Chirurgia (2013) 108: 530-534
No. 4, July - August

Age Dependent Influence of External Temperature on the Pathogenesis of Idiopathic Lower Extremity Deep Vein Thrombosis

Z. Damnjanović[1], M. Jovanović[1,2], M. Stojanović[2,3], M. Radojković[2,3], D. Bogdanović[4], M. Potić[2,5], A. Bogičević[1], V. Cvetanović[1]

[1]Vascular Surgery Department, Clinical Center of Niš, Serbia
[2]University of Niš, School of Medicine, Serbia
[3]Serbia General Surgery Department, Clinical Center of Niš, Serbia
[4]Department for biochemical and medical sciences, The State University of Novi Pazar, Serbia
[5]Urology Department, Clinical Center of Niš, Serbia

Rezumat

Influența temperaturii externe în patogeneza trombozei venoase profunde idiopatice de membre inferioare în funcție de vârstă

Scopul lucrării: Scopul acestui studiu a fost investigarea relației între incidența trombozei venoase profunde idiopatice a membrelor inferioare, vârsta și localizarea trombusului în funcție de modificările de temperatură.
Material și Metodă: Într-o perioadă de 2 ani, între mai 2009 și aprilie 2011 inclusiv, în Clinica de Chirurgie Vasculară "Centrul Clinic Niš", Serbia, au fost diagnosticați 124 de pacienți consecutivi cu tromboză venoasă profundă idiopatică de membre inferioare.
Rezultate: La pacienții cu vârsta sub 45 de ani, creșterea temperaturii medii zilnice cu 1 grad Celsius 7 zile înainte de apariția evenimentului a fost asociată ($p < 0,05$) cu o scădere a riscului de apariție a trombozei venoase profunde idiopatice a membrelor inferioare cu 3,6% (0,4-6,7%) și de asemenea a trombozei venoase profunde deasupra genunchilor ($p < 0,01$) cu 4,7% (1,3-8%). La pacienții cu vârsta de 45 ani și peste 45 ani creșterea temperaturii medii zilnice cu 1 grad Celsius 7 zile anterior de apariția evenimentului a fost asociată ($p < 0,01$) cu creșterea riscului de apariție a trombozei venoase profunde sub genunchi cu 9,4% (3,3-15,9%).
Concluzie: Conform datelor acestui studiu, putem concluziona că influența modificărilor temperaturii externe asupra incidenței și localizării trombozei venoase profunde este dependentă de vârstă.

Cuvinte cheie: tromboză venoasă profundă idiopatică a membrelor inferioare, localizarea trombusului, temperatură, vârsta

Abstract

Aim: The aim of the present study was to investigate the relationship between the incidence of idiopathic lower extremity deep vein thrombosis (DVT), age, location of the thrombus, and changes of temperature.
Material and method: During the two-year period between May 2009 and April 2011, inclusive, 124 consecutive patients were diagnosed as having idiopathic lower extremity DVT at the Vascular Surgery Clinic "Clinical Center of Niš", Serbia.
Results: In patients younger than 45 years, the increase in average daily temperature with 1 degree C 7 days before the event took place was associated ($p < 0.05$) with a decrease of the risk of occurrence of idiopathic DVT of the lower limbs of 3.6% (0.4 – 6.7%) as well as DVT above the knees

Corresponding author: Zoran Damnjanović, MD
Clinical Center of Niš, Vascular Surgery Clinic
48 Zorana Đinđića Blv., 18000 Niš, Serbia
Tel.: +381 60 0798310; Fax: +381 184238770
E-mail: damnjanovicz@yahoo.com

($p < 0.01$) of 4.7 % (1.3 – 8.0%). In patients of the age of 45 years and over the age of 45 years the increase of average daily temperature with 1 degree C 7 days before the event took place was associated ($p < 0.01$) with the increase of the risk of occurrence of DVT below the knees of 9.4% (3.3 - 15.9%).

Conclusion: According to the results of this study, one can conclude that the influence of external temperature change on DVT incidence and location is based on age.

