Original Article

Significant Pulmonary Hypertension in Acute Pulmonary Embolism: Concepts and Facts

Mahsa Behnemoon[*1]*, Elham Laleh*[2]

Received 02 May 2023, **Accepted** for publication 10 June 2023

Abstract

Background & Aims: Acute pulmonary thromboembolism with a mortality of about 15-20% is the third leading cause of death from vascular disease after myocardial infarction and cerebrovascular disease. Considering the ominous nature of the disease and our experience of observing significant degrees of pulmonary hypertension among these patients, we decided to evaluate the prevalence of echocardiographic findings and its relationship with in-hospital mortality of affected patients.

Materials & Methods: In this cross-sectional study, we enrolled 183 patients with a definitive diagnosis of pulmonary embolism having admission echocardiography. Clinical and echocardiographic findings were extracted from patients' medical records. Patients were grouped as survivors to hospital discharge and non-survivors, and the relationship between echocardiographic findings and in-hospital mortality was evaluated. All data analysis was performed using SPSS software version 22 and the significance level was considered less than 0.05.

Results: In-hospital mortality rate of our patients was 20.2%. Dyspnea and chest pain were the most prevalent symptoms, while tachycardia, tachypnea and hypotension were the most frequent signs. Average systolic pulmonary artery pressure was about 50.82±22.88 mmHg with significant difference between deceased and discharged subjects. We also reported a significant relationship between in-hospital mortality and TR severity and right ventricular dysfunction. Severe pulmonary hypertension was present in 42% of the patients, and about one third of them didn't survive to the hospital discharge. However, only 14 patients with less than severe PH on presentation expired during hospital stay (p=0.002).

Conclusion: High frequency of severe pulmonary hypertension observed in our acute presenting patients could be a sign of combined PH etiologies and warrant further evaluation of secondary causes.

***Keywords*:** Acute Pulmonary Embolism, Echocardiography, Pulmonary Artery Pressure, Right Ventricular Dysfunction

***Address*:** Department of Cardiology, Urmia University of Medical Sciences, Urmia, Iran

***Tel*:** +984432234897

***Email*:** behnamoon.mahsa870@gmail.com

Introduction

Pulmonary embolism and deep venous thrombosis represent the spectrum of one disease that primarily originates from deep vein thrombosis of the lower limbs (1-3). Genetic and acquired factors are involved in developing venous thromboembolism. Factors such as long-haul flights, obesity, smoking, oral contraceptives, postmenopausal hormone replacement therapy, surgery,

[1] *Assistant Professor of Cardiology, Department of Cardiology, Urmia University of Medical Sciences, Urmia, Iran (Corresponding Author)*
[2] *Medical Doctor, Medical Center, Urmia University of Medical sciences, Urmia, Iran*

cancer, systemic arterial hypertension, and chronic obstructive pulmonary disease are

among the acquired underlying risk factors (3,4).

The incidence of pulmonary embolism in the United States is estimated as 1 in 1,000 people, and the mortality rate of the disease in the first three months after diagnosis reaches more than 15%, resulting primarily from right ventricular failure (5-7). There is no exact epidemiologic data on its prevalence in Iran, but some reports suggest that it may account for 2% of emergency visits and 8-13% of post mortal cases of acute presenting dyspnea (8-9).

According to previous studies, dyspnea, chest pain, cough and hemoptysis account for 73%, 66%,37%, and 13% of the disease manifestation, respectively. On physical examination, about two third of subjects have tachypnea and one third have tachycardia at arrival, while hypotension and hemodynamic instability can compromise the disease course in massive or saddle emboli cases (7,10).

Since clinical manifestations of pulmonary emboli in many cases might be variable or nonspecific, careful evaluation of the patient and application of diagnostic tests play a vital role in early diagnosis. Chest radiography, electrocardiography, serum D-dimer level, lung CT scan, perfusion ventilation scan, and echocardiography could be done initially as appropriate, according to the patients' symptoms and the disease probability. However, despite its invasive nature and risks of contrast application, pulmonary angiography remains the gold standard for confirming the diagnosis in equivocal cases (10-13).

