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Original Article

Circadian variation of cardiogenic pulmonary oedema

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ABSTRACT

Introduction: Circadian variation of in-hospital acute cardiogenic pulmonary oedema (CPE) with the highest occurrence in the early morning has been reported repeatedly. However, no study evaluating circadian variation of CPE in the field has been published. Therefore, we decided to evaluate the circadian variation of CPE in the Central Bohemian Region of the Czech Republic in the patients treated by regional emergency medical service (EMS) and analyse its association with baseline blood pressure in the field.
Methods: We extracted all dispatches to CPE cases from EMS database for the period from 1.11.2008 to 30.6.2014 and analysed for circadian variation. We identified the patients presenting with CPE coupled with arterial hypertension (systolic blood pressure >140 mm Hg) and hypotension (systolic blood pressure <90 mm Hg) and compared the subgroups (both subgroups include 2744 subjects).
Results: In 4747 episodes of CPE, maximal occurrence was detected in the ninth hour in the morning, representing 7.7% of all CPE episodes ($p < 0.05$). While CPE with hypertension (2463 subjects) reached maximal occurrence also in the ninth hour (7.4% of all cases, $p < 0.05$), CPE with hypotension (281 patients) was most frequent in the fourteenth hour (8.6% of all cases, $p < 0.05$).
Conclusion: The highest occurrence of CPE was observed in the ninth hour in the morning in our study. Moreover, differences in circadian variation between CPE with hypertension and hypotension were identified. Knowledge of these patterns may have an impact on the logistic of prehospital emergency care and on preventive measures in the patients who have previously undergone CPE.

1. Introduction

Cardiogenic pulmonary oedema (CPE) is a common indication for dispatch of emergency medical services. Pattern of circadian variation of CPE episodes has been published by several epidemiological studies [1–3]. Most of them described the peak incidence in the morning, other identified it during night hours [2–9]. However, the studies analysed especially the population of CPE patients in hospitals or emergency departments, which can be burdened by error of selection. There has not been presented any study that would address circadian variation of CPE and its clinical subgroups in prehospital emergency care. Recognition of regular variations of occurrence of cardiovascular emergencies in time may be of major importance for optimising the operation of emergency medical services and also for implementation of chronotherapeutic approach to the management of the diseases. Therefore, we decided to evaluate the circadian variation of CPE in the Central Bohemian Region of the Czech Republic in the patients treated by regional emergency medical service and analyse its association with baseline blood pressure in the field.

2. Materials and methods

Emergency medical service of the Central Bohemian Region is the exclusive provider of primary prehospital emergency care in the Central Bohemian Region, Czech Republic. The region includes both the rural and urban population, in total of 1 315 299 inhabitants on a total area of 11 015 km^2. A computer search of patients with dyspnoea between 1.10.2008 and 30.6.2014 was conducted. Only those with CPE were entered in the study. Each patient was managed by a physician in the field. Criteria for considering the patient having CPE were leading complaint

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of shortness of breath, presence of bilateral pulmonary rales on the prehospital physical examination, and the absence of another explanation of the clinical setting. The criteria were evaluated by two investigators independently. The results of their analysis were compared with the diagnosis established by the physician in the field. In case of full accordance to the diagnosis of CPE, the patients were selected for the analysis. In the case that both investigators and the physician in the field excluded pulmonary oedema, the patient was not included. If there was a partial mismatch, the case was carefully re-evaluated including personal consultation with the EMS physician and in-hospital documentation.

We analysed the occurrence of episodes of CPE in 24 hours during the defined period. The 1st hour has been the period from 00:00:01 to 01:00:00, the 24t^h hour has been the period from 23:00:01 to 24:00:00. The time of the occurrence was defined as time of received call to dispatch centre. While for circaseptan variation analysis, the same collection period as for circadian was used, for circannual variation, only patients from 01.01.2009 to 31.12.2013 were included.