Key words: idiopathic lower extremity deep vein thrombosis, location of the thrombus, temperature, age

Introduction

Significant associations have been described between climatic factors and human health (1). The relationship between deep vein thrombosis (DVT) and meteorological factors is complex because of the big number of potentially relevant meteorological factors, differences in study design and in climate between the geographical areas where the studies were conducted. In most studies, the seasonal occurrence of DVT during the cold periods of the year was reported (2-9). However, several studies have shown no seasonal variations of DVT (10-13).

The research carried out on the territory of South Serbia showed a seasonal pattern in the incidence of idiopathic leg DVT, with the highest frequency in the cold period of the year and the peak in January (14). The research carried out on the territory of the city of Niš, the capital city of South Serbia, showed a correlation between the incidence and location of leg DVT and changes in the atmospheric pressure (15). There is no data about the relationship between the changes in average daily temperature and the incidence and location of lower extremity idiopathic DVT.

Therefore, the aim of the present study was to investigate the relationship between the incidence of idiopathic lower extremity DVT, age and location of the thrombus, and the changes of the average daily values of temperature on the territory of the city of Niš, Serbia.

Methods

During the two-year period between May 2009 and April 2011, inclusive, 124 consecutive patients were diagnosed and hospitalized on the territory of the city of Niš, Serbia, as having idiopathic lower extremity DVT at the Vascular Surgery Clinic "Clinical center of Niš", Serbia. There were 68 (54.8%) females and 56 (45.2%) males of the average age of 56.87 ± 11.45 years included in this retrospective study, identified by manual search of the prospectively maintained Vascular Surgery Clinic Patient Registry.

Out of the total number of patients with idiopathic lower extremity DVT, there were 95 (76.62%) patients with above-knee DVT and 29 (23.38%) patients with below-knee DVT. There were 43 (34.66%) patients younger than 45 years and 81 (65.34%) patients of the age of 45 and over.

The diagnosis of lower extremity DVT was made according to the anamnestic data, clinical features, biochemical and duplex scanning. The extent of the thrombus was determined by duplex sonography for all the patients.

In the present study only patients with idiopathic lower extremity DVT were included. Exclusion criteria were the presence of malignancy, biological thrombophilia (e.g. factor V Leiden, deficiency of protein C or protein S, presence of antiphospholipid antibodies), surgery, injury and pregnancy or puerperium.

The patients were divided into subgroups by age and the location of the thrombus. The subgroups in relation with the location of the thrombus were: the above-knee DVT group, which included DVT of the thigh and pelvic veins, and the below-knee DVT group, which included patients with DVT in the veins of the lower leg. The subgroups in relation with age were: the group of patients younger than 45 years, and the group of patients of the age of 45 and over.

The mean daily temperature values for the city of Niš, Serbia, were obtained from the National Meteorological Department. The range of average daily values of temperature was 12.91 ± 8.86 (-8.70 to 29.80) degrees C (°C).

Statistical analysis

To investigate the association between the incidence of lower extremity DVT and the temperature, we used the negative binomial regression model. This model included daily DVT counts as the dependent variable and average daily values of temperature as the independent variable. A negative binomial model was used to account the over dispersion, as well as the number of days with zero cases. The relationship between temperature and DVT risk after lags for 0, 3 and 7 days, as well as the cumulative lags for 0-3 and 0-7 days, was examined. The incidence rate ratios of idiopathic lower extremity DVT for a 1°C change in daily average values of temperature were calculated. Analyses were performed using R: a language and environment for statistical computing, version 2.12.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The incidence rate ratios of DVT and the location of the thrombus for a 1°C change in daily average values of temperature for patients of all ages are shown in *Table 1*.

The increase in average daily temperature of 1 degree C 3 days before the event took place (Lag 3), as well as 7 days before the event took place (Lag 7), was associated with a decrease in the above-knee idiopathic DVT occurrence risk ($p < 0.05$) by 2.5% (0.1 – 0.2% to 4.9%). The increase in average daily temperature with 1 degree 7 days before the event took place (Lag 7), was associated with the increase of the below-knee DVT occurrence risk ($p < 0.01$) by 8.5% (3.2 – 14.1%).

