

Review

Circadian Rhythms and Acute Coronary Syndrome in the Elderly

Clemencia de Rueda^{1,†}, Pablo Díez-Villanueva^{1,*,†}, Clara Bonanad², Fernando Alfonso¹

¹Cardiology Department, Hospital Universitario de La Princesa, 28006 Madrid, Spain

²Cardiology Department, Hospital Clínico Universitario de Valencia, 46010 Valencia, Spain

*Correspondence: pablo_diez_villanueva@hotmail.com (Pablo Díez-Villanueva)

[†]These authors contributed equally.

Academic Editor: Katarzyna Anna Cieslik

Submitted: 11 December 2021 Revised: 15 February 2022 Accepted: 16 February 2022 Published: 5 March 2022

Abstract

Ischemic heart disease is the leading cause of death in Western countries. The incidence, prevalence and mortality rate of acute cardiac events increase with age. Circadian rhythms allow organisms to prepare for their daily fluctuations brought on by day-night cycles, thus playing an important role in the cardiovascular physiology. This can be sometimes a double-edged sword, since exaggerated responses may not be beneficial or may be even harmful in individuals susceptible to adverse acute cardiovascular events. Remarkably, occurrence of such events has been related to a circadian pattern with a peak in the morning hours. Of interest, elderly patients seem to have an increased risk of acute coronary events, especially in the morning, though a bimodal distribution has also been observed. Further studies are required to get more insights on age-related differential circadian patterns in acute coronary syndromes patients.

Keywords: circadian rhythm; acute coronary syndrome; elderly

1. Introduction

Ischemic heart disease (IHD) is the leading cause of death in Western countries. Age is one of the main risk factors for the development of coronary artery disease. Advances in medical knowledge during the past few decades have associated longer life expectancy, resulting in aging population in developed and developing countries. Subsequently, the overall incidence of acute coronary syndromes (ACS) is continually increasing especially within the elderly population [1]. Besides, both incidence and prevalence of acute myocardial infarction (AMI) increase with age, also entailing worse outcomes in terms of morbidity and mortality. As a matter of fact, more than 60% of AMI in the United States occur in population older than 65 years, and approximately one third in people older than 75 years [2].

Cardiovascular risk factors are known to predispose to the development of IHD, both in chronic and acute settings. These factors have long been studied regarding their influence on the epidemiology, pathophysiology, management and prognosis in these patients. Interestingly, some other issues have been proposed to be involved in the pathophysiology of acute events, like circadian variability [1]. Actually, acute events, like ACS, sudden cardiac death, silent ischemia, and stroke have been linked to a circadian pattern of occurrence with a peak in the morning hours [3].

Our aim was to review the evidence regarding the relationship between circadian rhythm and ACS in the elderly.

2. Pathophysiology of Circadian Rhythms

Circadian rhythms allow organisms to prepare for the daily fluctuations brought on by day-night cycles, aligning internal biological functions with environmental changes. They are closely regulated by internal circadian clocks. The “primary clock” is in the suprachiasmatic nucleus of the hypothalamus (SCN), comprising around 20,000 neurons. This central clock is connected with the peripherals, which can be found in almost every tissue through neurohumoral signals [4]. This all starts at the genetic level with a rhythmic expression of clock-controlled genes. Interestingly, it is thought that around 10% of genes are regulated by the circadian clock [5]. The SCN is critically important regarding coordination of molecular rhythms in all organs and cells of the body. In all nucleated cells, four families of core clock genes (Clock, Bmal1, Period and Cryptochrome) form a transcription-translation feedback loop that cycles every approximately 24 hours [6]. Besides, all such internal clocks play an important role in the cardiovascular physiology, since most factors involved in the cardiovascular system show significant circadian variations [6].