It is well known that patients presenting with sustained hypotension (systolic blood pressure less than 90 mm Hg for more than 30 minutes) or a pressure drop greater than or equal to 40 mmHg from baseline are at increased risk of premature death due to early right ventricular failure (13). On the other hand, the presence of moderate to severe right ventricular (RV) failure according to the echocardiographic data in patients with stable systolic arterial pressure is a potential sign of increased short- and long-term mortality. However, the appropriate strategy for the management of hemodynamically stable patients remains controversial and attention to the cardiac biomarkers and RV dysfunction are proposed to decide which one of thrombolytic administration or anticoagulant therapy is considered beneficial for the patient (14-19). Echocardiography has a unique role in identifying patients with increased pulmonary arterial pressure in whom significant pulmonary emboli is suspected (90% sensitivity). In these patients right ventricular (RV) dilatation, RV free wall hypokinesia and flattening of the interventricular septum can address the severity of the underlying disease (20, 21).

Considering the ominous nature of acute pulmonary emboli and our experience of observing significant degrees of pulmonary hypertension among this category of patients, we decided to evaluate echocardiographic and clinical findings and its correlation with in-hospital mortality of affected subjects in a five-year survey of our educational hospitals.

Materials & Methods

In this cross-sectional study, we evaluated medical records of all patients admitted to our two educational centers between 2014 and 2019 with a diagnosis of pulmonary embolism including massive, sub massive or small types. Inclusion criteria were as follows: 1) age above 18 years, 2) definite diagnose of acute pulmonary embolism on initial contrast computed tomography (pulmonary CT angiography), 3) having baseline echocardiography data on the first day of admission. Exclusion criteria were incomplete medical records or having simultaneous comorbidities affecting the degree of pulmonary artery pressure (e.g., decompensated heart

failure, infection and sepsis, or collagen vascular disease). During the 5-year time interval (2014-2019) a total of 321 patients with the diagnosis of acute pulmonary embolism were admitted to our hospitals. We excluded 120 cases with lacking echocardiographic data, and 18 subjects due to the underlying comorbidities affecting the results of pulmonary artery pressure. Ultimately, 183 patients enrolled our study. Initial vital signs including blood pressure, heart rate, respiratory rate, past medical history and echocardiographic data on right ventricular size and function, tricuspid regurgitation (TR) severity and pulmonary artery systolic pressure (SPAP) were extracted from patients' medical records. Right ventricular function was assessed using tricuspid annular plane systolic excursion (TAPSE) and values below 17 considered abnormal (reduced RV systolic function). SPAP was calculated using the formula: 4(TR peak velocity) ^{2} + right atrium pressure. Finally, we analyzed the relationship between mentioned variables and in-hospital mortality of our studied patients.

Data analysis:

We expressed continuous variables as mean ± standard deviation values and descriptive variables as numbers and percentage values. Student's t-test and Mann–Whitney U test were applied to compare continuous variables and descriptive data were compared using Chi-square or Fisher's exact test as appropriate**.** All data analysis was performed using Windows SPSS software version 22 and the significance level was considered less than 0.05.

Ethics:

The study was in accordance with the Ethics Committee of Urmia University of Medical Science which waived the informed consent due to its observational and cross sectional nature. The approval ID is IR.UMSU.REC.1397.055

Results

In this study, 45.4% (n=83) of the patients were male, and the remaining (n=100) were female with the mean age of 61.15(±18.98 SD). In-hospital mortality rate of the affected subjects was 20.2% (n=37). The major causes for death was massive pulmonary embolism and RV collapse. 17 patients experienced nonfatal bleeding complications of thrombolysis or anticoagulant therapy and only one patient died due to extensive intraventricular cerebral hemorrhage 3 days after thrombolysis.

Dyspnea and chest pain were the most prevalent symptoms with the frequency of 88% and 49.2%, respectively. Hemoptysis and syncope were present in 13.1% and 7.1% of patients, respectively. On physical examination at arrival hypotension was observed in 37.2% of patients, whereas either tachycardia or tachypnea was seen in 54.1% of our study population (Table 1).

