

## CIRCADIAN PATTERN OF DEEP VEIN THROMBOSIS - TRUE OR FALSE

Zoran Damnjanović

Depending on the pattern length, biological rhythms are divided into three main categories: circadian rhythms (a 24 hour period), ultradian rhythms (a period of less than 24 hours) and infradian rhythms (a period longer than 24 hours). The cardiovascular system is organized on the basis of the weather conditions that oscillate in nature due to which most of the functions follow circadian and seasonal rhythms. The patterns of the maximum and minimum values of the cardiovascular system functions such as blood pressure, heart rate, vascular tone, coagulation and fibrinolysis are well known. Understanding the circadian pattern contributes to the additional clarification of deep vein thrombosis (DVT) pathogenesis and provides the ability to prevent the occurrence of DVT more effectively due to the predictability of critical periods during the day for the origin of an increase in the risk of DVT.

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**Key words:** circadian pattern, deep vein thrombosis, pathogenesis

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Clinic of vascular surgery, Clinical Center of Niš, Serbia

Contact: Zoran Damnjanović  
Bulevar Zorana Djindjića 48, 18000 Niš, Serbia  
E-mail: damnjanovicz@yahoo.com

### Introduction

Depending on the pattern length, biological rhythms are divided into three main categories: circadian rhythms (a 24 hour period), ultradian rhythms (a period of less than 24 hours) and infradian rhythms (a period longer than 24 hours). If under certain experimental conditions the biological organism got isolated from the synchronizing environmental sensitivity changes, some of the circadian rhythms would disappear. On the other hand, the endogenous circadian rhythms would continue to exist even under these conditions, but they wouldn't be connected to the day and night change pattern (1).

The cardiovascular system is organized on the basis of the weather conditions that oscillate in nature due to which most of the functions follow circadian and seasonal rhythms. The patterns of the maximum and minimum values of the cardiovascular system functions such as blood pressure, heart rate, vascular tone, coagulation and fibrinolysis are well known. Besides, there is a growing body of evidence supporting the existence of correlation between the time of day, day of the week, months of the year

and both morbidity and mortality of certain cardiovascular diseases (2). These patterns exist as a result of the interaction of the rhythms of causal factors of diseases and physiological rhythms of the body. The interactions define the chronorisk concept where the causative factor is probably not powerful enough to bring to the formation of the disease, but in a certain period of time it becomes efficient (3).

### Circadian pattern and deep vein thrombosis

The biological mechanisms causing circadian variations are poorly understood. As already known, the circadian rhythm is generated by a central circadian oscillator in the suprachiasmatic nucleus of the hypo-thalamus. Studies in the field of biological rhythms over the last decade have shown that the circadian rhythm in biological, physiological, and behavioral processes has been found in mammals, animalia and plantae organisms (4). The circadian rhythm controls various biological functions in mammals including xenobiotic metabolism and detoxification, immune functions, cell cycle events, apoptosis and angiogenesis. The importance of the circadian rhythm is well known in the chronopharmacology that deals with the biological rhythm dependencies of drugs and examines circadian variations of drug (5). This suggests that chronotherapeutic approaches should be taken for many drugs to enhance their effectiveness. Currently chronotherapeutic approaches are successfully applied in the treatment of peptic ulcer, asthma bronchiale, angina inversa, migraine, allergic rhinitis, rheumatic gout, depressive illness, cardiac infarct, brain infarct, osteoarthropathy and cutaneous hypersensitivity (6,7). Circadian rhythms are controlled by a cyclical expression of circadian genes.

Mutations in these genes lead to the modification and / or disruption of the circadian oscillator. The investigation of novel genes involved in circadian rhythm - related disease will open up new possibility for therapy and they can be used as markers for improved diagnosis and prognosis (8).

As circadian rhythms modulate vital processes, it is not surprising that several health problems can be associated with the disruption of these rhythms in humans including: gastrointestinal, menstrual irregularities, and sleep disorders (9), but in the past few years, special attention has been paid to the impact of circadian rhythms on the development of deep vein thrombosis (DVT).

The research conducted in Italy by Bilora et al. (10), which included 212 patients diagnosed with deep vein thrombosis and pulmonary embolism (PE) proved the existence of peak for DVT manifestation at 12: 26h, while the most cases of PE were recorded at 10: 26h. The research conducted by Gallerani et al. (11), which included the analysis of autopsy findings of 507 patients with sudden death in the period from 1983 to 1989, confirmed that the morning hours was the time when the peak for PE occurrence was recorded.