The importance such pathways has been demonstrated in animals, since disruptions may cause significant CV disease. Thus, for instance, Bmal1 knockout in mice causes dilated cardiomyopathy, as well as heart failure and early mortality [6]. Moreover, Bmal1 gene removal in murine vascular smooth muscle cells entails that there are no longer circadian variation in pressure [5,6]. Also of interest, there is a study carried out with mice with the aim of demonstrating that the circadian clock within the cardiomyocyte influences diurnal variations in myocardial biology. Au-



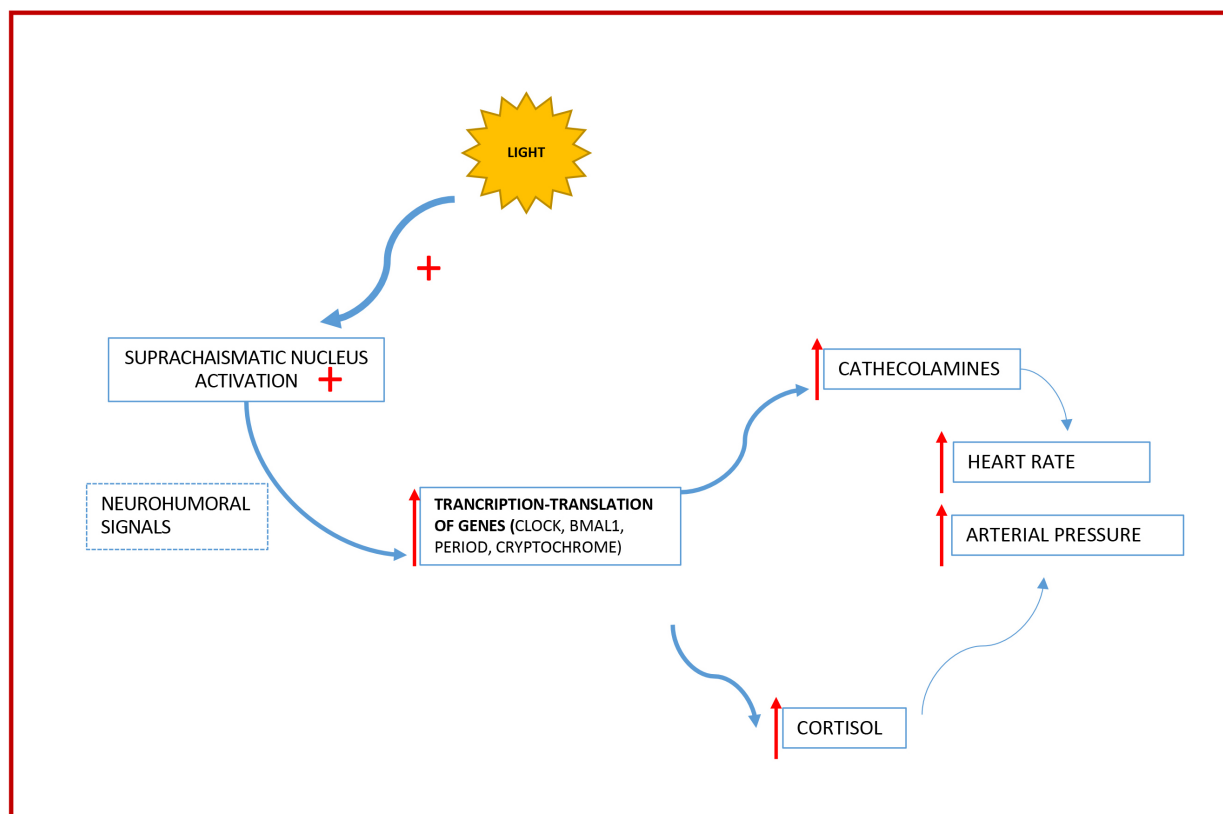


Fig. 1. The suprachiasmatic nucleus (SNC) is the central clock, thus being critically important in coordination of molecular rhythms in all organs and cells of the body. By neurohormonal signals, the SNC activates clock genes (Clock, Bmal1, Period and Cryptochrome), that forms a transcription-translation feedback loop that cycles every approximately 24 hours. That provokes a morning peak of catecholamines, cortisol triggering higher heart rate and arterial pressure [4,6,8,9].

thors generated a cardiomyocyte-specific circadian clock mutant (CCM) mouse to test this hypothesis through MHC-promoter-driven expression of the CLOCK. In such mice, attenuation of heart rate diurnal variations and bradycardia was observed. In addition, myocardial oxygen consumption and fatty acid oxidation rates increased, whereas cardiac efficiency decreased [7].