According to the first measured systolic blood pressure (SBP) in the field, we assigned the patients into two groups for further analysis: CPE with hypertension (SBP > 140 mm Hg, CPE_{hyper}) and CPE with hypotension (SBP < 90 mm Hg, CPE_{hypo}) and compared occurrence of CPE events in the groups within 24 hours. While CPE cases with normotension (SBP ≥ 90 and ≤ 140 mm Hg) represent a grey zone for emergent distinguishing the causes of CPE in the field, this subgroup was not undertaken to further analysis. Initial blood pressure measurement was taken once, using oscillometric automatic sphygmomanometer validated according to standardised protocol and checked periodically through calibration. Repeated initial measurement was performed only by individual clinical needs in some cases.

2.1. Statistical analysis

For analytic purposes, mean values ± SD or percentages were calculated as necessary. Differences between groups were compared using the χ^2 test, and statistical significance was calculated by the Fischer exact test for alternative variables. Statistical significance for continuous variables was determined by the paired Student t-test. Comparison of subgroups according to systolic blood pressure was performed by ANOVA analysis. Data were analysed using Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and JMP 3.2 statistical software (SAS Institute, Cary, NC, USA). A p value of <0.05 was considered statistically significant.

Table 1
Baseline characteristics of CPE patients.

VARIABLE	All CPE episodes	CPE_{hyper} episodes	CPE_{hypo} episodes	p
Number of the cases (n)	4747	2463	281	
Age (years, mean ± SD)	75.0 ± 10.5	75.2 ± 10.3	73.4 ± 11.1	0.006
Men/women (%)	49/51	49/51	47/53	>0.050
Diabetes mellitus (n/%)	1424/30.0	726/29.5	83/29.5	>0.050
COPD/asthma bronchiale (n/%)	513/10.8	263/10.7	31/11.0	>0.050
Number of STEMI patients (n/%)	222/4.7	74/3.0	51/18.1	<0.001
Initial heart rhythm				
Sinus rhythm (n/%)	2668/56.2	1379/56.0	158/56.2	>0.050
Atrial fibrillation (n/%)	1239/26.1	643/26.1	74/26.3	>0.050
Other rhythm/not known (n/%)	840/17.7	441/17.9	49/17.5	>0.050
Systolic arterial blood pressure (mm Hg, mean ± SD)	148 ± 39	178 ± 25	81 ± 9	<0.001
Diastolic arterial blood pressure (mm Hg, mean ± SD)	84 ± 22	97 ± 16	46 ± 19	<0.001
Mean arterial blood pressure (mm Hg, mean ± SD)	105 ± 26	124 ± 17	57 ± 12	<0.001
Heart rate (beats/min., mean ± SD)	99 ± 27	101 ± 24	97 ± 31	0.010
SpO_2 (%, mean ± SD)	85 ± 13	85 ± 11	80 ± 17	<0.001
Breath rate (breaths/min., mean ± SD)	24 ± 6	24 ± 6	23 ± 7	0.009

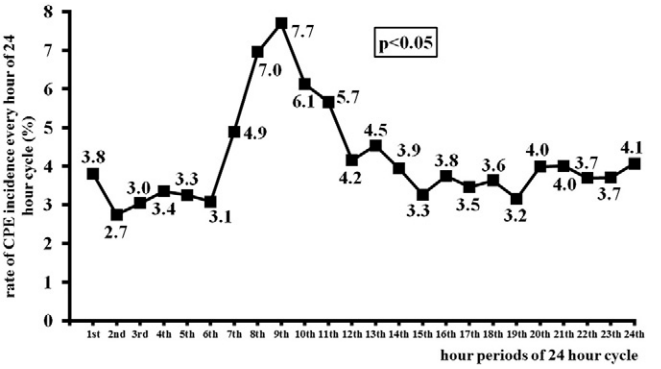

Fig. 1. Circadian variation of CPE episodes in all patients. CPE, cardiogenic pulmonary oedema.

3. Results

For the period from 1.10.2008 to 30.6.2014, a total of 15 000 EMS dispatches for dyspnoea was identified, 4747 were classified as CPE. This group was the subject of further analysis. Table 1 provides baseline clinical characteristics of the patients. As much as 51.9% CPE episodes were classified as CPE_{hyper}, 5.9% as CPE_{hypo}, and 40.3 % were accompanied by normotension. In 89 patients, values of blood pressure were not available.

