Diurnal variation in acute thrombotic cardiovascular events

Akut trombotik kardiyovasküler olaylarda diürnal varyasyon

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ABSTRACT

Circadian clocks affect cardiovascular system and thought to be responsible for the increased vascular events during certain periods. Determination of the diurnal variation of acute vascular thrombotic events might help us for protection of patients during vulnerable periods. In this review, we investigate diurnal variation in acute thrombotic vascular events in the light of recent information.

(Anadolu Kardiyol Derg 2013; 13: 67-71)

Key words: Circadian, stent thrombosis, acute coronary syndrome, acute arterial thrombosis, acute venous thrombosis

ÖZET

Sirkadiyan ritmin kardiyovasküler sistemi etkilediği ve vasküler olayların belli zaman periyotlarında artış göstermesinden sorumlu olduğu düşünülmektedir. Akut vasküler olaylarda diürnal varyasyonun saptanması hastaların korunmasız olduğu bu periyotlarda daha dikkatli olmamız açısından önemlidir. Bu derlemede son bilgiler ışığında akut trombotik vasküler olayların diürnal varyasyonunu araştırdık

(Anadolu Kardiyol Derg 2013; 13: 67-71)

Anahtar kelimeler: Sirkadiyan, stent trombozu, akut koroner sendrom, akut arteriyel tromboz, akut venöz tromboz

Introduction

Circadian clocks affect cardiovascular system and thought to be responsible for the increased vascular events during some periods. Depending on the cell type within which they are found, the mammalian circadian clocks can be divided into two major classes: central and peripheral circadian clocks. The central circadian clock is located within the suprachiasmatic nucleus (SCN), which is located in the hypothalamus. On the other hand, peripheral clocks are those clocks found within all non-SCN cells of the organism, including other regions of the central nervous system. By light, the central clock is reset, but peripheral circadian clocks are influenced by various neurohumoral factors.

Previous studies have evaluated the predictive factors of vascular thrombosis, the results of which may contribute to improved understanding the cause of acute vascular events. There have been repeated reports of circadian, day of-week, and seasonal variability in certain acute arterial and venous thrombotic events, including stroke, myocardial infarction (MI), limb ischemia, deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) (1-5). For the recognition of mechanisms that might trigger acute vascular events, this variability would be important especially for its prevention, and for the management of emergency care systems.

In this review, we investigate diurnal variation in acute thrombotic vascular events in the light of recent information.

De-novo acute vascular thrombotic events

Circadian variation

Daily activities are of matter in triggering vascular thrombosis is based, in part, on studies results that the events caused by

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Accepted Date/Kabul Tarihi: 13.06.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 19.10.2012

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doi:10.5152/akd.2013.009

thrombosis do not occur randomly throughout the day. However, they occur in a prominent circadian pattern with an increased frequency toward the morning. Tsementzis et al. (1) showed that cerebral infarction occurred more frequently during sleep or was noticed on waking in the 245 patients with thromboembolic cerebral infarction. A meta-analysis by Elliott et al. (6) showed a peak from 6 am to 12 noon for all kinds of stroke. The morning excess was 55% for ischemic stroke and 50% for transient ischemic (TIA) attack compared with the rest of the 24 hours in the day. Similarly, Butt et al. (7) showed significant circadian variation was found in cerebral infarction more likely occurred between 4 am-8 am. Additionally, Bowden et al. (8) reported that there is a significantly increased rate of postoperative embolization for carotid endarterectomies operations begun earlier in the day. They suggested that carotid endarterectomies performed in the afternoon may be at less risk of developing postoperative thrombotic stroke. Cohen et al. (2) reported that acute myocardial infarction (MI) have a circadian pattern of occurrence with a peak in the morning hours in a meta- analysis of 30 studies out of 66.635 non fatal acute MI. They suggested that approximately 1 of every 11 acute MIs are attributable to this morning excess. Muller et al. (9) showed that acute MI is 1.28 times more likely to begin between 6:00 A.M. and 12:00 P.M. than during the other three 6-hour intervals of the day in Multicenter Investigation of Limitation of Infarct Size (MILIS) study. In another study it was shown that acute limb ischemia occur more frequently during the morning period. The same hourly pattern was found also after separate analysis of upper and lower limb ischemia (5). In addition, some studies showed not only the acute thrombotic arterial events but also acute venous events happened during the similar hours. Colantonio et al. (3) showed that the maximum incidence of fatal PTE episodes occurred between the hours of 5:00 and 11:00 A.M. Hakim et al. (10) showed that massive PTE showed a statistical increase in onset in the morning period with peak of occurrence between 9:00 to 10:00 A.M. Although only a minority of the previous studies present wake-time adjusted data, the morning peak in acute vascular events is somewhat sharper when the time of awakening and arising from bed is taken into account. It is therefore possible that the true population- attributable risk percent of morning events is slightly larger than that estimated. However, it is unlikely that the magnitude of this underestimation is very great. There are rare studies that have controversial result of the vast majority of the studies, which shows acute thrombotic vascular events occur mostly during the late period of night and early period of morning. Besides some studies shows acute MI increases significantly after afternoon or during evening hours (11). Some recent reports have suggested that the onset of acute MI shows two peaks, which occur in the morning and evening (12, 13). Itaya et al. (13) showed that there were two peaks in the onset of ST Elevation Myocardial Infarction (STEMI) throughout the day, which were at 7:00-10:00 A.M and 7:00-9:00 P.M. In some studies done with different subgroups of patients such as patients older than 70 years of age, smokers, diabetics, and a group of patients who were taking beta-blocker therapy showed that MI occurs more frequently during night period (14,15). Although mental stress, overtime work, smoking and drinking have been accused, the reasons for the evening peak are unknown clearly (16-18).