Accordingly, heart rate and blood pressure increase during the day and decrease at night, depending on sympathetic and parasympathetic modulation. Thus, sleep-to-wake transitions occurring in the morning have been associated with maximal shifts towards sympathetic autonomic activation as compared to those occurring during the rest of the day [8]. This is a result of higher levels of catecholamines epinephrine and norepinephrine in the morning. Similarly, cortisol has a morning peak [9,10] (Fig. 1, Ref. [4,6,8,9]).

In addition, fibrinolytic activity has also been shown to follow a diurnal rhythm. Fibrinolysis is initiated by tissue-type plasminogen activator (t-PA), an enzyme secreted by endothelia cells which, in presence of fibrin, converts the proenzyme plasminogen into its active form, plasmin. In turn, plasmin proteolytically degrades the fibrin that holds the thrombus together. The level of t-PA activity in

blood is regulated by a specific fast-acting plasminogen activator inhibitor (PAI-1). PAI-1 activity and t-PA antigen have been observed to be significantly higher in the morning. Thus, diurnal variations may reduce fibrinolytic activity in the morning in healthy individuals and in patients with coronary artery disease [11]. Furthermore, greater platelet reactivity and aggregation has been observed in the morning, with highly significant endogenous circadian rhythms (with peaks between 8:00 AM and 9:00 AM) in platelet surface activated glycoprotein (GP) IIb-IIIa, GPIb and P-selectin [12].

This self-regulation can sometimes be a double-edged sword. Morning exaggerated responses may not be beneficial or may be even harmful in individuals susceptible to adverse cardiovascular events, since increased vasoconstriction and blood pressure due to catecholamines can precipitate both plaque erosion and rupture. This decreased fibrinolytic activity and greater platelet aggregability may increase the risk of more aggressive thrombosis or clot formation [5].

Finally, there are age-related genomic elements of some coagulation proteins. According to this, advanced age has been directly associated with increased ischemic and bleeding risks. So, higher levels of fibrinogen, factors VIII

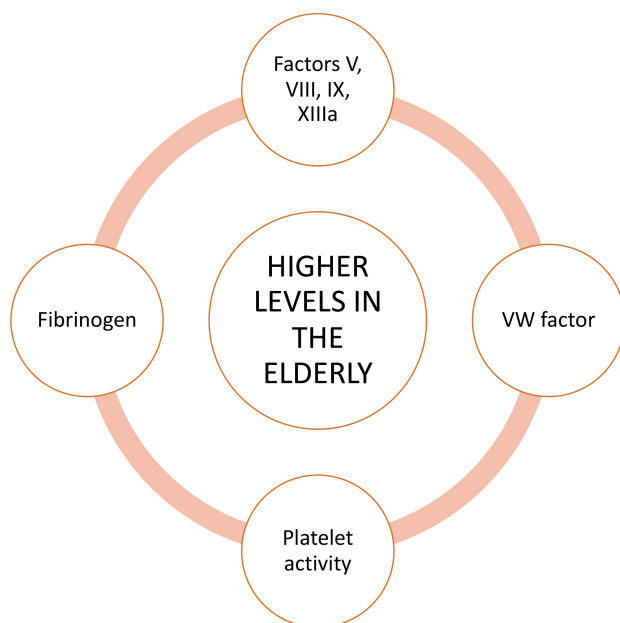


Fig. 2. Levels of coagulation factors V, VIII, IX, XIIIa, fibrinogen, von Willebrand factor and platelet activity in the elderly, higher than those of their younger counterparts. This implies an amplified thrombotic risk in the elderly [13].

and IX, and other coagulation proteins, without a proportional increase in anticoagulant factors have been observed [12]. Moreover, elderly patients may have an inflammatory state with increased levels of interleukin-6 (IL-6) and C-reactive protein, which may stimulate the formation of plug, erosion or plaque rupture [13]. Interestingly, one of the genes for aging-associated thrombosis is plasminogen activator inhibitor-1 (PAI-1), a principal inhibitor of fibrinolysis. PAI-1 could play a key role in the progression of cardiovascular aging by promoting thrombosis and vascular atherosclerosis [14].

