

CHRONOBIOLOGICAL RHYTHMS IN ONSET OF MASSIVE PULMONARY EMBOLISM IN IRANIAN POPULATION

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Abstract

Background: To investigate whether there is any chronobiological rhythms in onset of massive pulmonary embolism in Iranian population and to study any time variation in occurrence of this disease in patients' subgroups.

Methods: This study was conducted in an emergency department of a referral teaching hospital from March 2003 to March 2007. All medical records of patients with definite diagnosis of massive pulmonary embolism were reviewed for chronobiological rhythms in hourly, daily, monthly and season periods.

Results: One hundred and twenty patients (49 women and 71 men) included in the study. The mean age of patients was 63.63 ± 17.21 years. Massive pulmonary embolism showed a statistical increase in onset in the morning period ($p = 0.004$) with peak of occurrence between 9:00 to 10:00, in the first three day of the week ($p < 0.001$), and during winter ($p = 0.003$). In addition, hourly and weekly rhythms in onset of massive pulmonary embolism in diabetic patients is different from non-diabetic patients and occur most frequent in evening hours and in the end of week.

Conclusion: Our findings revealed that massive pulmonary embolism has a peak of onset during morning hours and in the winter. We also found that massive pulmonary embolism also has a weekly rhythm. Circadian and weekly rhythms of massive pulmonary embolism were different in diabetic patients and this is a novel finding of this study.

Keywords: Chronobiology, Circadian Rhythm, Pulmonary Embolism

Introduction

Pulmonary embolism (PE) is an important cause of morbidity and mortality in the world¹. This disease is a common health problem, with an annual incidence of about 60-70 per 100,000 in general population². Pulmonary embolism is divided into 1) massive: with a systemic hypotension, 2) sub-massive: right ventricular hypokinesia with no systemic hypotension, and 3) small to moderate: normal systemic arterial pressure without any signs of right ventricle dysfunction³.

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Acute massive PE is a rare disease⁴ with a high risk of death in the first hours of onset because of right ventricle failure⁵. It is obvious that primary embolectomy or thrombolytic therapy can be lifesaving approaches in treatment of massive PE⁶ and survival from this disease depends on rapid reduces in the pressure of right ventricle⁷. If untreated, massive PE is a fatal disease⁸. Thus, early diagnosis is vital element in treatment of massive PE and finding any patterns in onset of it can help early diagnosis and prevent many deaths from this fatal disease.

It has previously been demonstrated that many of biological processes and functions of the body are well organized in time named as chronobiologic rhythms, as evidenced by the expression of circadian (approximately 24-h), circamensual (approximately monthly), and circannual (approximately yearly) rhythms⁹.

Previous studies indicated that many cardiovascular diseases follow chronobiological rhythms.¹⁰⁻¹² But, there were few studies that investigated the chronobiologic rhythms in onset of massive PE. These studies found that massive PE has circadian and seasonal rhythms with peak of onset in the morning and in the winter.¹³⁻¹⁵ In addition, we could not find any study that investigate the weekly rhythms in onset of and the chronobiological rhythms of massive PE with regard to patients' characteristics and risk factors.

The aim of present study was to investigate chronobiological rhythms in occurring massive PE in Iranian population and compare the results with those from other populations and to find any difference in chronobiological rhythms in subgroups of patients according to patients' characteristics and risk factors.

Methods and Materials

This was a retrospective, cross-sectional, non-interventional study that assesses the chronobiological rhythms in onset of massive PE in Iranian population. The study was approved by the Research Ethics Committee of Madani Heart Hospital affiliated to Tabriz University of Medical Science, Iran. This Hospital is specialized Heart Center which serves as a major referral center for a large geographic area of the north west of Iran.

The study population included all patients' records admitted with massive PE diagnosis, over a four-year period from March 2003 to March 2007. In this period 120 patients (49 women and 71 men) admitted in our Institute with massive PE diagnosis. The principal criterion in the diagnosis of acute massive PE was a massive systemic arterial hypotension (SBP \leq 90 mmHg)⁴. Other signs and symptoms that helped in the diagnosis of massive PE included: dyspnea of sudden onset, syncope or near-syncope, tachypnea, right-sided heart failure, cyanosis, clinical signs of organ hypoperfusion and hypoxia. The diagnosis of massive PE in all patients was confirmed by using diagnostic methods (chest CT angiography or high probability lung Ventilation/perfusion scan) or postmortem examination. The time of onset of massive PE was documented for each patient by review patients' medical records and research criterion for onset was the patients' report of beginning signs and symptoms.

