

Chronobiology of non fatal pulmonary thromboembolism

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Background. It has been demonstrated that acute myocardial infarction, sudden cardiac death, stroke, and fatal pulmonary embolism show an increased onset rate during certain periods of the day, week, or year. According to some authors, the highest risk appears to occur in the morning, on weekends and during winter. This paper, therefore, intends to examine whether a circadian, weekly, or annual rhythm in the incidence rate of deep vein thrombosis (DVT) and non-fatal pulmonary embolism (PE) in ageing patients does exist.

Methods. A survey was conducted into 212 patients affected by DVT and PE, admitted to the Second Medicine Institute of Padua, Italy, over a period of two solar years. Thromboses were diagnosed via echo-Doppler examination of the legs and pulmonary embolism via perfusive and ventilatory scintiphotographs.

Results. In the overall sample, a circadian variation was found, both for deep vein thrombosis (peak at 12:26 hrs, $p=0.001$), and pulmonary embolism (peak at 10:26 hrs, $p=0.001$). A weekly, rhythmic recurrence was also found for the two complaints, with a peak on Saturdays, while no significant annual rhythmic recurrence was found. There was, however, a tendency towards an increase during the winter and summer months.

Conclusions. The results may have important clinical applications, both in prevention and in the "timing" of drug dosage.

KEY WORDS: Circadian rhythm, pulmonary - Embolism - Aged - Venous thrombosis.

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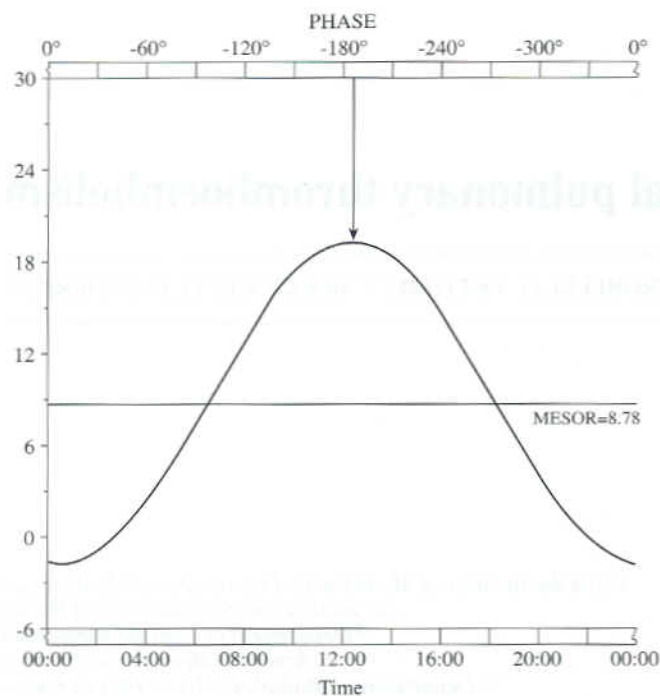
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It has long been recognised that the onset and the severity of symptoms of many clinical complaints have been linked to time variations.¹ Acute myocardial infarction,² sudden cardiac death,^{3,4} angina pectoris,⁵ transitory ischaemic attacks, and stroke⁶⁻⁸ have a typical circadian rhythm with a peak during the morning hours. This rhythm has also been seen in heart rate and output variations,⁹ concentrations of circulating catecholamine^{10,11} arterial blood pressure,¹²⁻¹⁴ and secretions of renin and aldosterone.^{15,16} All these parameters are closely linked to cardiovascular pathology.

It would appear, furthermore, that circadian, weekly, and annual variations also exist for deep vein thrombosis and fatal pulmonary embolism¹⁷ both for hospital inpatients¹⁸⁻²³ and outpatients.^{24,25} As far as fatal attacks of PE are concerned, several authors have noted a circadian rhythm peaking at 09:00-14:30 hrs in outpatients, which conforms very closely to the data available for inpatients.¹⁷