Fig. 1 shows circadian variation of all episodes of CPE during defined period. There is increase of occurrence in the period from the 8th to the 11th hour with a peak in the 9th hour ($p < 0.05$). Analysis of circadian variation in each year separately reflected the same pattern with the maximal incidence in the 9th hour.

Fig. 2 demonstrates circadian variation of CPE episodes in the CPE_{hyper} and CPE_{hypo} groups. While the former followed the pattern with the peak occurrence in the 9th hour, CPE_{hypo} group exhibited an increase in incidence during the period from the 8th to 14th hour with the peak in the 14th hour.

Breath rate, heart rate, presence of atrial fibrillation, diabetes mellitus, chronic pulmonary obstructive disease, and peripheral oxygen saturation had no significant impact on circadian variation of CPE. In the subgroup of the patients presenting with CPE_{hypo} due to ST segment elevation myocardial infarction (STEMI), the peak incidence was observed in the 11th hour (23.5 %, $p = 0.010$).

Circaseptan variation of CPE episodes shows Fig. 3. In unselected group of CPE patients and in the CPE_{hyper} group the peak incidence was on Monday, while minimal occurrence on Thursday ($p < 0.05$).

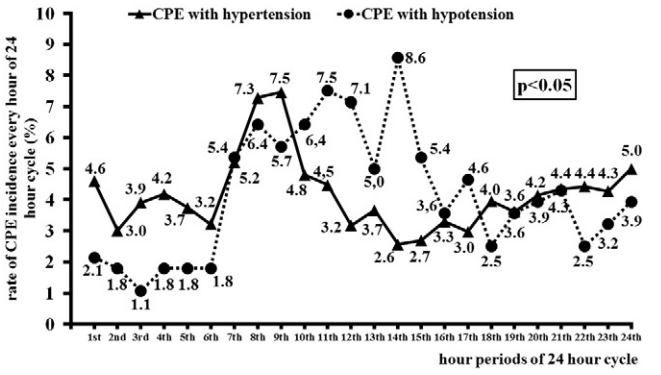

Fig. 2. Circadian variation of CPE episodes in patients presenting with hypertension and hypotension. CPE, cardiogenic pulmonary oedema

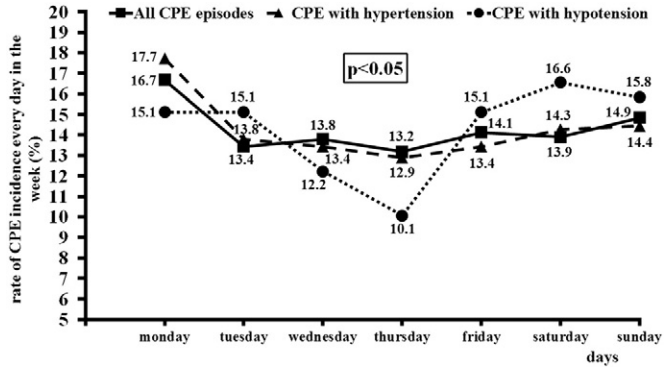

Fig. 3. Circaseptan variation of CPE episodes in all patients, in the group of CPE patients with hypertension and with hypotension. CPE, cardiogenic pulmonary oedema.

CPE_{hypo} patients presented with maximal occurrence on Saturday and minimal on Thursday ($p = 0.081$). Circannual occurrence variation of all CPE episodes and CPE_{hyper} group episodes culminated in May and declined in December ($p < 0.05$) (Fig. 4). Biphasic pattern was observed in the group CPE_{hypo}, with significant amplitude ($p = 0.009$).

4. Discussion

The main finding of the present study is that there is a significant circadian variation of prehospital occurrence of cardiogenic pulmonary oedema treated by emergency medical service with the peak in the 9th hour in the morning. Clinical setting of CPE_{hyper} was associated with different circadian pattern than CPE_{hypo}.