If the atherosclerotic plaque is vulnerable, it can cause thrombotic vascular events with a few systemic physiologic processes. The most probable process that may explain why the acute thrombotic vascular events mostly occur during the late night and early morning are increase in plasma renin activity (19), increase in blood pressure and heart rate due to catecholamine which increases the shear stress in vessels (20), increase of coronary spasm which may lead to thrombus formation (21), increase in platelet aggregation (22), elevation in levels of PAI (23) and low level of tissue plasminogen activator indicating the hypo-fibrinolytic state. These all occur during night time sleep, and a then there is a trough in the morning. Andreotti et al. (23) showed that the plasminogen activator inhibitor (PAI) activity decreased throughout the day reaching trace activity at 6 P.M. and the inhibitor activity then increased at 3 A.M. The serum cortisol release has an endogenous circadian process, not dependent on daily activity (24), might increase the sensitivity of the arteries to the vasoconstrictor effects of catecholamine (25), that have a prominent occur after assumption of the upright posture (22). The reduction in cerebral auto regulation during the early morning may facilitate the onset of cerebrovascular accidents (26). Additionally with awakening the sympathetic tone is increases and this may favor embolic detachments and therefore PTE (27).

Daily variation

Although there are some controversial results, most of the previous studies shows acute vascular thrombotic events mostly occur on Monday. Manfredini et al. (28) reported that TIA was most frequent on Monday. Spielberg et al. (29) reported the highest MI occurrence was on Mondays and the lowest on Saturdays; data for both days were statistically significant. When data on working and retired patients were separated, dependence of infarction occurrence on the day of the week was similar in the two patient subsets. Occurrence on Mondays was increased by 19% for retired patients and by 24% for working patients. In another study, Manfredini et al. (30) showed that acute MI was mostly occurred on Monday and lastly on Sunday. For total, nonfatal and fatal cases, comparing observed vs. expected events there was a significantly higher frequency of cases on weekdays and reduced on weekends. Hakim et al. (10) showed that massive PTE showed a statistical increase in the first three day of the week. There are also converse studies. Some authors reported an increased occurrence of MI on the weekend (31, 32).

The most claimed factors that why acute vascular events occur mostly on Monday is the increased mental stress. The probable explanation why increased mental stress trigger the

acute vascular events is; the increased systemic arterial pressure, heart rate, coronary vascular resistance and the platelet activities (33, 34). After a rest period of weekend the work stress on Monday induce the hemodynamic changes and this is thought to be a trigger of the acute vascular events. In this respect, also some studies reported no significant difference between working and retired patients. Probably, because for retired people also there is a marked lifestyle difference between weekdays and weekends because most of them are still part of a public life.

Seasonal variation

In previous studies, it has been demonstrated that acute vascular thrombotic conditions are more likely to occur in winter. Manfredini et al. (28) reported that TIA was most frequent in autumn and winter and less common in spring and summer, with the highest number of cases in October and the lowest in February. In another study Manfredini et al. (30) reported acute MI was most frequent in winter and least in summer. The highest number of cases was recorded in January and the lowest in July. Spielberg et al. (29) reported MI occurred more during the winter from January to March compared with other seasons. Some studies show not just the acute arterial events but also the acute venous events increase in winter. Gallerani et al. (35) reported seasonal a significantly reduced frequency of DVT events in summer and increased in winter. Similarly, chronobiological analysis yielded a significant seasonal variation, with a peak in December (35). In another study, Manfrenidini et al. (36) reported the winter peak of PTE and they suggested that this circadian variation is not influenced by the underlying clinical conditions such as DVT or surgical operation. Fatal PTE has also been reported more often in winter after total hip arthroplasty and the incidence from November through February was 1% as compared with 0.42% for the remainder of the year (37). There are inconsistent studies. Bodis et al. (38) showed the peak period of TIA incidence was during spring, while lowest number of events occurred during autumn. Bounameaux et al. (39) were found no differences for the monthly or seasonal distribution of the suspected events or confirmed DVT events.. The probable causes of the conflicting results of this study are the length of months not equal in that region, and the wide variations in weather conditions may occur within any given month.