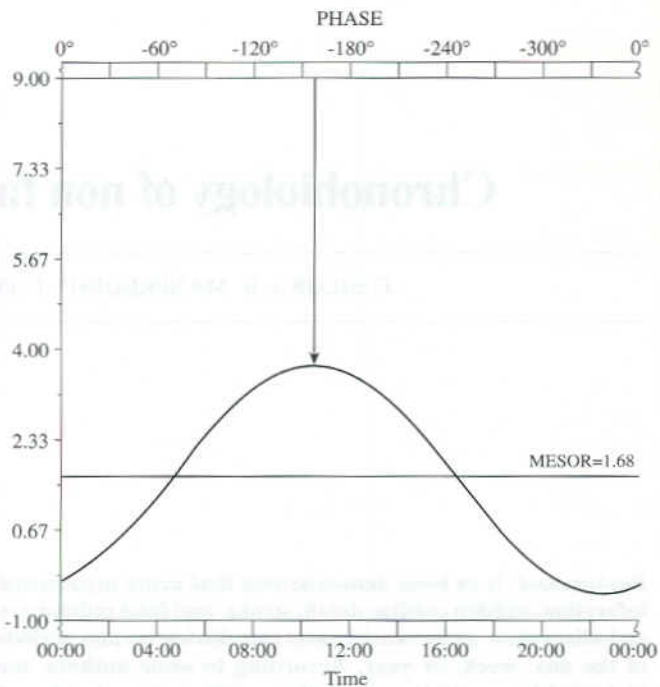
These conditions also show a greater incidence in weekends^{1,26} and during the months from December to April,¹⁸ with a peak in January, for both inpatients and outpatients. These results are determined by daily and seasonal variations in coagulation and fibrinolysis factors.¹⁷



REF. TIME: 199801010000
FITTED PERIOD (hours)=24.000

SINGLE COSINOR						
KEY	#pts	PR	p	MESOR±s.e.	AMP±s.e.	ACR±s.e.
a—a	25	47.7	<0.001	8.78 1.69	10.48 2.3	-186.4 13.3

Fig. 1.—Circadian distribution of deep vein thrombosis.



REF. TIME: 199801010000
FITTED PERIOD (hours)=24.000

SINGLE COSINOR						
KEY	#pts	PR	p	MESOR±s.e.	AMP±s.e.	ACR±s.e.
a—a	25	51.3	<0.001	1.68 0.31	2.08 0.4	-156.4 12.2

Fig. 2.—Circadian distribution of pulmonary thromboembolisms.

This paper intends to verify whether daily, weekly, or yearly variations in deep vein thrombosis and non fatal pulmonary embolism in a sample of elderly hospital inpatients do exist.

Materials and methods

A record was kept of all patients who were hospitalised for deep vein thrombosis or pulmonary embolism at the Second Medical Clinic, Padua University Hospital, Italy, during the period 1995-1996. Details were taken of the day, month, year, and time of onset of the symptoms.

Chronobiological analysis was performed using Halberg's Single Cosinor Test, in which the cosine curve best fitting the data is determined by multiple linear regression. The equation of the curve is $y(t)=M+A \cos(\omega t+\Phi)$, where M =mesor, A =amplitude, Φ =acrophase and (t) =time. Each of the values

has an estimate of variance. In addition, the χ^2 test, when appropriate, was utilized to compare grouped data. Values of $p<0.05$ were considered significant.

Results

We examined 212 patients (98 male and 114 female), aged 68.6 ± 7.1 years, affected by deep vein thrombosis and non fatal pulmonary embolism.

There was a significant circadian peak in the morning ($p<0.001$), both for DVT (acrophase at 12:26 hrs), and PE (acrophase at 10:26 hrs) (Figs. 1, 2). No sex related differences were found.

A significant weekly rhythm ($p<0.001$) on Saturdays was also discovered for the incidence of thromboembolism (Fig. 3). With regard to a possible annual periodicity, none was found with statistical significance, although there was indeed a tendency to increased DVT and PE during the winter and summer months (Fig. 4).

Discussion and conclusions

Many investigators have found circadian rhythms for cardio- and cerebrovascular events; others, for deep vein thrombosis and fatal pulmonary embolism. All these conditions present a morning peak.¹⁸ Our findings confirm previous literature reports concerning DVT and PE, peaking in the morning, on Saturdays and, although it cannot be significantly shown, during winter and summer months.^{18 20 21 23 27}

The results can be explained by considering the circadian morning peak variations for parameters such as haematocrit,²⁸ blood viscosity,²⁹ fibrinogen,³⁰ factor VIII, platelet aggregation and adhesiveness,^{31 32} and white blood cell aggregability.³³ Reduced fibrinolytic activity³⁴ (minimum between 04:00 and 06:00 hrs), and antithrombin values, associated with greater platelet aggregability in the morning, can rapidly determine

thrombus formation. These factors can also increase the number and the dimensions of both venous and cardiac thrombi, and aid detachment. Other determinants are represented by an increase in sympathetic activity and the associated changes in posture and in muscle tone (which cause changes in venous tone and heart rate) after awaking, provoking detachment of emboli, and thus PE.²²

Some studies have shown that ischaemic heart disease, stroke and fatal PE, tend to be more frequent during weekends.^{1 26 35} Our data confirm these observations also for non fatal PE. Lifestyle changes and variations in the quality and quantity of health care during weekends could well determine the weekly rhythms of PE. Furthermore, the reduced fibrinolytic activity during weekends may also play an important role.^{8 35}

As far as yearly variations are concerned, many studies have shown an increased incidence of fatal PE during winter,²¹ with two peaks in January and April.