Circadian variation of physiological functions in time is a natural characteristic of living organisms. Therefore, it is not a surprise that the incidence of acute cardiovascular events such as stroke, acute aortic syndrome, acute coronary syndromes, sudden cardiac death, pulmonary embolism, and cardiogenic pulmonary oedema has been shown to be closely related to 24-hour variation [2,10–13]. Buff et al. examined 154 consecutive episodes of CPE treated in community hospital to assess potential cyclic pattern of its onset. They found a rhythmicity with maximal occurrence between 06:00 and 11:59 a.m. [2]. Kitzis et al. analysed 460 in-hospital patients admitted for CPE not associated with acute myocardial infarction. They found similar pattern of its onset as Buff et al., accompanied by a second peak incidence late in the evening. Moreover, they described significantly more admissions for CPE in the period from December to May [8]. Manfredini et al. collected 1321 CPE episodes in emergency department of teaching hospital. Unlike previous authors, they observed rhythmicity with peak incidence at night. This night-time preference was independent of all

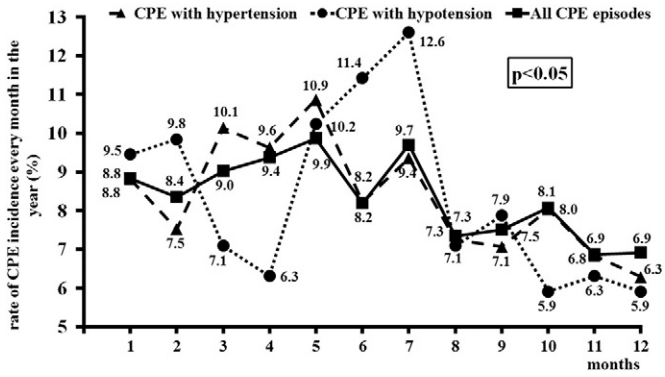

Fig. 4. Circannual variation of CPE episodes in all patients, in the group of CPE patients with hypertension and with hypotension. CPE, cardiogenic pulmonary oedema.

demographic features or clinical causes [9]. However, the studies included in-hospital patients or patients in emergency department. Potentially, pattern of circadian variation of CPE occurrence may differ in these populations from out-of-hospital patients, while it can be influenced by different and selected spectrum of in-hospital and emergency department patients, different daily program of in-hospital patients including diet, intensity of physical activity, different timing of drug use and by in-hospital management itself, by way of organising of emergency department and also by catchment area of emergency department. In out-of-hospital patients, there may be variable delay from the onset of symptoms to EMS arrival, but it covers unselected population in predefined geographical region and in health care system of the Czech Republic, this ensures that almost all out-of-hospital patients with CPE were included, since only few patients are looking for a different kind of assistance. However, our results confirm the previous in-hospital observations of peak occurrence of CPE episodes in the morning [2,8]. The new finding is that patients with CPE associated with hypertension exhibited a different circadian pattern from CPE patients with hypotension. These two groups represent two pathophysiologically and clinically different manifestations of acute heart failure, often requiring different management. Patients who develop CPE_{hyper} usually present with preserved left ventricular systolic function. Diastolic left ventricular dysfunction and hypertension are mainly involved in the development of the disease. The main therapeutic target is to decrease elevated blood pressure [14,15]. On the contrary, clinical setting of CPE_{hypo} is usually associated with severe left ventricular systolic dysfunction and/or with severe valvular disease. The patients are at risk of developing cardiogenic shock and require complex therapy including inotropic and ventilatory support, early coronary revascularization, and mechanical circulatory support, if indicated [16,17]. The CPE patients with normotension represent a grey zone of causes and therapeutic goals. Therefore, this group of the patients was not the subject of our subgroup analysis.

