Clin Appl Thrombosis/Hemostasis 8(3):231–237, 2002

Seasonal Variation in the Incidence of Deep Vein Thrombosis in Patients With Deficiency of Protein C or Protein S

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Summary: An attempt was made to identify circaseptanal or seasonal variation of deep vein thrombosis (DVT) in a population with protein C or protein S deficit. Forty-four patients with DVT and protein C or protein S deficit were studied for 1 year. A significant circannual rhythm was found for the total population that peaked during winter. There was also a significant falling circaseptanal rhythm on Fridays. These observations may optimize an adequate and precise anticoagulant therapy in patients with protein C or protein S deficits.
Key Words: Circannual rhythm—Circaseptanal rhythm—Deep vein thrombosis—Protein C—Protein S.

Many fatal or potentially fatal diseases such as myocardial infarction, stroke, sudden death, and fatal thromboembolism (PTE) present a circadian and seasonal periodicity (1–4).

These reports are very interesting because they open up the potential for treating cardiovascular diseases by giving drugs at a carefully selected time of the day or year.

It was recently shown that PTE and deep vein thrombosis (DVT) reach a peak in winter (5-7). On the basis of these preliminary findings, we tried to identify circaseptanal or seasonal variation of DVT in a selected population with protein C or protein S deficiency. The following year, January 1998 to December 1999, every 4 months, we examined patients with DVT who were receiving anticoagulant treatment (April, August and December) to test the levels of protein C and protein S. This was done to verify if possible differences in values of protein C or S could be correlated to DVT peaks of the past year. This investigation might appear to be without meaning because these deficits are congenital and so their secondary DVT should be equally distributed over the whole year. Nevertheless, we think that if some temporal variations are demonstrated, these could be very important for potential timing and monitoring of anticoagulant therapy.

METHODS

The study population consisted of all DVT patients with isolated deficit of C or S protein observed at our Department from January to December, 1997. Other coagulation defects were excluded.

We regularly noted the date of incidence of DVT. The total number of patients investigated was 44 (22 M and 22 F). DVT was documented by echo-color doppler in all cases. Phlebography was carried out in doubtful cases. Routine coagulation tests were carried out as previously reported (8).

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TABLE 1. Circannual Variability of DVT in Subjects with Protein C or Protein S Defect

Month	Subjects with DVT (cases) No.	%
January	7	15.9
February	4	9.1
March	5	11.4
April	3	6.8
May	1	2.3
June	2	4.5
July	1	2.3
August	2	4.5
September	2	4.5
October	2	4.5
November	8	18.1
December	7	15.9

Protein C or S deficit was demonstrated by enzyme-linked immunoassay (ELISA) assay and photometric assay (9). All protein C patients were heterozygotes for this abnormality. The protein S patients showed reduction of free protein S.

We then compared these patients with an age- and sex-matched control group composed of 44 DVT subjects who were known to have no coagulation defects.

Data were analyzed by single cosinor test (10,11) in which the cosinor curve best fitting the data is determined by the method of least squares.

RESULTS

We examined 44 subjects (22 M, 22 F) with protein C or S deficit and DVT (mean age, 45 ± 7 years) and 44 subjects (22 M, 22 F) with idiopathic DVT (mean age, 42 ± 6 years).

A significant circannual pattern was detected for the total population with protein C and/or S deficit ($p = 0.002$), with peak in November (Table 1, Fig. 1). We also found a significant circaseptanal rhythm with incidence peak during the weekend, particularly on Fridays ($p < 0.001$) (Table 2, Fig. 2).

In the control population, the circannual pattern was also detected for all subjects peaking in December ($p < 0.001$) (Table 3, Fig. 3). A significant circaseptanal rhythm was not found

