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Time and Conditioning

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This issue of Conditioning Medicine is dedicated to circadian medicine and the relationship between conditioning and circadian rhythms. Circadian is derived from the Latin "circa diem" and circadian rhythms refer to biochemical, physiological, and behavioral variations during the 24-hour cycle. The time and timing of interventions and treatments impact their effectiveness in cardiovascular disease. For example, dosing blood pressure medications before sleep instead of upon awakening reduces stroke and myocardial infarction by targeting night time BP (Hermida et al., 2020) Moreover, neuroprotectants show efficacy in stroke during the rodent's sleep time but not the awake time (Esposito et al., 2020) This may account for some of the translational failures in stroke clinical trials when the drugs are given during the human wake period.

The paper by Ko et al (2021) reviews circadian effects on clinical outcomes from myocardial infarction and cardiac interventions including cardiac surgery. It is well established that myocardial infarction peaks in the early morning hours between 6 and 10 am. It is less clear if there is higher mortality and worse clinical outcomes depending on the time of day of the myocardial infarct or when procedures and cardiac surgery are performed. This extensive review of many studies is inconclusive as to whether circadian rhythm influences clinical outcomes. The analysis is complicated by biological and non-biological factors such as health care workers' fatigue and availability during off hours.

Similar to myocardial infarction, strokes occur most commonly in the early morning hours between 6 and 10 am, and like myocardial infarction, it not clear if the size of cerebral infarcts and clinical outcomes are dependent upon the time of day of the stroke. In a mouse study using the middle cerebral artery occlusion (MCAO) model, Kamat and colleagues (2021) randomly assigned seven to eight-month-old C57BL/6J mice (n = 10-12 mice/group) to undergo middle MCAO for 60 minutes at different time points during the 24h day at zeitgeber time (ZT) ZT0 (6 am), ZT6 (noon), ZT12 (6 pm), and Z18 (midnight). Functional outcome as measured by the Corner test was significantly more impaired (right turn preference) at noon/ZT06 compared to the fully awake period (midnight, ZT18) period and ZT0 (6 am). Similarly, the infarction volume was significantly higher during the sleep (ZT06, noon) period than when the ischemic mice were fully awake during the midnight/ZT18 period. This suggests that brain infarcts in mice are larger and functional outcome worse during the mouse's sleep period. A recent study in humans has come to a similar conclusion. In a pooled analysis of 583 patients with anterior circulation large vessel occlusion who underwent computer tomography perfusion, infarct cores were larger at night than during the day (40.2 ml vs. 33.1 ml) and infarct growth with peak infarct volume at 11 pm (Reidler et al., 2021) Larger studies are needed to confirm these findings. Moreover, it will be important to define the mechanisms of this effect as this may lead to targetable pathways in stroke.

Esposito et al (2021) present the concept of 'negative conditioning". Classical "positive" conditioning is the concept that small, sublethal doses of an insult (ischemia) protect against later lethal insult. In negative conditioning from stress, or circadian disruption such as lack of sleep, sublethal insults may lead to greater injury and increase the susceptibility of organs to injury. The molecular mechanisms of negative conditioning are not presently known; one theory posits that the same pathways are involved in positive and negative conditioning but the duration and intensity of the stimulus differs. There is a known association between insomnia and dementia but the direction of causality is not clear. The authors review a recent study showing that short sleep duration (< 6 hours) in midlife is associated with higher late life risk of dementia (Sabia et al., 2021).

The concept that the efficacy of conditioning to reduce ischemia-reperfusion injury may be influenced by circadian rhythms has been suggested but not yet studied (Miller and

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Quindry, 2020). In the preclinical setting, there is solid evidence suggesting that melatonin, well known as a key component that regulates circadian rhythms, can protect against ischemia-reperfusion injury. Unfortunately, this benefit has not been observed in most clinical studies. In this issue, Lourens et al (2021) review possible factors that may help to explain the lack of translation, including age, co-morbidities, and co-medications, all of which have not been taken into consideration in preclinical models. The authors also highlight that melatonin failed to protect in non-rodent models (rabbits and pigs) and that the positive findings in studies conducted in rodents need to be taken with extreme caution due to the fact that their circadian rhythms largely differ from humans.

Conflict of interest statement

The authors report no conflict of interest.

References

Esposito E, Li W, T. Mandeville E, Park JH, Şencan I, Guo S, Shi J, Lan J, Lee J, Hayakawa K, Sakadžić S, Ji X, Lo EH (2020) Potential circadian effects on translational failure for neuroprotection. Nature 582:395–398.

Esposito E, Li W, Mandeville ET, Lok J, Merrow M, Klerman EB, Scheer FAJL, Ning MM, Selim M, Lo EH (2021) Commentary and hypothesis: circadian and/or sleep disruption may cause negative conditioning in the brain. Condition Med 4:257-261.

Hermida RC, Hermida-Ayala RG, Smolensky MH, Mojón A, Crespo JJ, Otero A, Ríos MT, Domínguez-Sardiña M, Fernández JR (2020) Does timing of antihypertensive medication dosing matter? Curr Cardiol Rep 22:118.

Kamat PK, Khan MB, Wood K, Siddiqui S, Rudic DR, Dhandapani K, Waller J, Hess DC (2021) Preclinical evaluation of circadian rhythm in ischemic stroke outcomes. Condition Med 4:280-284.

Ko J, Sia CH, Hausenloy DJ (2021) Circadian effects on clinical outcomes following acute myocardial infarction, cardiac procedures, and surgery. Condition Med 4:262-270.

Lourens R, Imamdin A, Lecour S (2021) Melatonin and cardioprotection: is it ready for clinical translation? Cond Med. 4:271-279.

Miller LE, Quindry JC (2020) Exercise and cardioprotection against ischemia reperfusion injury: A review. 3:59-70.

Reidler P, Brehm A, Sporns PB, Burbano VG, Stueckelschweiger L, Broocks G, Liebig T, Psychogios MN, Ricke J, Dimitriadis K, Dichgans M, Kunz WG, Tiedt S (2021) Circadian rhythm of ischaemic core progression in human stroke. J Neurol Neurosurg Psychiatry:1–4.

Sabia S, Fayosse A, Dumurgier J, van Hees VT, Paquet C, Sommerlad A, Kivimäki M, Dugravot A, Singh-Manoux A (2021) Association of sleep duration in middle and old age with incidence of dementia. Nat Commun 12:2289.