HHS Public Access

Author manuscript

Chronobiol Int. Author manuscript; available in PMC 2024 April 19.

Published in final edited form as:

Chronobiol Int. 2023 January ; 40(1): 1–3. doi:10.1080/07420528.2022.2151862.

Cardiovascular research and the arrival of circadian medicine

Tami A. Martino,

Centre for Cardiovascular Investigations, Biomedical Sciences, University of Guelph, Guelph, Ontario, Canada

Brian P. Delisle

Department of Physiology, University of Kentucky, Lexington, Kentucky, USA

The journal Chronobiology International was launched in 1984 by co-Editors-in-chief Alain Reinberg and Michael Smolensky as a visionary step forward for the emerging science of chronobiology (Reinberg and Smolensky 1984). The first issue included many studies relevant to human health including cardiovascular disease, neurobiology, cancer, bone growth, metabolic pathways, as well as cosinor bioinformatics programs for the Apple II microcomputer, and several papers on other organisms. Over the decades, it has become the leading journal of biological and medical rhythm research. As of 2023, there are now 40 volumes of Chronobiology International, and the importance of applying circadian biology to clinical medicine has become increasingly apparent. The published papers encompass a wide range of clinical conditions, incorporate the latest state-of the-art technologies, challenge us to better understand human physiology and pathophysiology, and apply our circadian research as a basis for new treatments for disease.

Importantly, we now know that circadian rhythms are especially relevant to cardiovascular physiology. For example, circadian rhythms underlie our daily rhythmic variation in heart rate, blood pressure, and the day/night biases of our autonomic nervous system. Circadian rhythms also underlie the timing of the onset of adverse cardiovascular events such as myocardial infarction, ventricular tachyarrhythmias, sudden cardiac death, and dissection or rupture of aortic aneurysms (Martino and Sole 2009). Moreover, circadian rhythms are highly relevant to clinical cardiology therapies, such as chronotherapy for hypertension, (Mistry et al. 2017) circadian lighting in intensive care units (Alibhai et al. 2014), and can influence morbidity and mortality following surgical procedures such as percutaneous coronary intervention, or angioplasty, or aortic valve replacement. (Khaper et al. 2018). Recently the important role of biological sex and gender on chronobiology and chronotherapies (Glen Pyle and Martino 2018), and development of the novel field of rest for befitting cardiac repair have been discovered (Reitz et. al 2022).

The idea for this special collection of articles in Chronobiology International was developed following an NIH workshop on Understanding the Circadian Mechanisms of Sudden Cardiac Death in Bethesda MD in 2019 (Delisle et al. 2021b, 2021a). Building on this prestigious meeting, we reached out to Dr. Mike Smolensky (Editor-in-Chief 1984– 2021)

brian.delisle@uky.edu .

and later Dr. Roberto Refinetti (Editor-in-Chief from 2021). Our idea was to bring together scientists from around the world and compile a leading edge series reflecting current day cardiovascular and circadian research and its many and varied exciting new applications to clinical medicine.

“Cardiovascular Research and Arrival of Circadian Medicine” is the exciting special collection of papers that resulted from these eforts, and it contains original research, perspectives, meta-analysis, and review articles from many of the world’s experts in this field.

“Timing of food intake in mice unmasks a role for the cardiomyocyte circadian clock mechanism in limiting QT-interval prolongation” is an original research article by Schroder and colleagues that builds on previous studies showing that the cardiomyocyte circadian clock is an important modifier of cardiac excitability and ventricular repolarization (Schroder et al. 2022). In this study, the authors found that, while the cardiomyocyte circadian clock is not obligatory for 24-h rhythms in RR- or QT-interval in mice, it is important for limiting QT- interval prolongation at slow heart rates.

“Circadian regulation of cardiac muscle function and protein degradation” by Dr. Yoo is a review article that highlights the evidence that supports an important and underappreciated role for the circadian clock regulation of the function and integrity of sarcomeres (Yoo 2021). The review raises an intriguing possibility that targeting the circadian clock regulation of the cardiac muscle protein turnover may represent a therapeutic strategy to treat cardiovascular disease.