Since many studies have verified the circadian variation of the cardiovascular system, the use of chronotherapy has been postulated with the aim of improving response to treatment together with avoiding side effects. Aspirin is the mainstay of treatment in both primary and secondary prevention of cardiovascular events. Given the predominance of cardiovascular events in the morning hours, it can be essential to ensure adequate platelet inhibition during such hours. Moreover, it has been observed that taking aspirin at night leads to greater platelet inhibition than taking it in the morning [15,16]. Regarding antihypertensive therapies, hypertensive dippers benefit from taking treatment early in the morning, while non-dippers may need to add an evening dose or even use a single evening dose [17]. Also, in patients with a history of ischemic heart disease, beta-blockers are more effective than calcium channel blockers in reducing ischemic events during the night and early morning [17].

3. Circadian Rhythm and Coronary Events in Clinical Practice

There are multiple studies that support the hypothesis of this circadian variability regarding acute coronary events. In this regard, the use of long-acting medications has been proposed for prevention of ACS since they also confer protection in the morning hours [3].

A meta-analysis performed in 1997 including data from 30 studies and more than 65,000 patients with AMI analyzed the circadian pattern of AMI onset and sudden cardiac death. Authors estimated the expected number of events that could occur between 6 AM. and noon using the average number of events in the remaining 18 hours of the day. In this study, the incidence rate of AMI onset was 40% higher in the morning period than during the rest of the day [3]. Moreover, an analysis performed in 2013 using a large American National Registry (NDCR) of patients with ST-segment elevation myocardial infarction (STEMI) (N = 45,218) thus classifying them by time of symptoms onset, showed that patients with symptoms onset between 6:00 AM and 2:00 PM were significantly older than those from other times of the day [18].

Furthermore, this circadian variability has been associated not only with the frequency of AMI but also with its size. A study carried out in a total of 108 patients with STEMI showed a significant association between the onset of symptoms and the size of the necrosis independent of the time of onset of the ischemic event. This finding was significantly higher when the onset of symptoms was between 12:00 AM and 12:00 PM compared to the rest of the day [19]. Two additional studies have supported this association between infarct size and circadian variability. Firstly, a retrospective analysis of 252 patients with AMI showed a larger infarct size (measured by ultrasound and CK levels) when it started between 6:00 AM and noon, compared to the period from noon to 6:00 PM and 6:00 PM to midnight [20]. Secondly, a retrospective single-center analysis including 811 STEMI patients admitted between 2003 and 2009 revealed a circadian variation regarding infarct size. Both CK and TnI curves described similar patterns over time, with maximum levels in patients presenting in the morning hours, from 6:00 AM to noon, and minimum values in those presenting from noon to 6:00 PM [21].

Besides that, a prospective cohort of older adults in Hong Kong with a median follow-up of 11 years showed an association between light at night and the risk of hospitalization and mortality from ischemic heart disease. This exhibited a monotonic exposure-response function with no variation across strata of the hypothetical risk factors [22].

4. Peculiarities in the Elderly Population

Age itself, together with traditional cardiovascular risk factors, such as hypertension, hyperlipidemia and diabetes, particularly prevalent in the elderly population, play a significant role in the development of cardiovascular events