For assessing circadian distribution in onset of massive PE, the day was divided into twenty-four hours and four 6-hour intervals (24:00 to 5:59, 6:00 to 11:59, 12:00 to 17:59, and 18:00 to 23:59). The daily and monthly distributions were expressed as the number of massive PE cases per day and per month admissions. To assess the seasonal distribution, the year divided into 4 seasons: winter (December 21st to March 20th), spring (march 21st to June 20th), summer (June 21st to September 20th), autumn (September 21th to December 20th).

We analyzed possible differences in chronobiological rhythms in onset of massive PE with regard to the following patients' characteristics and risk factors: sex (men, women), age (<60 years, \geq 61 years), history of hypertension (hypertensive, normotensive), history of diabetes mellitus (diabetic, non-diabetic), smoking habit (smoker, non-smoker), history of previous surgery (in last six month), using oral contraceptives (for women), history of ischemic heart disease (IHD), history of chronic obstructive pulmonary disease (COPD), history of receiving streptokinase (SK) for prevent attack, and patients' outcome (death or alive on hospital discharge).

All obtained data were analyzed by SPSS software version 13.0 (SPSS Inc., Chicago, IL). Chi-square test for goodness-of-fit was used to determine

whether massive PE uniformly occurred during days, weeks, months, and sessions. For comparing the distribution of massive PE in patients' subgroups (binary variables), Chi-square test with continuing correction was used. A p value < 0.05 was considered statistically significant.

Results

One hundred and twenty patients' medical records with definite diagnosis of massive PE were reviewed. 59.2% of patients were males, with the mean age of 63.63 ± 17.21 years ranging from 17 to 86 years. Table 1 shows the distribution of other patients' characteristics and risk factors.

Circadian rhythm

The onset of massive PE showed a circadian

variation with the morning peak between 9:00 and 10:00 (Fig. 1). Using 6-hour intervals, the frequency of massive PE are significantly higher in the morning period between 6:00 to 11:59 compared with other 6-hour intervals ($\chi^2 = 13.46$, $df = 3$, $p = 0.004$) (Fig. 1). Most frequent hours and day intervals in onset of massive PE reported for all patients' subgroups in Table 1.

On further analysis no significant variation in 6-hour intervals could be found within subgroups of sex ($\chi^2 = 0.82$, $df = 3$, $p = 0.84$), age ($\chi^2 = 1.15$, $df = 3$, $p = 0.76$), history of hypertension ($\chi^2 = 5.27$, $df = 3$, $p = 0.15$), smoking habit ($\chi^2 = 3.74$, $df = 3$, $p = 0.29$), history of previous surgery ($\chi^2 = 0.98$, $df = 3$, $p = 0.80$), history of IHD ($\chi^2 = 2.12$, $df = 3$, $p = 0.54$), history of COPD ($\chi^2 = 1.06$, $df = 3$, $p = 0.78$), receiving SK ($\chi^2 = 4.70$, $df = 3$, $p = 0.19$), and patients' outcome ($\chi^2 = 0.87$, $df = 3$, $p = 0.83$). But in history of

Table 1
Most frequent time variation in onset of massive pulmonary embolism with regard to patients' characteristics and risk factors

Patients' characteristics	Subgroups	N*	Hour**	Day intervals**	Day**	Month**	Season**
Sex	Men	71	9	6:00 to 11:59	Sat	Feb	Winter
	Women	49	10	6:00 to 11:59	Sun	Feb	Winter
Age	< 60 years	43	9	6:00 to 11:59	Sat	Feb	Winter
	≥ 61 years	77	10	6:00 to 11:59	Sun	Jan	Winter
History of HTN	Hypertensive	51	10	6:00 to 11:59	Sun	Feb	Winter
	Normotensive	69	9	6:00 to 11:59	Sun	Feb	Winter
History of DM	Diabetic	17	17	12:00 to 17:59	Sun	Mar	Winter
	Non-diabetic	103	10	6:00 to 11:59	Sun	Feb	Winter
Smoking habit	Smoker	37	10	6:00 to 11:59	Sun	Aug	Summer
	Non-smoker	83	10	6:00 to 11:59	Sun	Feb	Winter
History of surgery	Previous surgery	18	10	6:00 to 11:59	Mon	Feb	Winter
	No previous surgery	102	10	6:00 to 11:59	Sun	Feb	Winter
Using OCP***	Using OCP	13	3	24:00 to 5:59	Sun	Feb	Winter
	No using OCP	36	10	6:00 to 11:59	Sun	Jan	Winter
History of IHD	Previous IHD	34	9	6:00 to 11:59	Mon	Feb	Winter
	No previous IHD	86	10	6:00 to 11:59	Sun	Jan	Winter
History of COPD	Previous COPD	31	9	6:00 to 11:59	Sun	May	Spring
	No previous COPD	89	10	6:00 to 11:59	Sun	Feb	Winter
Receiving SK	Receiving SK	59	9	6:00 to 11:59	Sun	Feb	Winter
	No receiving SK	61	10	6:00 to 11:59	Mon	Jan	Winter
Patients' outcome	Dead	40	10	6:00 to 11:59	Sun	Jan	Winter
	Alive	80	9	6:00 to 11:59	Sun	Jan	Winter