“Circadian Rhythms in Cardiac Metabolic Flexibility” by Young and Latimer distills the current state of research on what is known about the temporal partitioning of myocardial metabolic processes across the 24-h cycle (Young and Latimer 2021). The heart exhibits remarkable metabolic flexibility at the level of glucose, fatty acid and amino acid metabolism, and the temporal partitioning of myocardial metabolism is regulated by the cellular cardiomyocyte circadian clock mechanism. The regulation of cardiac metabolism by the circadian clock allows the heart to align metabolism with predictable fluctuations in the environment and behavior. Data now suggest that disruptions in normal predictable environment or food consumption can impact these metabolic processes and precipitate the development of cardiometabolic disease.

“Targeting circadian PER2 as therapy for myocardial ischemia and reperfusion injury” by Oyama and colleagues is a review article that begins to bridge the gap between environmental and circadian clock molecular signaling in a way that identifies potential strategies to improve outcomes in cardiovascular disease like myocardial ischemia (Oyama et al. 2021). Advances in this research area are now stimulating clinician scientists to investigate how manipulation of cellular circadian clock factors may represent an important mechanism to promote cardioprotection.

“The emerging significance of circadian rhythmicity in microvascular resistance” by Kroetsch and colleagues is a perspective article focusing on circadian rhythms in arterial resistance, a key driver for tissue perfusion, total peripheral resistance, and systemic arterial

blood pressure (Kroetsch et al. 2022). They highlight intriguing research evidence that suggests rhythms in myogenic reactivity are locally generated at the level of smooth muscle cells in a vascular bed-specific manner. This article discusses how circadian clocks and signalling pathways regulate the reactivity of microvascular beds in diferent tissues, and the research raises the potential for new interventions in the treatment of vascular pathologies such as hypertension.

“Shift Work and Cardiovascular Health” by Gohari and colleagues is a review article that focuses on the important health consequences of shift work. Shift work can work schedules outside of regular daytime working hours and can cause people to sufer circadian misalignment (Gohari et al. 2021). It is known that people who do shift work have an increased risk for cardiovascular disease. The authors discuss recent data identifying the possible reasons as to why people who do shift work have irregular sleep schedules. Data now show that these workers can have an increased risk for obstructive sleep apnea and disrupted autonomic regulation of the heart.

The topic of circadian disruption and its impact on cardiovascular health has been extensively reviewed in “Circadian Rhythms of Risk Factors and Management in Atherosclerotic and Hypertensive Vascular Disease: Modern Chronobiological Perspectives of an Ancient Disease” by Geng and colleagues (Geng et al. 2022). This article is a review of the progress that has been made in understanding circadian regulation of vascular cell function, inflammation, hemostasis, and atherothrombosis. The data reviewed in this article suggest that the successful mitigation and management of atherosclerotic and hypertensive diseases may be achieved by chronotherapeutic control of the atherogenic/ hypertensive pathological sequelae.

“Elevated Asleep Blood Pressure and Non-dipper 24 h Patterning Best Predict Risk for Heart Failure that can be Averted by Bedtime Hypertensive Chronotherapy: A Review of the Published Literature” by Hermida and colleagues reviews the literature underscoring the clinical significance of the abnormal elevated asleep blood pressure and blunted sleep-time decline in systolic blood pressure, referred to as “non-dipping” (Hermida et al. 2021b). They summarize findings that show that the asleep systolic blood pressure and its relative decline are significant prognostic indicators for cardiovascular disease risk, as well as the work showing treatment that lowers the asleep systolic blood pressure and increases in sleep-time decline in systolic blood pressure can combine to significantly protect against heart failure and major cardiovascular disease events.

“Systematic Review and Quality Evaluation of Published Human Ingestion-time Trials of Blood Pressure-lowering Medications and their Combinations” by Hermida and colleagues reviews prospective human trials that investigate individual hypertension medications and their combination for ingestion-time diferences in blood pressure lowering, safety, adherence, and markers of kidney and cardiac pathology (Hermida et al., 2021a). Their systematic review of 155 trials comprising almost 24,000 hypertensive individuals found that almost 85% of the human trials reported clinical benefits when hypertension medications were ingested at bedtime/evening rather than upon waking/morning.