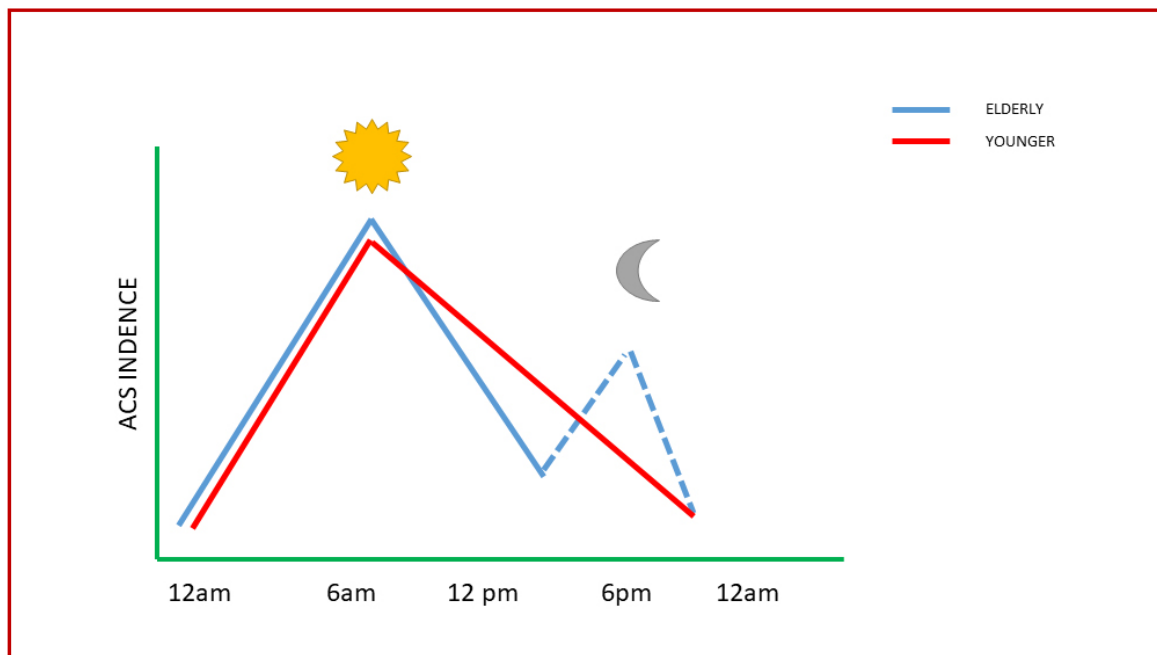


Fig. 3. Suggested bimodal pattern of acute coronary events related to circadian rhythms in the elderly in opposite with the unimodal pattern described in their younger counterparts.

[2]. In addition, hemostasis also seems to be affected by age. Relevant, an increase of coagulation factors V, VIII, IX, XIIIa, fibrinogen and von Willebrand factor and an increase of platelet activity have been observed with age. Fibrinogen is the immediate precursor of fibrin and it is converted by thrombin with the release of fibrinopeptides [13]. The rise in fibrinogen has been documented over the age range of 18 to 85 years in response to IL-6. Such increased levels of IL-6 strongly correlate with aging, possibly induced by higher catecholamines and lower sex steroid levels in the elderly. Therefore, this prothrombotic situation implies an amplified thrombotic risk in the elderly [23] (Fig. 2, Ref. [13]). On the other hand, comorbidities and geriatric conditions are common in real-life elderly patients [24], also contributing to worse prognosis [25–27], so that a multidisciplinary approach is of great importance in this scenario. However, whether ageing itself affects clocks and thereby constitutes a driver of cardiovascular disease or it is a risk factor for with affected clocks as a side-effect still needs to be elucidated.

Observational studies provide most of the available information regarding circadian rhythm and acute cardiovascular events in the elderly. Primary, an accentuation of this morning peak has been observed, associated with high plasma levels of catecholamines. Remarkably, a second evening peak has also been described. This is in contradistinction to the findings in younger patients. Indeed, there are several studies in which this bimodal presentation pattern of acute cardiac events has been observed. First, an observational study including 4796 patients found this peak in the onset of morning symptoms but there was also