This distribution may be due to the characteristically lower temperatures of these months, which are associated with reduced antithrombin, and an increase in plasma viscosity, fibrinogen, red blood cells and platelet levels, arterial blood pressure,¹³ and catecholamine secretion.^{18 23} These factors, and reduced physical exertion during winter, may contribute to a greater risk of thromboses.¹⁷ In our study, we saw a tendency towards increased DVT and PE in winter and summer months. A determining factor must surely be the above-mentioned variations in plasma viscosity and reduced physical exertion, as well as frequent bed confinement, concomitant chronic cardiopulmonary diseases, neoplasias, surgical operations and traumas.

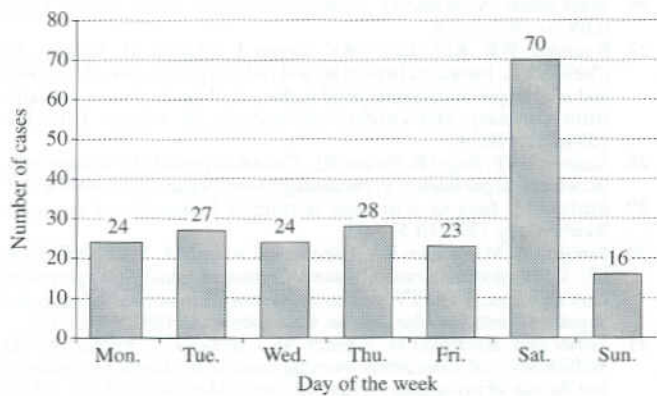


Fig. 3.—Circaseptan distribution of pulmonary thromboembolism.

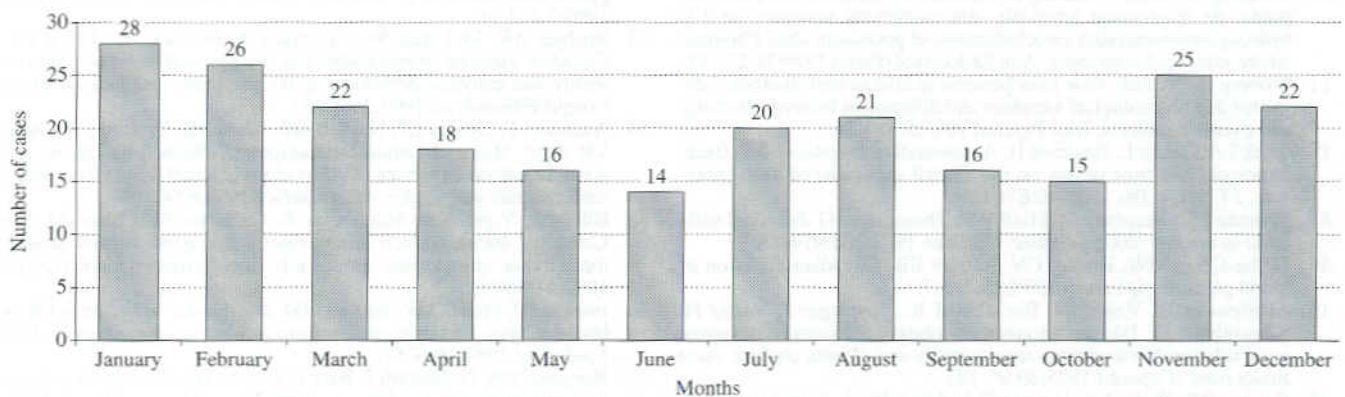


Fig. 4.—Circannual distribution of thromboembolism.

The summer peak observed in cerebral ischaemia,³⁷ is probably due to the viscosity variation secondary to dehydration. All these findings are particularly evident in the ageing patients of our sample.^{24 25}

Our results may suggest an improved approach to deep vein thrombosis and pulmonary embolism: prevention, *i.e.* the monitoring of periods known to be high-risk, and an improvement in pharmacological treatment, *i.e.* intensifying the "timed" dosage of drugs in the morning, at weekends, or during winter or summer months in patients who are at risk from these conditions or who have already had these diseases.

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