The potential benefits of taking anti-hypertensive medication at bedtime/evening are also explored in “Ingestion-time Diferences in the Pharmacodynamics of Dual-combination Hypertension Therapies: Systematic Review and Meta-Analysis of Published Human Trials.” Hermida-Ayala and colleagues’ review article clearly shows that the majority of reported dual-combination hypertension ingestion-time trials substantiate the benefit of ingesting medications at bedtime/evening for enhanced blood pressure-lowering eficacy (Hermida-Ayala et al. 2022). A systematic and comprehensive review of the literature reveals that no dual-combination hypertension trial reported significantly better benefit than the conventional upon-waking/morning hypertension treatment scheme.

“Understanding the determinants of circadian health disparities and cardiovascular disease” by Johnson and colleagues is a review article that summarizes the emerging research suggesting that sleep contributes to racial disparities in cardiovascular disease (Johnson et al. 2021). This article highlights the need for more work in this research area, because very few studies have examined the contribution of circadian disparities in health as it relates to cardiovascular disease. Given the fact that racial minorities are disproportionately afected by cardiovascular disease, work in this area underscores that improving circadian health may represent a key intervention in lowering cardiovascular disease risk among racially minoritized populations.

We anticipate that this timely series of the leading edge of translational circadian biology will provide an outstanding foundation for future research in the cardiovascular field and will inspire new researchers in cardiovascular and health sciences. Moreover, we hope that a better understanding of how circadian clocks can be harnessed as clinical tools will also stimulate the initiation of new clinical trials to benefit patients, leading to longer and healthier lives.

Acknowledgments

This work was funded by grants to Tami A. Martino (T.A.M.) from the Canadian Institutes of Health Research (CIHR) and to Brian P. Delisle (B.P.D) from the National Heart Lung and Blood Institute (NHLBI, R01HL153042 and R01HL141343).

T.A.M is a Career Investigator of the Heart and Stroke Foundation of Canada (HSFC) and the Distinguished Chair in Molecular Cardiology at the University of Guelph.

References

Alibhai FJ, Tsimakouridze EV, Chinnappareddy N, Wright DC, Billia F, O’Sullivan ML, Pyle WG, Sole MJ, Martino TA. 2014. Short-term disruption of diurnal rhythms after murine myocardial infarction adversely afects long-term myocardial structure and function. Circ Res. 114(11):1713–22. doi:10.1161/CIRCRESAHA.114.302995. [PubMed: 24687134]

Delisle BP, George AL, Nerbonne JM, Bass JT, Ripplinger CM, Jain MK, Hermanstyne TO, Young ME, Kannankeril PJ, Dufy JF, et al. 2021a. Understanding circadian mechanisms of sudden cardiac death: A report from the national heart, lung, and blood institute workshop, Part 1: Basic and translational aspects. Circ Arrhythm Electrophysiol. 14:e010181. doi:10.1161/CIRCEP.121.010181. [PubMed: 34719240]

Delisle BP, George AL, Nerbonne JM, Bass JT, Ripplinger CM, Jain MK, Hermanstyne TO, Young ME, Kannankeril PJ, Dufy JF, et al. 2021b. Understanding circadian mechanisms of sudden cardiac death: A report from the national heart, lung, and blood institute workshop, Part 2:

Population and clinical considerations. Circ Arrhythm Electrophysiol. 14: e010190. doi:10.1161/CIRCEP.121.010190. [PubMed: 34719257]

Geng YJ, Smolensky MH, Sum-Ping O, Hermida R, Castriotta RJ. 2022. Circadian rhythms of risk factors and management in atherosclerotic and hypertensive vascular disease: Modern chronobiological perspectives of an ancient disease. Chronobiol Int. 1–30. doi:10.1080/07420528.2022.2080557. [PubMed: 34353204]

Glen Pyle W and Martino TA. 2018. Circadian rhythms influence cardiovascular disease diferently in males and females: role of sex and gender. Current Opinion in Physiology. 5:30–37. doi:10.1016/j.cophys.2018.05.003.