According to current knowledge, circadian variation of CPE occurrence is probably related to circadian pattern of blood pressure and cardiovascular functions in general [18–20]. In healthy individuals, blood pressure declines to lowest levels during night-time sleep, rises with morning awakening, and attains increased during the daytime. Nighttime blood pressure is lower by 10–20% than daytime. This profile is called dipping pattern. Moreover, there are two daytime peaks of blood pressure around 9 a.m. and 7 p.m. [20–22]. Major determinants of circadian blood pressure regulation are neuroendocrine mechanisms. It is influenced by central and peripheral regulatory circuits including nucleus supraopticus, a wide variety of hormones and neurotransmitters and oscillation of sympathetic and vagal tone [20,23]. In patients with hypertension, dipping pattern can be impaired and patients may be classified as extreme dippers (diurnal/nocturnal blood pressure ratio ≥20%), non-dippers (diurnal/nocturnal ratio <10%), and risers (ratio <0%, indicating nocturnal blood pressure above the diurnal mean) [20,22]. The last two profiles are associated with significantly increased risk of cardiovascular events [24]. Irrespective of these profiles, intensity of morning blood pressure increase (morning surge) may have also an impact on cardiovascular prognosis. It has been shown that excessive morning surge is associated with increased risk of ischemic stroke and acute myocardial infarction [10,11,25,26]. It is likely that this mechanism is crucial in development of CPE_{hyper} and therefore, why CPE_{hyper} episodes in our study followed blood pressure profile.

We can only speculate why CPE_{hypo} profile exhibit different circadian variation of occurrence than CPE_{hyper}. Clinical setting of CPE_{hypo} is a syndrome with various causes. When the cause of CPE is acute myocardial infarction, it may be assumed that the circadian variation will copy variation of acute myocardial infarction. It has been reliably demonstrated that the frequency of AMI onset during the 24 hours is highest during the initial hours of diurnal activity, between 6 a.m. and noon [10]. We can also assume that the CPE_{hypo} does not arise in a very early phase of acute myocardial infarction, but with some delay. This

may be a potential explanation for the finding in our study that maximal occurrence of CPE_{hypo} in the setting of acute myocardial infarction was the 11th hour of the day. The patients presenting with CPE_{hypo} without ongoing acute myocardial infarction are mostly patients with acute decompensation of congestive heart failure. One of the etiological factors of deterioration may be increased physical exertion, which occurs during daytime hours and which may cause that maximal incidence was observed between the 8th to the 14th hour in our study. There are also limited data, that in congestive heart failure patients, up to 78% of them are presented as non-dippers or risers [27,28]. During 4 years of follow-up of 118 congestive heart failure patients, Shin et al. showed that non-dipper and riser profile were independent predictors of death or hospitalization due to heart failure exacerbation (OR 1.65, 95% CI 1.08–2.50 and OR 2.72, 95% CI 2.29–3.13, respectively) [28]. Thus, pathological pattern of circadian variation of blood pressure may induce cyclic occurrence of CPE_{hypo} episodes, similarly to CPE_{hyper} events.

We believe that a setting of different clinical types of CPE in the context of their specific circadian variation may affect the management of the patients. Chronotherapy is the approach of administration-time-dependent therapy according to a schedule that corresponds to circadian or other rhythmic cycles in order to maximise effectiveness and minimise side effects of the therapy. It is used in depression, bipolar disorder, hypercholesterolemia, hypertension, and recently, in cancer [29]. It is based on the evidence-based idea that timing of the medication is the other useful dimension of therapy reflecting an observation that a medication given in some defined biological time may be therapeutic and safe, but less effective and/or less tolerated at another time, even when administered in the same dose. This property has been observed in many drugs as a molecule-specific effect or class-specific effect, for example, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, simvastatin, proton pump inhibitors, etc. [30]. Although there has not been published any clinical study evaluating specific chronotherapy in patients with different types of CPE, chronotherapy of cardiovascular diseases, especially of arterial hypertension and coronary artery disease has been evaluated in a growing number of prospective studies. However, there has not been found clear evidence of superiority of this approach in affecting prognosis of the patients. Therefore, it is not addressed in the recent guidelines and careful individual selection of candidates for antihypertensive chronotherapy is required [19,31,32]. Nevertheless, the patients in the risk of CPE, especially those with hypertension accompanied with left ventricular diastolic dysfunction, non-dipper/riser profile, excessive morning surge, and particularly the patients who have a history of CPE, may become the target population for chronotherapy, although knowing that further research is needed. Ambulatory blood pressure monitoring may identify the pattern of circadian blood pressure variation and therapy can be tailored to modify blood pressure profile to dipper type. This can be easily achieved by moving antihypertensive medications from morning to bedtime administration. The next potential target for chronotherapeutic approach may be the level of physical activity. Structured exercise training and regular physical activity are recommended for the patients with heart failure. It has been demonstrated that it improves exercise capacity, health-related quality of life, and may reduce mortality and hospitalization rate in patients with mild-to-moderate chronic heart failure, if indications and contraindications are respected [33]. On the other side, we can speculate that in the patients on the edge of indications and contraindications emphasis may be given to reduce excessive physical activity during the period of the highest probability of CPE occurrence. It should be avoided in unstable and decompensated patients.