Table 1. *Incidence rate ratios (95% confidence interval) of deep vein thrombosis and location of thrombus for 1°C change in daily average values of temperature in all ages patients*

Temperature (1°C)	Location of thrombus		
	All locations	Above-knee	Below-knee
Lag 0	0.999 (0.978-1.021)	0.981 (0.958-1.005)	1.062 (1.013-1.114)*
Lag 3	0.996 (0.975-1.018)	0.975 (0.951-0.998)*	1.076 (1.024-1.130)**
Lag 7	0.999 (0.977-1.021)	0.975 (0.951-0.999)*	1.085 (1.032-1.141)**
Lag 0-3	0.994 (0.972-1.016)	0.976 (0.952-1.000)	1.057 (1.008-1.109)*
Lag 0-7	0.995 (0.972-1.018)	0.976 (0.951-1.001)	1.061 (1.010-1.115)*

*p < 0.05; **p < 0.01

Incidence rate ratios of DVT and the location of the thrombus for a 1°C change in daily average values of temperature for patients younger than 45 years are shown in *Table 2*.

In the group of patients younger than 45 years, the increase of the average daily temperature for 1 degree C 7 days before the event took place (Lag 7) was associated ($p < 0.05$) with the decrease of the lower limb DVT occurrence risk by 3.6% (0.4 – 6.7%) as well as the risk of above-knee DVT ($p < 0.01$) by 4.7 % (1.3 – 8.0%).

Incidence rate ratios of DVT and the location of the thrombus for a 1°C change in daily average values of temperature for patients of the age of 45 and over are shown in *Table 3*.

In the subgroup of patients of the age of 45 years and over, the increase in average daily temperature of 1 degree C 7 days before the event took place (Lag 7) was associated ($p < 0.01$) with the increase of the risk of occurrence of below-knee DVT by 9.4% (3.3 -15.9%).

Discussion

The presented study shows that the increase of average daily temperature by 1°C 3 days before the event took place, as well as 7 days before the event took place, was associated with the decrease of the above-knee idiopathic DVT occurrence risk. Despite this, the increase in average daily temperature from all observed time intervals is associated with the increase of the below-knee idiopathic DVT occurrence risk, while the most significant confirmed correlation is with the increase in temperature 7 days before the event took place.

For patients younger than 45, the increase in daily temperature influenced the decrease of the lower limb idiopathic DVT occurrence risk, above-knee DVT occurrence risk, while the most significant confirmed correlation is with the increase in temperature measured 7 days before the event took place. In the subgroup of patients of the age of 45 and over, the increase of the daily temperature influenced the increase of the below-knee idiopathic DVT occurrence risk and the most significant confirmed correlation is with

Table 2. *Incidence rate ratios (95% confidence interval) of deep vein thrombosis and location of thrombus for 1°C change in daily average values of temperature in patients younger than 45 years*

Temperature (1°C)	Location of thrombus		
	All locations	Above-knee	Below-knee
Lag 0	0.978 (0.947-1.010)	0.966 (0.934-1.000)	1.072 (0.965-1.192)
Lag 3	0.974 (0.943-1.006)	0.963 (0.931-0.997)*	1.061 (0.958-1.175)
Lag 7	0.964 (0.933-0.996)*	0.953 (0.920-0.987)**	1.050 (0.950-1.159)
Lag 0-3	0.971 (0.940-1.004)	0.961 (0.927-0.995)*	1.058 (0.953-1.174)
Lag 0-7	0.965 (0.932-0.999)*	0.955 (0.920-0.990)*	1.047 (0.944-1.160)

*p < 0.05; **p < 0.01

Table 3. *Incidence rate ratios (95% confidence interval) of deep vein thrombosis and location of thrombus for 1°C change in daily average values of temperature in patients of the age of 45 and over the age of 45 years*

Temperature (1°C)	Location of thrombus		
	All locations	Above-knee	Below-knee
Lag 0	1.015 (0.988-1.043)	0.997 (0.965-1.029)	1.059 (1.005-1.116)*
Lag 3	1.013 (0.986-1.041)	0.987 (0.957-1.019)	1.079 (1.021-1.140)**
Lag 7	1.023 (0.995-1.052)	0.996 (0.965-1.028)	1.094 (1.033-1.159)**
Lag 0-3	1.011 (0.983-1.039)	0.992 (0.960-1.024)	1.056 (1.001-1.114)*
Lag 0-7	1.017 (0.988-1.046)	0.997 (0.964-1.030)	1.064 (1.007-1.125)*

*p < 0.05; **p < 0.01

temperature increase 7 days before the event took place.