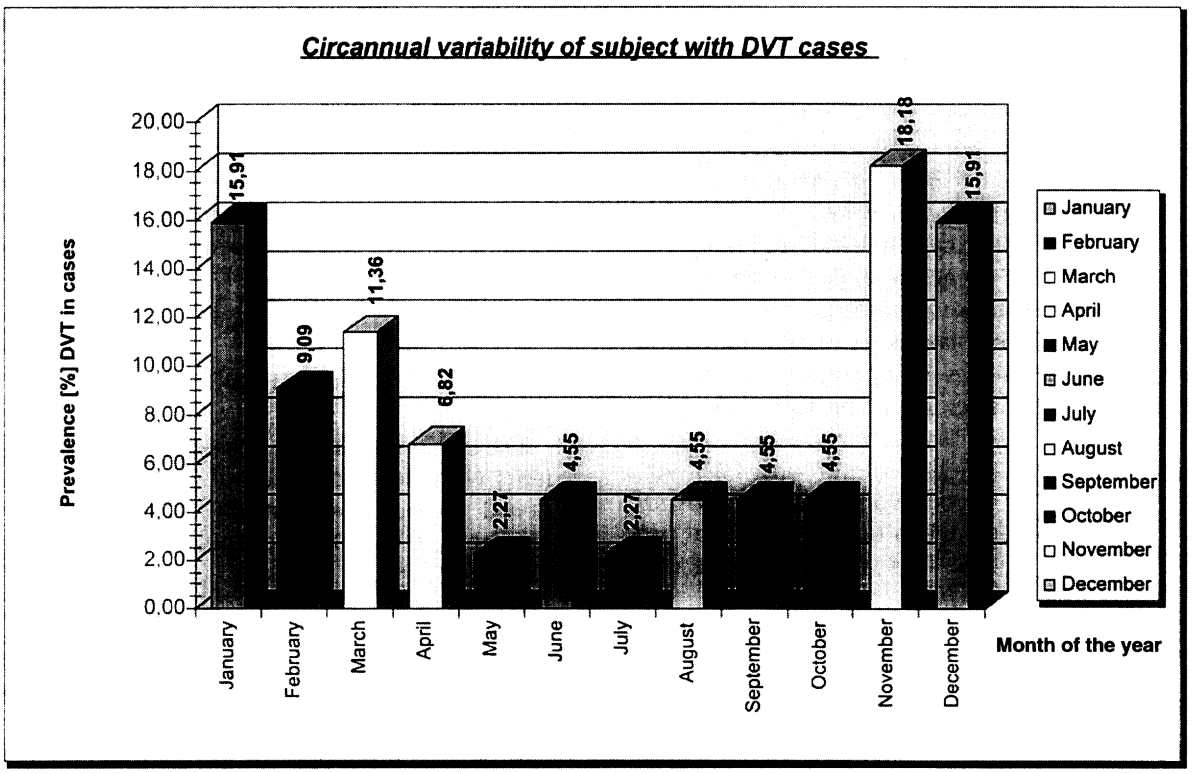

FIG. 1.

TABLE 2. Circaseptanal Variability of DVT in Subjects with Protein C or Protein S Defect

Days of Week	Subjects with DVT (cases) No.	%
Sunday	4	9.1
Monday	2	4.5
Tuesday	4	9.1
Wednesday	5	11.4
Thursday	1	2.3
Friday	20	45.5
Saturday	8	18.1

TABLE 3. Circannual Variability of DVT in Control Group

Month	Subjects with DVT (control) No.	%
January	5	11.4
February	4	9.1
March	2	4.5
April	3	6.8
May	1	2.3
June	2	4.5
July	1	2.3
August	1	2.3
September	2	4.5
October	3	6.8
November	5	11.4
December	15	34

(Table 4, Fig. 4). Nevertheless, there was a higher incidence of events during the weekend. The median levels of C and S protein measured in April, August, and December compared with median levels of C and S protein during DVT peak did not show a circannual variability as during DVT (Table 5).

In Table 6 and Fig. 5, we report the data of DVT correlated to the physical and working activity of the two subpopulations examined. There is a significant reduction of physical activity, during the weekend, for the subjects with protein C and S deficit.