* Number of each groups reported

** Most frequent times reported

*** Reported for female patients

HTN: Hypertension; DM: Diabetes mellitus; OCP: oral contraceptives; IHD: Ischemic heart disease; COPD: Chronic obstructive pulmonary disease; SK: streptokinase.

using OCP ($\chi^2 = 8.10$, $df = 3$, $p = 0.04$) and history of diabetes mellitus ($\chi^2 = 9.19$, $df = 3$, $p = 0.02$) significant variation in 6-hour intervals found. In other words, in women that have a history of using OCP and in patients with diabetes the pattern of onset of massive PE were different from other patient and have a trend to occur in the evening hours (12:00 to 17:59).

Weekly rhythm

Significant variation in onset of massive PE was found in different days of the week ($\chi^2 = 47.88$, $df = 6$, $p < 0.001$) and showed a peak on the beginning of weeks (Saturday, Sunday, and Monday) (Fig. 2). Most frequent days in onset of massive PE reported for all patients' subgroups in Table 1.

On further investigation of subgroups no significant variation in onset of massive PE could be

Fig. 1
Circadian variation of massive pulmonary embolism

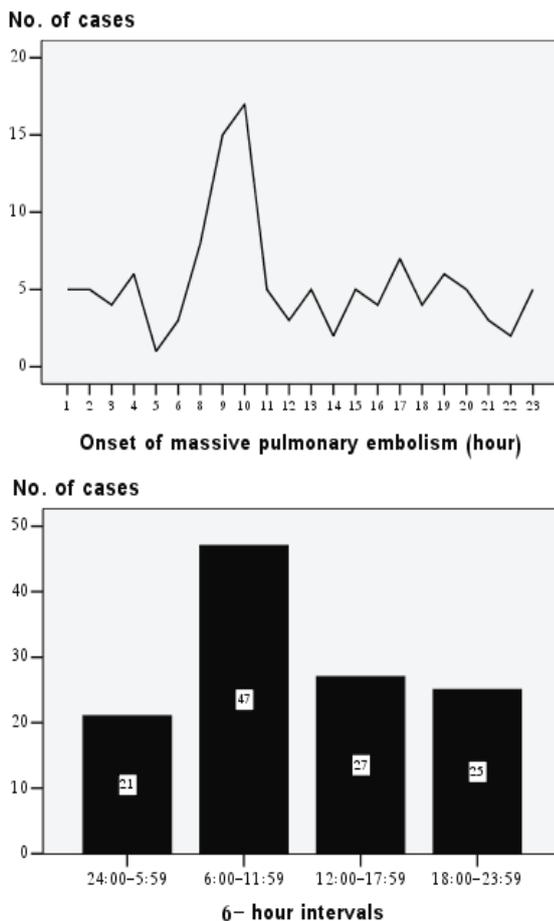
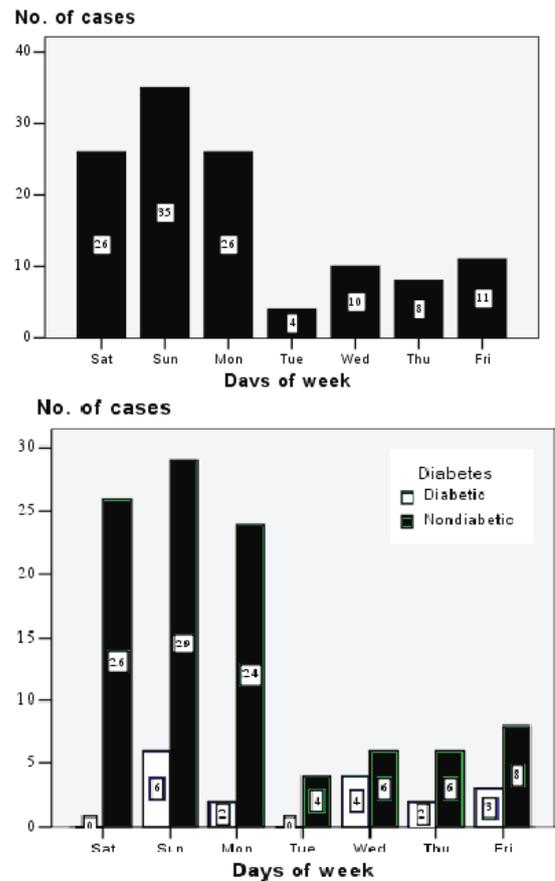