Table 1. baseline characteristics and clinical features.

variable	Number/average (total=183)	Percent (%)
Sex male	83	45.4%
female	100	54.6%
Age <40 y	29	15.8%
40-60 y	48	26.2%
60-70 y	37	20.2%
>70 y	69	37.7%

variable	Number/average (total=183)	Percent (%)
dyspnea	161	88%
Chest pain	90	49.2%
hypotension	68	37.2%
hemoptysis	24	13.1%
syncope	13	7.1%
tachycardia	99	54.1%
tachypnea	99	54.1%
death	37	20.2%

Echocardiography:

Mean left ventricle ejection fraction (LVEF) was 49.21% ±9.29% and right ventricle enlargement was observed in 66.7% of patients (n=122). LVEF was significantly lower in non-survivors versus discharged group (46.4±7.7% and 49.9±9.9%, respectively, p=0.04). Average systolic pulmonary artery pressure was about 50.82±22.88 mmHg with significant difference between deceased and discharged subjects (61.1±20.1 and 48.2±22.85 mmHg respectively, p value=0.03). We didn't observe significant tricuspid regurgitation (TR) in about 12.6% of the patient (i.e., trivial or no TR); However, 35.5% had mild, 28.4% had moderate, and 23.5% had severe TR in transthoracic echocardiography assessment (Table 2).

Table 2. Echocardiographic findings and its relationship with in-hospital mortality

		Total	Non-survivors	survivors	P value
TR severity	No TR or mild	88 (48.1%)	7(8%)	81(92%)	0.007
	Moderate or severe	95 (51.9%)	30(31.6%)	65(68.4%)	
RV dysfunction	Present	124 (67.8%)	30(24.2%)	94(75.8%)	0.03
	Absent	59 (32.2%)	7(11.8%)	52(88.2%)	
Average SPAP	50.8±22.8		61.1±20.1	48.2±22.8	
Systolic PAP	Normal	45 (24.6%)	3(6.6%)	42(93.4%)	0.002
	30-40 mmHg	19 (10.4%)	0(0%)	19(100%)	
	40-60 mmHg	42 (23%)	11(26%)	31(74%)	
	>60 mmHg	77 (42.1%)	23(29.8%)	54(70.2%)	
Average LVEF	49.2±9.3%		46.6±7.7%	49.9±9.5%	0.04

We observed a significant relationship between TR severity and in-hospital mortality (p=0.007). More than two third of deceased patients had at least moderate TR, among which 32.4% had severe TR. On the other hand, less than half of discharged patients had more than moderate TR (moderate to severe TR in 28.8% and severe TR in 15.8%).

We also reported a significant relationship between in-hospital mortality and right ventricular dysfunction in our study population. Variable degrees of right ventricular dysfunction were observed in 81.1% and 64.4% of non-survivors and discharged subjects, respectively (p=0.03). Severe pulmonary hypertension, defined as SPAP ≥60 mmHg, was present in 42% of patients (n=77), among which 48% (n=37) had hypotension on admission and about one third of them (n=23) didn't survive to the hospital discharge. While only 14 patients with less than severe PH on presentation, expired during hospital stay (13%, p=002) and interestingly no death was reported among patients presented with mild degrees of pulmonary hypertension (SPAP=30-40mmHg) (Table 3).

Table 3. Relationship between pulmonary artery pressure severity and shock state

		Shock state (Total=68)	**P value**
sPAP	normal	10(14.7%)	0.006
	30-40^{mmhg}	3(4.4%)	
	40-60^{mmhg}	18(26.5%)	
	>60^{mmhg}	37(54.4)	

The main finding of this study was the fact that we encountered more frequency of severe pulmonary hypertension among our patients as we expected, which warrants further evaluation of these critical cases in the follow up period for secondary causes of pulmonary hypertension such as chronic thromboembolic disease.

Discussion

In this study, we assessed the general characteristics, symptoms and sign, echocardiographic features and in-hospital outcome of acute pulmonary embolism patients. As expected, we observed a mortality rate of 20.2% in our affected population which is high enough even in treated cases, in line with other previous reports of 1:6 to 1:5 death rate (1, 2, 4, 5, 16, 22,23). The mean age of our studied patients was 61.15±18.98 years, and 54.6% were female, resembling that of reported by prior studies of evaluating clinical findings of pulmonary embolism which illustrated the highest percentage of patients being in middle-age group with the slight dominancy of female sex due to probable hormonal factors or high prevalence of inflammatory and rheumatologic disorders (23-25).

The most frequent symptoms and signs of our subjects on admission were dyspnea (88%), tachycardia (54.1%), tachypnea (54.1%), chest pain (49.2%), and hypotension (37.2%). We reported syncope and hemoptysis in 7.1% and 13.1% of patients, respectively, with relatively similar frequencies compared to other previous reports. In a study of Bajaj et al., most common clinical symptoms were dyspnea (72%), tachypnea (39%), chest pain (38%) and tachycardia (32.6%), whereas syncope (6%) and hemoptysis (4%) were less frequent, consistent with the present study (25). Moreover, hypotension was observed in about one third of our subjects, which was more prevalent compared to the previous reports. In the study of Grifoni et al., patients with latent hemodynamic instability following PE had 10% shock and 5% in-hospital mortality (26). Considering the older age of our patients, and the endpoint of shock versus hypotension in their report, these discrepancies would be expected.