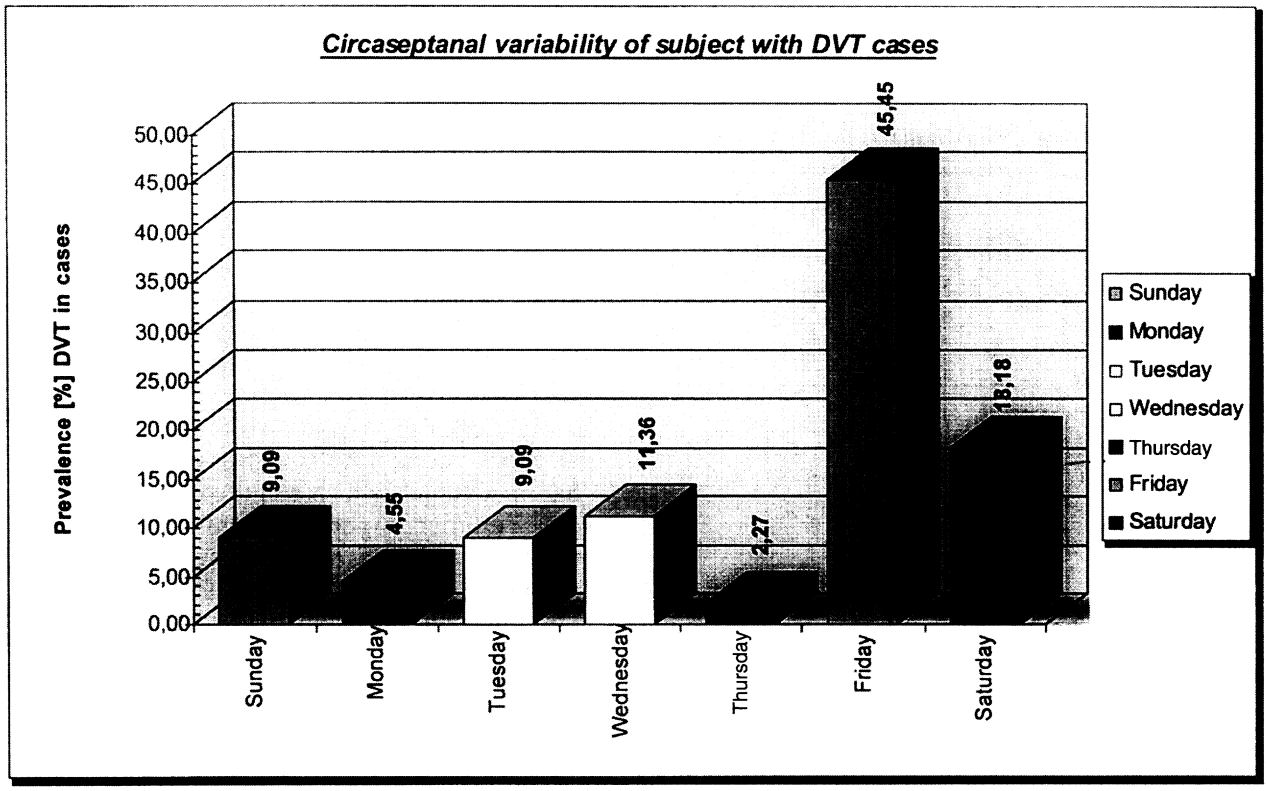

FIG. 2.