Even if we identified significant circaseptan and circannual variation, it is not possible to conclude from our results whether it is biologically and clinically relevant finding or random epiphenomenon.

The major limitation of presented study is that it is a retrospective and not a prospective survey with all general limitations. Another limitation lies in the selection of the patients with CPE. It was based on the prehospital clinical assessment. However, careful retrospective stepwise reevaluation of each event was performed to exclude all cases in which the cause of shortness of breath was other than CPE or the cause was unclear, to maximise homogeneity of the selected patients. The third limitation is the mode of initial blood pressure measurement for distribution of the patients into the groups according to blood pressure. Following the guidelines, blood pressure measurement should be performed in the sitting position after 3–5 minutes of rest and at least two blood pressure measurements spaced 1–2 minutes apart should be taken [31]. This approach is not carried out routinely in the emergency clinical setting in the field with limited human and material resources, while it can be associated with unintentional delay in administering appropriate therapy. Blood pressure was measured only once during initial investigation of the patients in our study. In most patients, blood pressure measurements were repeated during the prehospital management, but only for monitoring the effectiveness of treatment. It might influence accurate reliability of the findings; nevertheless, we are convinced that one initial measurement performed by proper technique and interpreted within the context of the clinical setting of cardiovascular emergency is sufficient for the analysis presented in our study.

Finally, the patients who died of the CPE before contacting EMS were not included. However, the latter is the common limitation of epidemiological studies.

In conclusion, we identified significant circadian variation of the prehospital occurrence of cardiogenic pulmonary oedema treated by emergency medical service with the peak of occurrence in the 9th hour in the morning. While cases of CPE_{hyper} copied this pattern, episodes of CPE_{hypo} reflected different profile with prolonged rise of incidence in the daytime with the peak in the 14th hour. Identification of prehospital circadian variation pattern of the occurrence of CPE or other cardiovascular emergencies is of great importance by our opinion. Besides allowing a more detailed insight into the pathophysiology, chronotherapeutic approach may address the large population of the patients with arterial hypertension and congestive heart failure. Optimising of long-term therapy with regard to the period of highest risk of deterioration may reduce the risk of recurrence of acute presentation of the disease. Moreover, extensive chronobiological analysis of the whole panel of the most common types of emergencies in a particular region can help optimise the operation of emergency medical services in terms of improving preparedness and allocation of staff in the field and in the dispatch center. Further studies focusing on these issues in prospective manner are warranted.

Conflict of interest

None.

References

[1] Quyyumi AA. Circadian rhythms in cardiovascular disease. Am Heart J 1990;120:726–33.
[2] Buff DD, Calikyan R, Neches RB, Bavli SZ. Circadian patterns in the onset of cardiogenic acute pulmonary edema. Clin Cardiol 1997;20:261–4.
[3] Pasqualetti P, Casale R. Daily distribution of episodes of acute cardiogenic pulmonary edema. Cardiology 88:509–12.
[4] Cugini P, Di Palma L, Battisti P, Leone G, Materia E, Parenzi A, et al. Ultradian, circadian and infradian periodicity of some cardiovascular emergencies. Am J Cardiol 1990;66:240–3.
[5] Bilora F, Vettore G, Maifredini C, Rocco S, Pastorello M, Petrobelli F. Chronobiology of acute pulmonary edema in an emergency service. Cardiologia 1998;43:303–7.
[6] Fava S, Azzopardi J. Circadian variation in the onset of acute pulmonary edema and associated acute myocardial infarction in diabetic and nondiabetic patients. Am J Cardiol 1997;80:336–8.
[7] Allegra JR, Cochrane DG, Biglow R. Monthly, weekly, and daily patterns in the incidence of congestive heart failure. Acad Emerg Med 2001;8:682–5.
[8] Kitzis I, Zeltser D, Kassirer M, Itzcowich I, Weissman Y, Laniado S, et al. Circadian rhythm of acute pulmonary edema. Am J Cardiol 1999;83:448–50 A9.
[9] Manfredini R, Portaluppi F, Boari B, Salmi R, Fersini C, Gallerani M. Circadian variation in onset of acute cardiogenic pulmonary edema is independent of patients' features and underlying pathophysiological causes. Chronobiol Int 2000;17:705–15.