Fig. 2
Weekly variation of massive pulmonary embolism regarding to history of diabetes mellitus



demonstrated in different days of the week within sex ($\chi^2 = 8.58$, $df = 6$, $p = 0.19$), age ($\chi^2 = 8.18$, $df = 6$, $p = 0.22$), history of hypertension ($\chi^2 = 5.92$, $df = 6$, $p = 0.43$), smoking habit ($\chi^2 = 7.10$, $df = 6$, $p = 0.31$), history of previous surgery ($\chi^2 = 6.65$, $df = 6$, $p = 0.35$), history of using OCP ($\chi^2 = 11.73$, $df = 6$, $p = 0.06$), history of IHD ($\chi^2 = 3.74$, $df = 6$, $p = 0.71$), history of COPD ($\chi^2 = 6.70$, $df = 6$, $p = 0.34$), receiving SK ($\chi^2 = 8.77$, $df = 6$, $p = 0.18$) and patients' outcome ($\chi^2 = 7.11$, $df = 6$, $p = 0.31$). But patients with a history of diabetes mellitus ($\chi^2 = 13.91$, $df = 6$, $p = 0.03$) showed significant variation in onset of massive PE during the days of week and in spite of other patients, the onset of their disease trended to occur in the end of the weeks.

Seasonal rhythm

Regarding monthly distribution, the onset of massive PE was obviously most frequent in February, January, and April and least frequent in October

and November (Fig. 3). But, this variation was not significant ($\chi^2 = 16.00$, $df = 11$, $p = 0.14$). On the other hand, further analysis showed significant seasonal variation in onset of massive PE, with the highest frequency during winter ($\chi^2 = 13.66$, $df = 3$, $p = 0.003$). Most frequent months and seasons in onset of massive PE reported for all patients' subgroups in Table 1.

No significant differences was found in onset of massive PE in subgroups of sex ($\chi^2 = 2.89$, $df = 3$, $p = 0.40$), age ($\chi^2 = 0.79$, $df = 3$, $p = 0.85$), history of hypertension ($\chi^2 = 2.30$, $df = 3$, $p = 0.51$), history of diabetes mellitus ($\chi^2 = 2.81$, $df = 3$, $p = 0.42$), smoking habit ($\chi^2 = 5.97$, $df = 3$, $p = 0.11$), history of previous surgery ($\chi^2 = 2.42$, $df = 3$, $p = 0.48$), history of using OCP ($\chi^2 = 2.47$, $df = 3$, $p = 0.48$), history of IHD ($\chi^2 = 0.96$, $df = 3$, $p = 0.81$), history of COPD ($\chi^2 = 2.58$, $df = 3$, $p = 0.46$), receiving SK ($\chi^2 = 1.49$, $df = 3$, $p = 0.68$), and patients' outcome ($\chi^2 = 3.01$, $df = 3$, $p = 0.38$).