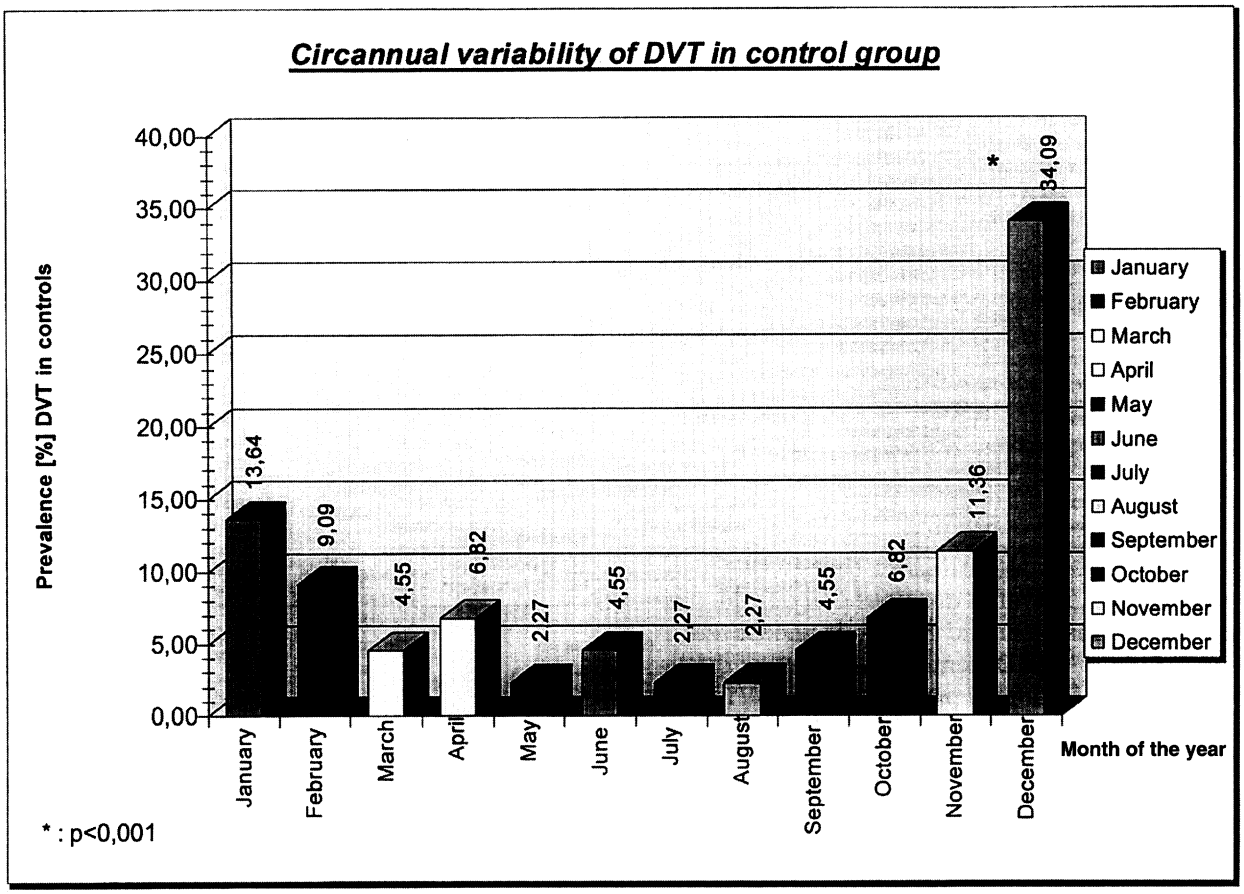

FIG. 3.

TABLE 4. Circaseptanal Variation of DVT in the Control Group

Day of the Week	Subjects with DVT (Controls) No.	%
Sunday	6	13.6
Monday	6	13.6
Tuesday	7	15.9
Wednesday	7	15.9
Thursday	6	13.6
Friday	5	11.4
Saturday	7	15.9

DISCUSSION

We found a winter peak for DVT in patients with protein C and S deficit. This result can be explained by the changes in the blood, including flow and coagulation system in winter (12).

Seasonal variations in these blood parameters have been described in relation to air temperature and surface cooling (13).

Moreover, in winter, decrease in antithrombin III levels, increase in blood viscosity and red blood cells and platelet counts at lower temperatures or in cold exposure have been reported (14,15). These variations could contribute to an increased risk of thrombosis for patients with congenital deficit of protein C or S. During the winter, furthermore, people are less physically active than in summer, which could contribute to DVT (16). Another important point is that in cold months individuals are more subject to febrile conditions, which may modify blood viscosity.

All these findings may help explain the significant incidence of DVT found in our subjects.

The results are even more significant because they are confirmed also in control groups as other authors have already noted (6,7).