a second lower peak (25%) in the afternoon, between 6:00 PM and 12:00 AM. Two peaks were then observed in patients older than 70 years of age ($n = 1422$) as opposed to those younger than 70 years in whom there was one single peak, only in the late morning, with no evidence of a secondary peak [28]. Morning and evening peaks have also been observed in two other studies, one conducted between 1973 and 1987 and including more than 10,000 patients with AMI in Sweden [29] and other conducted in nearly 1800 elderly patients undergoing surgical revascularization [30] (Fig. 3). On the other hand, in another study including nearly 55,000 patients with diagnosis of AMI and discharges from a Coronary Unit between 1994 and 2003, patients were stratified by age (younger than 65 years, 65–74 years, 75–84 years and older than 85 years). Authors observed that clinical presentation of AMI followed a circadian rhythm with a morning predominance between 6:00 AM and 12:00 PM in the morning in all age subgroups ($p < 0.001$). Curiously, however, the lowest frequency was observed between 12:00 AM and 6:00 AM in the morning, except in patients over 85 years of age, in whom the lowest incidence was between 6:00 in the afternoon and midnight (12:00 AM) [31]. This accentuation of the morning peak in the oldest patients may have been due to an increase in plasma concentrations of both epinephrine and norepinephrine, together with a greater reactivity of their receptors, something previously observed in studies in which norepinephrine excretion was found to be related to age and body weight [32]. Finally, this bimodal distribution was not observed in a Korean registry including nearly 20,000 patients (10% >70 years old) in which a morning dominance

Table 1. Main clinical studies about circadian rhythm and acute coronary syndrome.

Authors	Analysis	N	Peak of ACS
Cohen MC <i>et al.</i> [3]	Meta-analysis (30 studies)	66635	6:00 AM–12:00 PM in all ages
Mogabgan O <i>et al.</i> [18]	Restrospective analysis	45218	6:00 AM–2:00 PM in all ages
Arroyo úcara <i>et al.</i> [19]	Restrospective analysis	108	Larger infarct size between 12:00 AM–12:00 PM
Hatem A <i>et al.</i> [20]	Restrospective analysis	252	Larger infarct size between 6:00 AM–12:00 PM
Suárez-Barrientos A <i>et al.</i> [21]	Restrospective analysis	811	Larger infarct size between 6:00 AM–12:00 PM
Hjalmarson A <i>et al.</i> [28]	Restrospective analysis	4796	Two peaks in >70 years: 6:00 AM–12:00 PM 6:00 PM–12:00 AM
Hansen O <i>et al.</i> [29]	Restrospective analysis	10791	Two peaks in >70 years: 6:00 AM–12:00 PM 6:00 PM–12:00 AM
Mitrovic P <i>et al.</i> [30]	Restrospective analysis	1784 (10% >70 years old)	6:00 AM–12:00 PM in all ages 6:00 AM–12:00 PM in all ages
López-Messa JB <i>et al.</i> [31]	Restrospective analysis	54249	<85 years old: lowest peak 12:00 AM–6:00 AM >85 years old: lowest peak 6:00 PM–12:00 PM
Kim Oh H <i>et al.</i> [33]	Restrospective analysis	19915	>75 years: 6:00 AM–12:00PM

was observed in all patients irrespective of age [33]. Table 1 (Ref. [3,18–21,28–31,33]) summarizes most important clinical studies in this scenario.

5. Conclusions

In this review, addressing circadian variations in the appearance of ACS in the elderly population, a striking morning predominance is described as also found in younger patients. Interestingly, data postulating the possibility of a unique bimodal distribution pattern in older patients, are discussed. More studies are required to get further insights on age-related differential circadian patterns in ACS patients.

Author contributions

PD-V and CR—conception, design, and acquisition of data. All authors (CR, PD-V, CB, FA)—analysis and interpretation of data. All authors have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