Experimental studies show the influence of temperature change on the increased DVT occurrence risk. Mercer et al. (16) reported that a short-term period of exposing young healthy subjects to cold leads to hemoconcentration as indicated by an increase in the erythrocyte and granulocyte count. Kawahara et al. (17) reported that exposing young healthy subjects to cold leads to the increase of sympathetic nervous activity, which can contribute to the enhancement of platelet function.

The results of the present study differ from the results of the study of Chang et al. (18) where no relationship with DVT incidence was found. There are many reasons that can explain such difference in results. The Chang et al. study methodologically differs in the points of monitoring the correlation between DVT incidence and the changes in average monthly temperature with 5 degrees C. Simultaneously, the monitoring included all kinds of DVT and not only lower limb idiopathic DVT, as it is the case in the present study. The study of Schuh (19) reported that lower temperature is correlated with the incidence of DVT. Brown et al. (7) reported that seasonal variations in temperature were significantly associated with the seasonal variation in DVT.

The results of presented study contribute to the results of the studies that show that DVT occurs more frequently during cold periods of the year (2-9). Several multiple important factors may play a role in the winter preference for DVT. The increase in sympathetic activity and blood pressure levels with negative correlation between the ambient temperature and blood pressure during the cold season has been reported (20-21). Also, the increase of fibrinogen levels, platelet and red cell count during the colder months has been reported (22-23).

The mechanism which affects the location of the thrombus in the leg is still not understood. Fink et al. (6) showed that distal DVT of the leg was found to be more frequent during the winter halves of the year while proximal DVT was diagnosed more often during the summer halves. They hypothesized that the veins of the lower leg are more susceptible to low temperatures than the veins of the thigh or abdomen, which are better protected by muscles and fat.

The current study shows that an increase in average daily temperature is associated with the decrease of the above-knee idiopathic DVT occurrence risk, as well as the increased below-knee DVT occurrence risk. Disorders of the venous system are more frequent in elderly people with the localization below the knees (24), which can hypothetically be associated with the results of the presented study, with a different influence of temperature change on the location of a thrombus according to age.

The major limitation of our study is the fact that it is retrospective. However, it should be noted that all data were registered prospectively. Also, a certain number of patients with peroneal DVT can pass without any major clinical sings of the existence of the disease, which may affect the number of diagnosed patients with below-knee DVT.

The strengths of this study reside in the fact that this is the first study evaluating the relationship between the incidence of idiopathic lower extremity DVT, age and location of the thrombus, and changes in the daily average values of temperature. Further researches should be focused on investigating the connection between external temperature changes and systemic disorders in the organism for DVT patients, with the goal of additionally elaborating the pathogenesis of this disease.

Conclusion

According to the results of this study, one can conclude that the influence of external temperature change on DVT incidence and location is based on age.