Gohari A, Wiebe D, Ayas N. 2021. Shift working and cardiovascular health. Chronobiol Int. 1–6. doi:10.1080/07420528.2021.1933000.

Hermida-Ayala RG, Mojon A, Fernandez JR, Smolensky MH, Hermida RC. 2022. Ingestion-time diferences in the pharmacodynamics of dual-combination hypertension therapies: Systematic review and meta-analysis of published human trials. Chronobiol Int. 39(4):493–512. doi:10.1080/07420528.2021.2005084. [PubMed: 34906002]

Hermida RC, Hermida-Ayala RG, Mojon A, Smolensky MH, Fernandez JR. 2021a. Systematic review and quality evaluation of published human ingestion-time trials of blood pressure-lowering medications and their combinations. Chronobiol Int. 38:1460–76. doi:10.1080/07420528.2021.1931280. [PubMed: 34107831]

Hermida RC, Mojon A, Fernandez JR, Hermida-Ayala RG, Crespo JJ, Rios MT, Dominguez-Sardina M, Otero A, Smolensky MH. 2021b. Elevated asleep blood pressure and non-dipper 24h patterning best predict risk for heart failure that can be averted by bedtime hypertension chronotherapy: A review of the published literature. Chronobiol Int. 1–20.

Johnson DA, Cheng P, Farrhenderson M, Knutson K. 2021. Understanding the determinants of circadian health disparities and cardiovascular disease. Chronobiol Int. 1–8. doi:10.1080/07420528.2021.1966026.

Khaper N, Bailey CD, Ghugre NR, Reitz C, Awosanmi Z, Waines R, Martino TA. 2018. Implications of disturbances in circadian rhythms for cardiovascular health: A new frontier in free radical biology. Free Radic Biol Med. 119:85–92. doi:10.1016/j.freeradbiomed.2017.11.006. [PubMed: 29146117]

Kroetsch JT, Lidington D, Bolz SS. 2022. The emerging significance of circadian rhythmicity in microvascular resistance. Chronobiol Int. 39:465–75. doi:10.1080/07420528.2021.2009505. [PubMed: 34915783]

Martino TA and Sole MJ. 2009. Molecular Time. Circulation Research. 105(11):1047–1061. doi:10.1161/CIRCRESAHA.109.206201. [PubMed: 19926881]

Mistry P, Duong A, Kirshenbaum L, Martino TA. 2017. Cardiac Clocks and Preclinical Translation. Heart Fail Clin. 13(4):657–672. doi:10.1016/j.hfc.2017.05.002. [PubMed: 28865775]

Oyama Y, Walker LA, Eckle T. 2021. Targeting circadian PER2 as therapy in myocardial ischemia and reperfusion injury. Chronobiol Int. 38:1262–73. doi:10.1080/07420528.2021.1928160. [PubMed: 34034593]

Reinberg A, Smolensky MH. 1984. Editorial. Chronobiol Int. 1:i–i. doi:10.3109/07420528409059111.

Reitz CJ, Rasouli M, Alibhai FJ, Khatua TN, Pyle WG and Martino TA. 2022. A brief morning rest period benefits cardiac repair in pressure overload hypertrophy and post-myocardial infarction. JCI Insight. 7(22). doi:10.1172/jci.insight.16470010.1172/jci.insight.164700DS1.

Schroder EA, Burgess DE, Johnson SR, Ono M, Seward T, Elayi CS, Esser KA, Delisle BP. 2022. Timing of food intake in mice unmasks a role for the cardiomyocyte circadian clock mechanism in limiting QT-interval prolongation. Chronobiol Int. 39:525–34. doi:10.1080/07420528.2021.2011307. [PubMed: 34875962]

Yoo SH. 2021. Circadian regulation of cardiac muscle function and protein degradation. Chronobiol Int. 1–9. doi:10.1080/07420528.2021.1957911.

Young ME, Latimer MN. 2021. Circadian rhythms in cardiac metabolic flexibility. Chronobiol Int. 1–14. doi:10.1080/07420528.2021.1939366.