- [1] López Messa JB, Garmendia Leiza JR, Aguilar García MD, Andrés de Llano JM, Alberola López C, Ardura Fernández J, *et al.* Cardiovascular risk factors in the circadian rhythm of acute myocardial infarction. *Revista Española De Cardiología*. 2004; 57: 850–858.
- [2] Rich MW. Epidemiology, clinical features, and prognosis of acute myocardial infarction in the elderly. *The American Journal of Geriatric Cardiology*. 2006; 15: 7–11.
- [3] Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-Analysis of the Morning Excess of Acute Myocardial Infarction and Sudden Cardiac Death. *The American Journal of Cardiology*. 1997; 79: 1512–1516.
- [4] Crnko S, Du Pré BC, Sluijter JPG, Van Laake LW. Circadian rhythms and the molecular clock in cardiovascular biology and disease. *Nature Reviews Cardiology*. 2019; 16: 437–447.
- [5] Khaper N, Bailey CDC, Ghugre NR, Reitz C, Awosanmi Z, Waines R, *et al.* Implications of disturbances in circadian rhythms for cardiovascular health: a new frontier in free radical biology. *Free Radical Biology & Medicine*. 2018; 119: 85–92.
- [6] Thosar SS, Butler MP, Shea SA. Role of the circadian system in cardiovascular disease. *The Journal of Clinical Investigation*. 2018; 128: 2157–2167.
- [7] Bray MS, Shaw CA, Moore MWS, Garcia RAP, Zanquetta MM, Durgan DJ, *et al.* Disruption of the circadian clock within the cardiomyocyte influences myocardial contractile function, metabolism, and gene expression. *American Journal of Physiology-Heart and Circulatory Physiology*. 2008; 294: H1036–H1047.
- [8] Boudreau P, Yeh WH, Dumont GA, Boivin DB. A circadian rhythm in heart rate variability contributes to the increased cardiac sympathovagal response to awakening in the morning. *Chronobiology International*. 2012; 29: 757–768.
- [9] Turton MB, Deegan T. Circadian variations of plasma catecholamine, cortisol and immunoreactive insulin concentrations in supine subjects. *Clinica Chimica Acta*. 1974; 55: 389–397.
- [10] Giles TD. Circadian rhythm of blood pressure and the relation to cardiovascular events. *Journal of Hypertension*. 2006; 24: S11–S16.