The inflammatory process of DVT pathogenesis involves neutrophils, lymphocytes, platelets, and the integrin subunits  $\beta 2$  and  $\beta 3$ , which are connected to their ligands (12). The data found in experimental studies concerning the existence and impact of neutrophil extracellular traps in thrombus formation, have also been confirmed in the researches that involved patients with DVT. It is believed that the role of neutrophil extracellular traps is very important in the formation and maturation thrombus (13,14). The contribution of erythrocytes in the inflammatory pathogenesis of DVT has not been fully understood yet, despite the well-known fact that large amounts of these blood cells are present at an early stage of DVT (15). Erythrocyte cytoplasm is rich in iron which, due to its oxidative effects, can have highly inflammatory impact on the endothelium if released in the circulation. Hypothetically, it is considered that in the case of thrombus formation, oxidative radicals produced by leukocytes and endothelial cells of blood vessels lead to oxidation of hemoglobin from erythrocytes and the formation of methemoglobin. Methemoglobin contains  $Fe^{3+}$  ions that may have an inflammatory effect on the endothelium (16).

The circadian variation of blood coagulation and of the fibrinolytic system suggest a passable state of hypercoagulability in the morning hours. Literature data suggest a tendency to an increased coagulation in the morning hours, which matches the results of this study which show the correlation of the incidence with the time of DVT occurrence in lower limbs. The existence of the morning DVT peaks can be found in the literature data concerning the confirmed endogenous circadian rhythm of blood elements and enzymes. The research conducted by Scheer et al. (17) proved the morning peak activities of platelets (09:00h), with the most expressed aggregation tendency compared to the rest of the day. Recent studies have established that, of the

known components of the fibrinolytic system, only tissue-type plasminogen activator and its fast-acting inhibitor, plasminogen activator inhibitor- 1, show a marked circadian variation in plasma (18). Studies have shown that the inhibitor of plasminogen activator being an important inhibitor of fibrinolysis, expresses the peak of its activity in the morning (06: 30h), which may also explain the increased blood thrombogenicity in the morning (19,20). Additionally, the morning peak has been identified for the value of coagulation factors VIIa and fibrinogen, as well as for coagulation inhibitors such as protein C, protein S, and antithrombin III (21). The studies that included healthy volunteers have shown decline in endothelial function in the morning, while the blood pressure, heart rate and activity of the renin-angiotensin-aldosterone system have been increased (17,19).

Experiments conducted by Pinotte et al. in transgenic mice and in vitro studies demonstrated that variations of coagulation factor VII were controlled at the transcriptional level through the recruitment of circadian transcription factors (20,22). It was noticed that deletion or mutation of circadian transcription factors in mice changed the time to thrombotic vascular occlusion (23). Conducted studies indicate that blood coagulation is influenced by endogenous biological clocks and daylight, because circadian variations of mRNA expression of coagulation and fibrinolytic factors have been demonstrated in several murine organs (22,24). Scheer et al. found that other cardiovascular risk factors are under direct circadian control, including platelet activation, count, and aggregability, plasma epinephrine and norepinephrine, plasma cortisol, systolic and diastolic blood pressure, heart rate, and vagal cardiac modulation (19). On the other hand, some investigation showed that melatonin could be important signaling molecule for circadian rhythms of many biological processes, including arterial an venous thromboembolic episodes, indicating an association between blood clotting mechanisms and daylight patterns (25,26).

Previous investigations on the territory of Southern Serbia have revealed a seasonal pattern of the lower limb DVT appearance, with the highest incidence during the cold period of the year (October-March) (27). The connection between the DVT pathogenesis and the change of external temperature and atmospheric pressure has also been proven. This connection depends on the patient age and the thrombus localization (28,29).

## Conclusion

Further studies should additionally clarify the reasons for circadian DVT rhythm in the lower limbs. Understanding the circadian pattern contributes to the additional clarification of DVT pathogenesis and provides the ability to prevent the occurrence of DVT more effectively due to the predictability of critical periods during the day for the origin of an increase in the risk of DVT.

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## CIRKADIJALNI OBRAZAC TROMBOZE DUBOKIH VENA – ISTINA ILI ZABLUDA

*Zoran Damnjanović*

Klinika za vaskularnu hirurgiju, Klinički centar Niš, Niš, Srbija

*Kontakt:* Zoran Damnjanovic  
Bulevar dr Zorana Đinđića 48, 18000 Niš, Srbija  
E-mail: damnjanovicz@yahoo.com

U zavisnosti od dužine ciklusa biološki ritmovi su svrstani u tri glavne vrste: cirkadijalni (period od 24h), ultradijalni (period kraći od 24h) i infradijalni (periodi duži od 24h). Kardiovaskularni sistem organizovan je na osnovu vremenskih prilika koje osciliraju u prirodi usled čega većina funkcija prati cirkadijalni ili sezonski ritam. Obrasci maksimalnih i minimalnih vrednosti funkcija kardiovaskularnog sistema, kao što su arterijski pritisak, srčana frekvencija, vaskularni tonus, koagulacija i fibrinoliza dobro su poznati. Poznavanje cirkadijalnog obrasca doprinosi dodatnom razjašnjenju patogeneze tromboze dubokih vena (TDV) i pruža mogućnost efikasnije prevencije nastanka TDV usled predvidljivosti kritičnih perioda tokom dana za porast rizika od nastanka TDV.

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**Ključne reči:** cirkadijalni ritam, tromboza dubokih vena, patogeneza