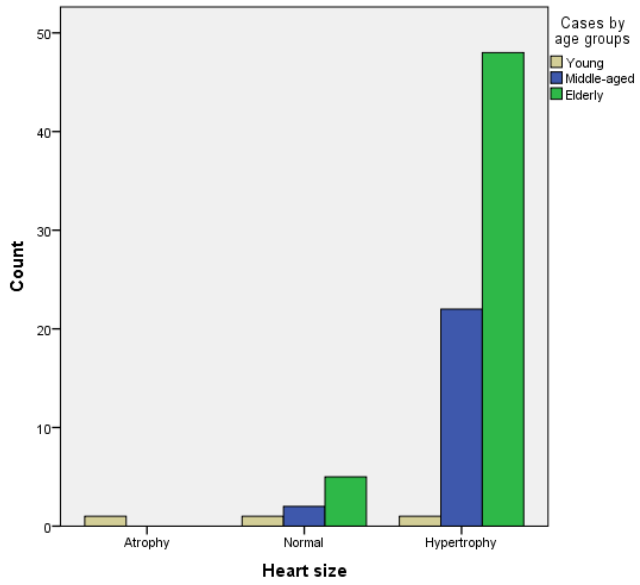
Effect of ethanol

Blood alcohol concentration (BAC) was measured in all cases. Ethyl alcohol was detected in blood samples in 11 (13.75%) cases. BAC ranged from 0.1‰ to 2.63‰, median 1.18‰. A study by Pahor et al. (1996) showed that moderate alcohol consumption is associated with reduced PTE risk in elderly people. According to a recent study by Shen et al. (2017) in China, alcohol intoxication increases risk of acute PTE up to 3.53 times.

Heart condition

The average gross heart weight was 469.43±111.49 g (males – 507.03±103.22 g, females – 437.07±109.22 g, p=n.s.). The normal gross heart weight range for men was – 273-374 g, for women – 236-325 g. Cardiac hypertrophy was observed in 71 (88.75%) cases. The middle aged and the elderly had cardiac hypertrophy more frequently (p=0.023). Heart size distribution by age groups is detailed in Figure 3.

Figure 3: Distribution of PTE cases according to heart size by age groups



Source: Authors

16 (20%) cases showed localized fibrosis of myocardium, which was attributed to a previous myocardial infarction. 14 (87.5%) of the deceased were >55 years old and 2 – middle aged. Concomitant cardiac hypertrophy was observed in all cases.

PTE is a frequent cause of death among cardiovascular patients (Pulido et al., 2006). Chronic PTE causes ventricular remodeling: thickening of the right heart wall, enlargement of the right ventricular cavity and atrophy of the right ventricle due to load reduction (Gerges et al., 2014). Acute PTE is associated with left or bilateral ventricular hypertrophy, post-infarction cardiac fibrosis or scarring, and a history of cardiac insufficiency (Lucena et al., 2009) (Yakar et al., 2016).

Conclusion

The prevalence of PTE and PTE-related deaths is not accurately assessed in official data due to multiple reasons: underdiagnosis, reduction of autopsy rates and peculiarities of medical death certification. Sudden death due to PTE usually occurs at an older age, without previously diagnosed DVT or history of chronic PTE, and in absence of medical care. Clinical symptoms of PTE are non-specific and

diagnosis may be difficult due to the sudden onset of the disease. PTE is common after sustaining severe traumatic injuries which, when not immediately lethal, are managed in hospital. Malignant tumors increase PTE risk. Cardiac hypertrophy and obesity may increase risk of sudden death due to PTE. Undiagnosed and untreated DVT is often the underlying cause of sudden death due to PTE.

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