- [11] Angleton P, Chandler WL, Schmer G. Diurnal variation of tissue-type plasminogen activator and its rapid inhibitor (PAI-1). *Circulation*. 1989; 79: 101–106.
- [12] Scheer FAJL, Michelson AD, Frelinger AL, Evoniuk H, Kelly EE, McCarthy M, *et al*. The human endogenous circadian system causes greatest platelet activation during the biological morning independent of behaviors. *PLoS ONE*. 2011; 6: e24549.
- [13] Wilkerson WR, Sane DC. Aging and thrombosis. *Seminars in Thrombosis and Hemostasis*. 2002; 28: 555–568.
- [14] Yamamoto K, Takeshita K, Kojima T, Takamatsu J, Saito H. Aging and plasminogen activator inhibitor-1 (PAI-1) regulation: implication in the pathogenesis of thrombotic disorders in the elderly. *Cardiovascular Research*. 2005; 66: 276–285.
- [15] Buurma M, van Diemen JJK, Thijs A, Numans ME, Bonten TN. Circadian Rhythm of Cardiovascular Disease: the Potential of Chronotherapy with Aspirin. *Frontiers in Cardiovascular Medicine*. 2019; 6: 84.
- [16] Bonten TN, Saris A, van Oostrom MJ, Snoep JD, Rosendaal FR, Zwaginga J, *et al*. Effect of aspirin intake at bedtime versus on awakening on circadian rhythm of platelet reactivity. A randomised cross-over trial. *Thrombosis and Haemostasis*. 2014; 112: 1209–1218.
- [17] Lemmer B. The importance of circadian rhythms on drug response in hypertension and coronary heart disease—from mice and man. *Pharmacology & Therapeutics*. 2006; 111: 629–651.
- [18] Mogabgab O, Wiviott SD, Antman EM, Foody JM, Wang TY, Sabatine MS, *et al*. Relation between time of symptom onset of ST-segment elevation myocardial infarction and patient baseline characteristics: from the National Cardiovascular Data Registry. *Clinical Cardiology*. 2013; 36: 222–227.
- [19] Arroyo Úcar E, Dominguez-Rodriguez A, Abreu-Gonzalez P. Influencia de la variabilidad diurna en el tamaño del infarto agudo de miocardio. *Medicina Intensiva*. 2012; 36: 11–14.
- [20] Ari H, Sonmez O, Koc F, Alihanoglu Y, Ozdemir K, Vatankulu MA. Circadian Rhythm of Infarct Size and Left Ventricular Function Evaluated with Tissue Doppler Echocardiography in ST Elevation Myocardial Infarction. *Heart, Lung & Circulation*. 2016; 25: 250–256.
- [21] Suárez-Barrientos A, López-Romero P, Vivas D, Castro-Ferreira F, Núñez-Gil I, Franco E, *et al*. Circadian variations of infarct size in acute myocardial infarction. *Heart*. 2011; 97: 970–976.
- [22] Sun S, Cao W, Ge Y, Ran J, Sun F, Zeng Q, *et al*. Outdoor light at night and risk of coronary heart disease among older adults: a prospective cohort study. *European Heart Journal*. 2021; 42: 822–830.
- [23] Jiménez-Méndez C, Díez-Villanueva P, Alfonso F. Non-ST segment elevation myocardial infarction in the elderly. *Reviews in Cardiovascular Medicine*. 2021; 22: 779–786.
- [24] Sanchis J, García Acuña JM, Raposeiras S, Barrabés JA, Cordero A, Martínez-Sellés M, *et al*. Comorbidity burden and revascularization benefit in elderly patients with acute coronary syndrome. *Revista Española De Cardiología*. 2021; 74: 765–772.
- [25] Rodríguez-Queraltó O, Formiga F, López-Palop R, Marín F, Vidán MT, Martínez-Sellés M, *et al*. FRAIL Scale also Predicts Long-Term Outcomes in Older Patients with Acute Coronary Syndromes. *Journal of the American Medical Directors Association*. 2020; 21: 683–687.
- [26] Díez-Villanueva P, García-Acuña JM, Raposeiras-Roubin S, Barrabés JA, Cordero A, Martínez-Sellés M, *et al*. Prognosis Impact of Diabetes in Elderly Women and Men with Non-ST Elevation Acute Coronary Syndrome. *Journal of Clinical Medicine*. 2021; 10: 4403.
- [27] García-Blas S, Cordero A, Díez-Villanueva P, Martínez-Avial M, Ayesta A, Ariza-Solé A, *et al*. Acute Coronary Syndrome in the Older Patient. *Journal of Clinical Medicine*. 2021; 10: 4132.
- [28] Hjalmarson A, Gilpin EA, Nicod P, Ditttrich H, Henning H, Engler R, *et al*. Differing circadian patterns of symptom onset in subgroups of patients with acute myocardial infarction. *Circulation*. 1989; 80: 267–275.
- [29] Hansen O, Johansson BW, Gullberg B. Circadian distribution of onset of acute myocardial infarction in subgroups from analysis of 10,791 patients treated in a single center. *The American Journal of Cardiology*. 1992; 69: 1003–1008.
- [30] Mitrovic P, Stefanovic B, Vasiljevic Z, Radovanovic M, Radovanovic N, Krljanac G, *et al*. The timing of infarction pain in patients with acute myocardial infarction after previous revascularization. *The Scientific World Journal*. 2008; 8: 598–603.
- [31] López-Messa JB, Garmendia-Leiza JR, Aguilar-García MD, Andrés de Llano JM, Ardura-Fernández J, Alberola-López C, *et al*. La edad como factor modificador del ritmo circadiano del infarto agudo de miocardio. *Medicina Intensiva*. 2005; 29: 455–461.
- [32] Jenner DA, Harrison GA, Prior IA, Leonetti DL, Fujimoto WY. 24-h catecholamine excretion: relationships with age and weight. *Clinica Chimica Acta*. 1987; 164: 17–25.
- [33] Kim HO, Kim JM, Woo JS, Park CB, Cho JM, Lee SU, *et al*. Circadian Distribution of Acute Myocardial Infarction in Different Age Groups. *The American Journal of Cardiology*. 2018; 121: 1279–1284.