Moreover, we observed a difference between cases and controls: unlike the cases, the control

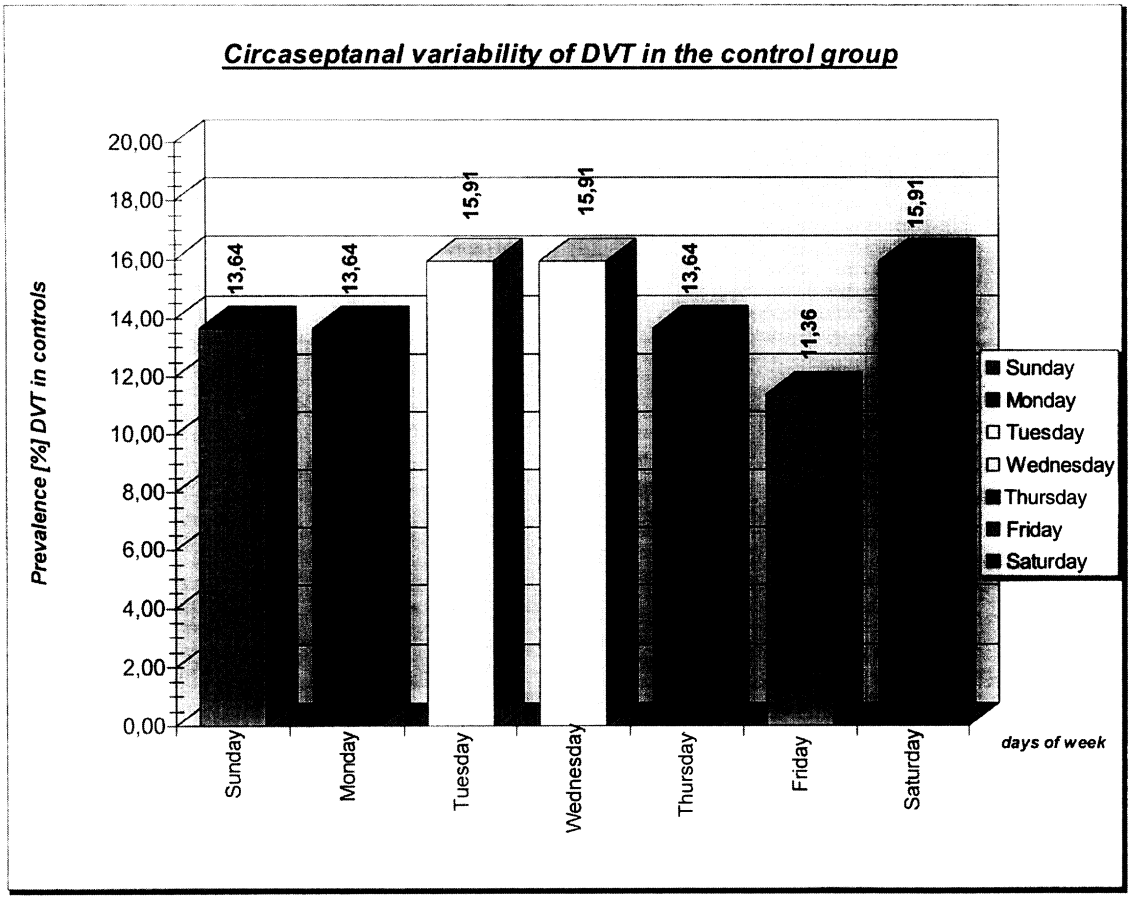

FIG. 4.

TABLE 5. Median Value of C or S Protein in April, August, and December Correlated with Seasonal Peak Incidence of DVT

Protein		April	August	December	Seasonal Peak DVT	p Value
C	Activity (80%-120%)	42.3%	40.5%	41.4%	44.1%	n.s.
S	Free (70%-130%)	75.7%	69.2%	71.3%	70.6%	n.s.
	Activity (70%-130%)	63.5%	60.3%	64.1%	66.2%	n.s.

TABLE 6. Jobs of Cases and Controls

Jobs	Cases		Controls		p Value
	No.	%	No.	%	
With physical activity	25	56.8	9	20.5	<0.001
Without physical activity	10	22.7	18	40.9	n.s.
Pensioners	9	20.5	17	38.6	n.s.