Physiologic variables with seasonal rhythmicity may be associated to the seasonal deviations in vascular events occurrence. The reasons underlying the higher occurrence of vascular diseases in winter have remained controversial. But investigators have mostly pointed to cold (40) and respiratory infections which may trigger attacks of vascular events, as they affect the blood coagulation factors (41), causing damage to vessel walls (42). Possible mechanisms include consequences resulting from increased blood pressure, hematological changes following cold-induced vasoconstriction and consequent loss of plasma fluid, which predispose the subject to vascular thrombosis (43, 44). Because of a high rate of reentry into professional life can be assumed for these months, the transition from low stress to higher stress work may be a contributory cause of the increases in vascular events occurrence. Also in winter season changes in blood flow in the legs after peripheral vasoconstriction might increased venous thrombosis (45).

Stent thrombosis

The previous studies have shown that not only the *de novo* acute thrombosis show a circadian rhythm but also the stent thrombosis (ST) (46, 47). Tamura et al. (47) demonstrated that sub-acute ST occurred more frequently during the morning. Mahmoud et al. (46) stated that early ST followed a circadian rhythm and occurred more often in the early morning hours. This pattern was not significant in late and very late ST. They found no weekly pattern in ST onset and ST was more likely to occur in the summer months. In a study that was performed by us successfully primary coronary bare metal stenting was performed in 1960 patients admitted with the diagnosis of ST- elevation MI were retrospectively evaluated for diurnal variation of early ST (48). Stent thrombosis was defined as the occurrence of any of the following events: angiographic proof of stent occlusion, post-procedural MI after successful stent implantation not clearly attributable to another coronary lesion, or unexplained deaths $\leq$30 days after the procedure. Early ST was defined as thrombosis that occurred in the first 30 days following the primary coronary stenting. Early ST was noted in 89 (4.5%) patients. We excluded three patients with an unknown date and time onset of symptoms. Therefore, the final 86 patients with early ST were investigated. We found that early ST was more likely to take place at night (00.00-6.00 A.M.) in patients who underwent primary coronary intervention due to ST-elevation MI. Occurrences throughout the week were equally distributed, but early ST was more likely to occur in the winter months (from December of the previous year to last day of March of the following year). The probable reasons why the early ST elevation happens during the late hours of night and winter are as previously claimed triggers of the thrombosis that are more active during these hours and season.

Clinical and research implications

The well-documented time dependence of the occurrence of these events indicates a general need for the development of specific treatment strategies aimed at reducing the morning, Monday and winter peak in acute vascular disease onset. For prevention and treatment of the cardiovascular diseases, the restoration of the normal rhythm should be one aim. For example the patient that are at risk for the acute cardiovascular events like the hypertensive ones, to get a nocturnal fall of the hypertension may be one point. In addition, another aim may be to provide the drug effectiveness at the time of the increased cardiovascular events. This can presumably to be provided either by administering medication with delayed action before going to bed or by

administering medication with immediate action before arising, or by a combination of both. For example, In the Beta Blocker Heart Attack Trial (BHAT), they suggests that beta blockade is protective during the morning hours after MI when a surge of sympathetic activity may increase the risk of sudden cardiac death (49). Moreover, another options may be using long-active, slow-releasing cardiovascular drugs. For example, Smith et al. (50) reported that Verapamil Chronotherapeutic Oral Drug Absorption System (CODAS-verapamil) that was designed for bedtime dosing and has controlled onset and extended-release properties.. The CODAS-verapamil was found to provide enhanced blood pressure reduction during the morning when compared with other intervals of the 24-hour dosing period. Making an aggressive treatment at the period of the increased frequency of the event may be thought. Not just the medications but also the lifestyle modifications are of importance for decrement of the frequency of the acute cardiovascular events. For prevention of the acute vascular events, especially the patients at high risk for cardiovascular events may work in a less mental stress environment or they should be more aware of the triggering factors like cold, infections. For a more vise evaluation of the effects of the both medications and life style changes on the cardiovascular events frequency large and prospective studies are needed.

Conclusions

It is supported with multiple studies that the acute vascular thrombotic events show a diurnal variation, with the increased frequency during late-night and early-morning hours, on Monday and in winter season. Determination of the diurnal variation of acute vascular thrombotic events might help us for protection of patients during vulnerable periods.

Conflict of interest: None declared

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - T.I. ; Design - T.I., E.A.; Supervision - E.A.; Resource - T.I., E.A.; Materials - E.A.; Data collection&/or Processing - E.A., H.U.; Analysis &/or interpretation - T.I, H.U; Literature search - T.I., H.U.; Writing - T.I.; Critical review-H.U.

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