Among echocardiographic findings, more than two third of our patients had right ventricular (RV) dysfunction and dilation and some degrees of pulmonary hypertension (PH), defined as systolic PAP more than 30 mm Hg. Interestingly, the rate of RV dysfunction and PH were higher in our report, in contrast to the study of Kurnicka et al. in Poland in 2016 reporting a frequency of 27.4% and 46.6% for RV enlargement and the presence of PH, respectively (24). The differences between two studies from the point of inclusion criteria, sample size, the diagnostic tests used for confirming the disease and possible late medical contact of our patients may explain these variations.

Moreover, we observed a significant relationship between initial reduced left ventricular ejection fraction and increased risk of mortality among our patients, demonstrating the importance of septal deviation and abnormal motion due to RV pressure overload, which in terms has a critical role in the preload-afterload balance of left ventricle, resulting in decreased cardiac output and high clinical risk of subjects presenting with reduced LVEF. Strategies to improve the LVEF and reduce the mortality of these patients may include early thrombolysis, mechanical circulatory support, or surgical embolectomy depending on the patients' presentation and risk of complications.

Based on our previous experience, we assessed the frequency of significant degrees of PH among our patients, and interestingly 42% of subjects had severe PH on initial echocardiographic assessment. It is well known that the normal right ventricle could not produce an average pressure above 40 mmHg in acute conditions, and in more elevated pressures, the gradient between RV and pulmonary artery would decrease due to secondary dilated and dysfunctional right ventricle (27). According to the Wood K.E. study in 2002, TR velocity greater than 3.7 (equivalent to 55 mmHg systolic PAP) may indicate previous underlying pulmonary disease such as chronic thromboembolism (CTEPH) (28). On the other hand, the risk of severe PH and CTEPH following pulmonary embolism based on meta-analysis reports was between 0.5-2.3% (29). However, more than one third of our patients who were presented with acute symptoms of PTE had shown severe pulmonary hypertension, which is contrary to the mentioned theoretical concepts. Delayed diagnosis, inadequate treatment, or underlying undiagnosed comorbidities of our patient which could lead to the occurrence of acute on chronic pulmonary embolism, may explain the high prevalence of RV failure and complications in this study. Considering the fact that we do not expect severe degrees of PH in pure acute pulmonary embolism, we can emphasize the need for further evaluation of discussed etiologies countering severe PH in acute settings of suspected pulmonary embolism. Regarding relatively high prevalence of severe PH observed in our study, we recommend rheumatologic counseling, complete laboratory evaluation of endocrine and metabolic disorders (e.g., thyroid abnormalities) and reinterpretation of pulmonary CT angiography by expert radiologists to confirm or rule out the presence of CTEPH as the probable causes of severe PH. In the absence of mentioned disorders and after adequate anticoagulant treatment for at least three months, we encourage the patients to be reevaluated for the presence of CTEPH and idiopathic PH in cases of persistent pulmonary hypertension, using step ward lung perfusion scintigraphy and right heart catheterization, as appropriate.

Limitations:

The study had the limitation of decreased sample size due to the incomplete medical records. Some patients were initially unstable and echocardiography could not be done for them on the first day of admission.

Besides, because of manual reports of some emergent echocardiographies, the illegible reports were excluded leading to missing data of some subjects. Moreover, we didn't follow the patients after hospital discharge to distinguish the probable chronic thromboembolic pulmonary hypertension which was out of the scope of the present study. According to the mentioned limitations and the relative high mortality rate of the disease, further local studies with larger sample size are needed to investigate the lacking information about local incidence of the disease and appropriate follow up protocols in the course of its management.

Conclusion

In our study, dyspnea, chest pain and tachycardia were the most frequent clinical presentation of pulmonary embolism and the presence of right ventricular dysfunction and significant tricuspid regurgitation could be considered as markers of increased in-hospital mortality. High frequency of severe pulmonary hypertension observed in acute presenting patients could be a sign of combined PH etiologies and warrant further evaluation of secondary causes.

Conflict of interest

No potential conflict of interest was reported by the author.

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