References

1. Rakhmanov RS, Gadzhiibragimov DA, Medzhikova MA, Kudriavtseva OA. Assessment of the significance of climato-geographic conditions as health risk factors. Gig Sanit. 2010;2:44-6.
2. Manfredini R, Imberti D, Gallerani M, Verso M, Pistelli R, Aqueno W, et al. Seasonal variation in the occurrence of venous thromboembolism: data from the MASTER Registry. Clin Appl Thromb Hemost. 2009;15(3):309-15.
3. Jang MJ, Kim HJ, Bang SM, Lee JO, Yhim HY, Kim YK, et al. Seasonal variation in the occurrence of venous thromboembolism: A report from the Korean Venous Thromboembolism Working Party. Thromb Res. 2012;130(4):199-202.
4. Boulay F, Berthier F, Schoukroun G, Raybaut C, Gendreike Y, Blaive B. Seasonal variations in hospital admission for deep vein thrombosis and pulmonary embolism: analysis of discharge data. BMJ. 2001;323(7313):601-2.
5. Montes Santiago J, Rey García G, Mediero Domínguez A. Seasonal changes in morbimortality caused by pulmonary thromboembolism in Galicia. An Med Interna. 2003;20(9):457– 60.
6. Fink AM, Mayer W, Steiner A. Seasonal variations of deep vein thrombosis and its influence on the location of the thrombus. Thromb Res. 2002;106(2):97-100.
7. Brown HK, Simpson AJ, Murchison JT. The influence of meteorological variables on the development of deep venous thrombosis. Thromb Haemost. 2009;102(4):676-82.
8. Dentali F, Ageno W, Rancan E, Donati AV, Galli L, Squizzato A, et al. Seasonal and monthly variability in the incidence of venous thromboembolism. A systematic review and a meta-analysis of the literature. Thromb Haemost. 2011;106(3):439-47.
9. Dentali F, Manfredini R, Ageno W. Seasonal variability of venous thromboembolism. Curr Opin Pulm Med. 2009;15(5):403-7.
10. Galle C, Wautrecht JC, Motte S, Le Minh T, Dehon P, Ferreira J, et al. The role of season in the incidence of deep vein thrombosis. J Mal Vasc. 1998;23(2):99-101.
11. Bounameaux H, Hicklin L, Desmarais S. Seasonal variation in deep vein thrombosis. BMJ. 1996;312(7026):284–5.
12. Stein PD, Kayali F, Olson RE. Analysis of occurrence of venous thromboembolic disease in the four seasons. Am J Cardiol. 2004;93(4):511-3.
13. Lee CH, Cheng CL, Lin LJ, Tsai LM, Yang YH. Epidemiology and predictors of short-term mortality in symptomatic venous

thromboembolism. Circ J. 2011;75(8):1998-2004.
14. Damnjanovic Z, Jovanovic M, Ilic N, Bogdanovic D, Kudumovic M, Kamenov A, et al. Seasonal variations in the incidence of idiopathic lower extremity deep vein thrombosis on the territory of South Serbia. HealthMED. 2012;6(7):2477-81.
15. Damnjanović Z, Jovanović M, Bogdanović D, Smiljković I, Ilić N, Damnjanović I. Relationship between the incidence of idiopathic lower extremity deep vein thrombosis and the location of the thrombus with changes of atmospheric pressure. Chirurgia (Bucur). 2012;107(4):483-7.
16. Mercer JB, Osterud B, Tveita T. The effect of short-term cold exposure on risk factors for cardiovascular disease. Thromb Res. 1999;95(2):93-104.
17. Kawahara J, Sano H, Fukuzaki H, Saito K, Hirouchi H. Acute effects of exposure to cold on blood pressure, platelet function and sympathetic nervous activity in humans. Am J Hypertens. 1989;2(9):724-6.
18. Chang CL, Shipley M, Marmot M, Poulter N. Lower ambient temperature was associated with an increased risk of hospitalization for stroke and acute myocardial infarction in young women. J Clin Epidemiol. 2004;57(7):749-57.
19. Schuh A. Not good for weak veins. Winter temperature promote thrombus formation. MMW Fortschr Med. 2003;145(35-36):31-2.
20. Hata T, Ogihara T, Maruyama A, Mikami H, Nakamaru M, Naka T, et al. The seasonal variation of blood pressure in patients with essential hypertension. Clin Exp Hypertens. 1982;4(3):341–54.
21. Kunes J, Tremblay J, Bellavance F, Hamet P. Influence of environmental temperature on the blood pressure of hypertensive patients in Montreal. Am J Hypertens. 1991;4(5):422–6.
22. Woodhouse PR, Khaw KT, Plummer M, Foley A, Meade TW. Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. Lancet. 1994;343(8895):435–9.
23. Keatinge WR, Coleshaw ERK, Easto JC, Cotter F, Mattock M, Chelliah R. Increases in platelet and red cell counts, blood viscosity, and arterial pressure during mild surface cooling: factors in mortality from coronary and cerebral thrombosis in winter. Br Med J. 1984;289(6456):1045–8.
24. Nüllen H, Noppeney T. Diagnosis and treatment of varicose veins. Part 1: definition, epidemiology, etiology, classification, clinical aspects, diagnostic and indications. Chirurg. 2010;81(11):1035-44.