Fig. 3
Monthly and seasonal variation in onset of massive pulmonary embolism

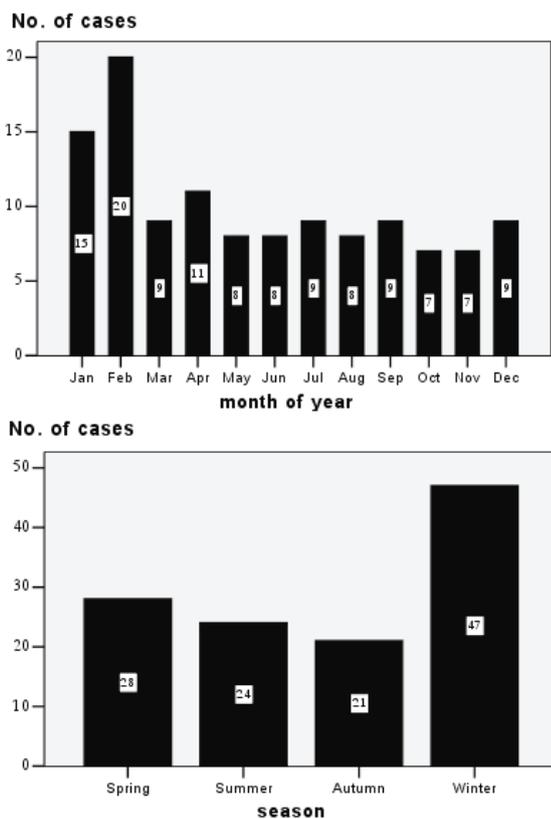


Figure 3. Monthly and seasonal variation in onset of massive pulmonary embolism

Discussion

The chronobiological rhythms in onset of massive PE in our Institute in four year period, from March 2003 to March 2007 was examined. Our findings demonstrated prominent chronobiological rhythms in onset of this disease, with a significant increase in the number of events during the morning hours, during first three days of week, and during January and winter.

The effect of chronobiologic rhythms on onset of many cardiovascular events has been demonstrated in previous studies. For example, patterns have been found for hemorrhagic stroke¹⁶, blood pressure¹⁷, myocardial infarction¹⁸, pulmonary edema¹⁹, and aortic dissection²⁰. There have been a few attempts to investigate the chronobiologic rhythms in onset of pulmonary embolism. For example, Sharma et al found pulmonary embolism has a significant acrophase in the morning hours and in winter²¹. This pattern was similar to that reported in other studies^{22,23}. Rhythmic occurrence of massive PE, however, has been reported in few studies^{13,15}. For example, Colantonio et al¹³ reported circadian and seasonal rhythms of fatal PE with a predominant onset in the morning hours (5 to 10) and the winter months. Gallerani et al²⁴ reported a similar chronologic pattern in 48 patients dying suddenly from pulmonary thromboembolism. Our experience indicates similar circadian and seasonal rhythms. But, we could not find any studies that investigate the onset of massive PE with regard to weekly rhythms. This weekly rhythms previously reported for some cardiovascular disease, for example aortic dissection²⁰. Our finding show that the massive PE events increase during the beginning of the week (Saturday, Sunday, and Monday).

We found no chronobiologic rhythms differences in onset of massive PE events between male and female patients. One important finding of this study was that the chronobiologic rhythms in occurrence of events in diabetic patients were different from non-diabetic patients in hourly and weekly rhythms. There were 17 diabetic patients with definite diagnosis of massive PE during the study period. In contrary to other patients the events of massive PE were most frequent during evening and end of the week. In pervious study Kitzis et al¹⁹ found such differences for diabetic patients in onset of acute pulmonary edema but this finding

was not reported for onset of massive PE previously. However, because of low number of diabetic patients in this study this finding need further investigation.

Many mechanisms have been proposed for the increased cardiovascular risk in the morning, in particular, an increase in blood pressure, heart rate, sympathetic activity, basal vascular tone, vasoconstrictive hormones, prothrombotic tendency, platelet aggregability, plasma viscosity, and hematocrit²⁵⁻²⁷.

Most available studies indicate a greater onset of massive PE during the winter months. These data are consistent with the seasonal pattern demonstrated for other major cardiovascular events¹⁹⁻²⁰. Cold exposure determines increased blood pressure²⁸, with increased platelet count and volume, red blood cell count, blood

viscosity²⁹, and clotting activity³⁰.

Regarding the study finding that the onset of massive PE has a frequency peak on first three days of the week we could not find proposed explanation for this finding. Perhaps the beginning of the week causing stress and this stress activated the sympathetic activity and enhance the release of embolus and cause PE. But this finding needs further investigation.

The findings of present study have diagnostic implications. Because this study confirms the hypothesis that massive PE has a predominant onset in the morning hours, in the beginning of week, and in the winter season, these findings raise the level of accurate and rapid diagnosis of this fatal disease and may prevent some death because of misdiagnosis.

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