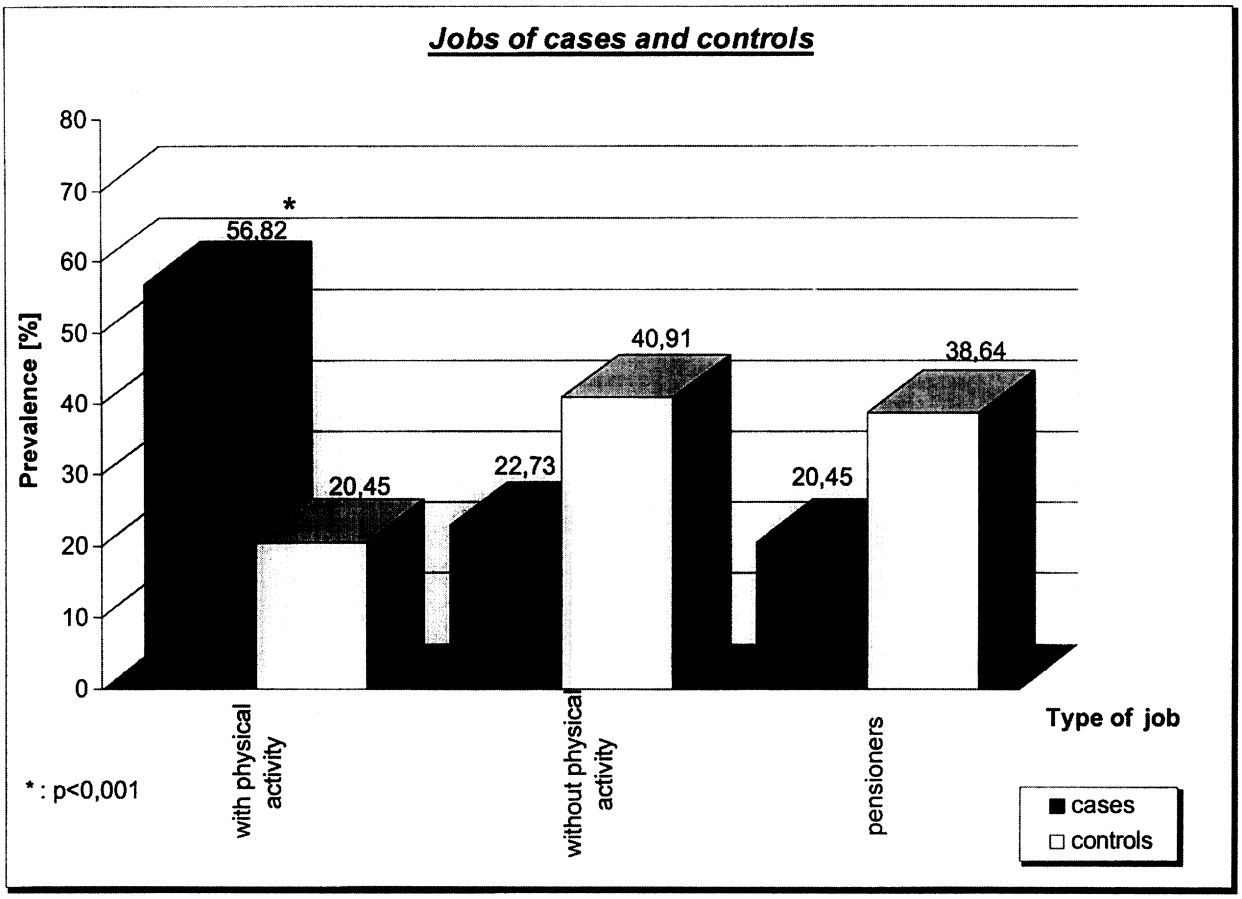

FIG. 5.

group did not present a circaseptanal incidence of DVT. We asked the patients about their occupation and found that case patients had a job that involved more physical activity than the control patients, who were clerks or pensioners. This can explain the different circaseptanal incidence of DVT. The case patients reduce their physical activity over the weekend. The control patients have a poor physical activity because of their job. Moreover, the case patients work in another town and must often travel great distances by car or train.

This situation correlates with DVT because it is well known that sitting with dangling legs favors stasis (17), which is important for the development of DVT particularly in subjects with other coagulation defects.

CONCLUSIONS

There is a seasonal variation in subjects with DVT and C or S protein defect like in other subjects with DVT.

Protein C or S levels do not seem to correlate with seasonal peak of DVT because their values are similar during the year. The circannual DVT risk is related to the same mechanism also described for other DVT. This result suggests the need of continuous anticoagulation therapy for subjects with protein C or S defect.

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