[10] Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman M. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol 1997;79:1512–6.
[11] Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. Stroke 1998;29:992–6.
[12] Hakim H, Samadikhah J, Alizadehasl A, Azarfarin R. Chronobiological rhythms in onset of massive pulmonary embolism in Iranian population. Middle East J Anesthesiol 2009;20:369–76.
[13] Vitale J, Manfredini R, Gallerani M, Mumoli N, Eagle KA, Ageno W, et al. Chronobiology of acute aortic rupture or dissection: a systematic review and a meta-analysis of the literature. Chronobiol Int 2015;32:385–94.
[14] Gandhi SK, Powers JC, Nomeir a M, Fowle K, DW Kitzman, KM Rankin, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001;344:17–22.
[15] Ford LE. Acute hypertensive pulmonary edema: a new paradigm. Can J Physiol Pharmacol 2010;88:9–13.
[16] Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. Eur Heart J 2015;36:1223–30.
[17] Sánchez Marteles M, Urrutia A. Acute heart failure: acute cardiogenic pulmonary edema and cardiogenic shock. Med Clin (Barc) 2014;142(Suppl):14–9.
[18] Fabbian F, Smolensky MH, Tiseo R, Pala M, Manfredini R, Portaluppi F. Dipper and non-dipper blood pressure 24-hour patterns: circadian rhythm-dependent physiologic and pathophysiologic mechanisms. Chronobiol Int 2013;30:17–30.
[19] Portaluppi F, Lemmer B. Chronobiology and chronotherapy of ischemic heart disease. Adv Drug Deliv Rev 2007;59:952–65.
[20] Hermida RC, Ayala DE, Portaluppi F. Circadian variation of blood pressure: the basis for the chronotherapy of hypertension. Adv Drug Deliv Rev 2007;59:904–22.
[21] O'Brien E, Atkins N, O'Malley K. Defining normal ambulatory blood pressure. Am J Hypertens 1993;6:201S–6S.
[22] Skulec R, Petr P, Matznerová Z, Kalová H, Ferebauerová M. 24-hour ambulatory blood pressure monitoring. Vnitřní Lékařství 2000;46:37–44.
[23] Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303–7.
[24] Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. J Hypertens 1997;15:357–64.
[25] Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, et al. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985; 313:1315–22.
[26] Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation 2003;107:1401–6.
[27] Mallion J-M, Neuder Y, Ormezzano O, Rochette GB, Salvat M, Baguet JP. Study of nycthemeral variations in blood pressure in patients with heart failure. Blood Press Monit 2008;13:163–5.
[28] Shin J, Kline S, Moore M, Gong Y, Bhanderi V, Schmalfuss CM, et al. Association of diurnal blood pressure pattern with risk of hospitalization or death in men with heart failure. J Card Fail 2007;13:656–62.
[29] Feillet C, van der Horst GTJ, Levi F, a. Rand D, F. Delaunay. Coupling between the circadian clock and cell cycle oscillators: implication for healthy cells and malignant growth. Front Neurol 2015;6:1–7.
[30] De Giorgi A, Mallozzi Menegatti A, Fabbian F, Portaluppi F, Manfredini R. Circadian rhythms and medical diseases: does it matter when drugs are taken? Eur J Intern Med 2013;24:698–706.
[31] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159–219.
[32] Stranges PM, Drew a. M, Rafferty P, JE Shuster, D. Brooks a. Treatment of hypertension with chronotherapy: is it time of drug administration? Ann Pharmacother 2014;49:323–34.
[33] Piepoli MF, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Heart Fail 2011;13:347–57.