Rhythm and cues: the role of chronobiology in perioperative medicine

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In 2017 the Nobel Prize for Medicine or Physiology was awarded to Jeffrey Hall, Michael Rosbash and Michael Young for their description of the molecular mechanisms that control circadian rhythms. Not long after this announcement came the discovery, published in The Lancet, that the influence of circadian rhythms extends to postoperative outcomes following aortic valve replacement.[1] This work consisted of a number of threads; a large cohort study (n=596), a smaller randomised controlled trial (RCT, n=88) and mechanistic ex vivo and transcriptomic work. The cohort study convincingly demonstrated much lower rates of major cardiac adverse events in the group who had their surgery in the afternoon compared with the morning (95% CI 0.32-0.77; p=0.0021). The RCT revealed lower mean postoperative cardiac troponin levels (up to 72 hours) in those patients undergoing afternoon surgery compared to surgery in the morning. The clinical studies were backed up by molecular analysis to provide a credible mechanistic explanation: the regulation of ischemia-reperfusion tolerance by altered expression of genes according to a circadian rhythm. This finding is complemented by a recent retrospective analysis of clinical data from the International Burn Injury database, which showed that healing times were 60% shorter in burns sustained in the daytime compared to those incurred at night. [2] The authors also demonstrated circadian regulation of actin-dependent processes in fibroblast cells, suggesting a possible mechanism underlying these circadian patterns in wound healing. [2]

Chronobiology is a broad field that describes the study of cyclic phenomena on biological processes. Key biological pathways in almost every cell in the human body oscillate with a period of approximately 24 hours ("*circa diem"*), in parallel with the rotation of the Earth and the light-dark cycle this creates. These circadian rhythms are observed in most life-forms, including plants and single celled organisms, all ultimately subject to the astronomical framework in which life exists. It is believed that the function of a circadian rhythm is to separate incompatible biological processes and to optimise function through anticipation of predictable activities such as sleeping, eating and movement.[3] Its commonality to all life suggests a profound survival advantage. Circadian rhythmicity is achieved through autonomous cellular 'clocks', which produce oscillations in gene/protein expression, and consequently influence the functions in which these proteins are involved (e.g. metabolism). This circadian process involves two transcriptional activators called *CLOCK* (circadian locomotor output cycles kaput) and *BMAL1* (brain and muscle *ARNT* (arylhydrocarbon receptor nuclear translocator) like protein) and two repressors called *CRY* (crytochrome) and *PER* (Period) working in a feedback loop. This mechanism controls roughly 10% of all gene products in humans, generating rhythmic circadian expression patterns which influence almost every known cellular pathway.[4] These peripheral rhythms are co-ordinated centrally, and synchronised to the demands of the environment, through the action of external cues (Zeitgebers, translated from the German 'time-givers') on the suprachiasmatic nucleus (SCN) of the hypothalamus. The most important Zeitgeber is light, but the SCN also integrates other external cues such as body temperature and feeding patterns, and in turn regulates the peripheral clocks through hormonal and neural outputs. For example, light signals are projected directly from non-visual retinal ganglion cells to the SCN, through which it suppresses melatonin secretion by the pineal gland. Melatonin is a pleiotropic hormone, signalling darkness, and one of its many putative roles is the harmonisation of the rhythms of clocks in remote tissues, synchronising them to the central pacemaker of the SCN, and thus to external time of day. Melatonin may also have a role in regulation of clock gene expression.[5] When Zeitgebers are displaced, for example by flying across time zones or switching to night shift work, the cellular clocks find themselves out of time with the new schedule, because they are still entrained to the previous time zone. The SCN receives inputs from the new zone, but the peripheral clocks take time to adapt, and different tissues respond at different rates. Loss of synchrony between peripheral clocks and the external environment (external dyssynchrony), and loss of synchrony between the clocks of different tissues (internal dyssynchrony), results in the overt symptoms of jet lag. Sufferers feel sleepy during the day resulting in fatigue, relative psychomotor impairment and gastrointestinal disturbance; while the hours of rest are disturbed by sleeplessness. These symptoms persist until such time as all the clocks are realigned to the SCN again; this takes roughly one day per time zone (i.e. 1 hour) crossed and melatonin is crucial to this correction. Recurrent clock desynchronisation, seen in night shift workers, has wide-ranging impacts on health, including chronic sleep disorders, obesity, metabolic syndrome and cancer.[6] These diverse pathologies point to pervasiveness of circadian rhythm dysrhythmia, with sleep-wake disturbance representing only the tip of the iceberg. Even one night without sleep has profound effects on gene expression. [7] Similar effects are seen in patients on intensive care units, where artificial light, noise at night, interruptions, sedation and displacement of other Zeitgebers such as meals and activity, affect melatonin levels and sleep patterns.[8 9] Circadian dysregulation is likely to be highly abnormal in the critically ill and could exacerbate the deleterious effects of disease. [10]. For example, circadian dysregulation has been implicated in the development of delirium in the critically ill.[11]

Time of day is a factor critical to most physiological functions. Most key global measures (such as physical and mental activity, heart rate, blood pressure and respiratory function), as well as a multitude of cellular pathways, from metabolism to redox homeostasis, oscillate in a circadian pattern.[12] Overlooking the influence of the *time of day* factor on the response to surgery and anaesthesia would therefore be unwise. Circadian rhythms will affect multiple patient factors: from the cardiovascular stress response, to immunity and wound healing. The pharmacokinetics and pharmacodynamics of drugs is also under the influence of our molecular clocks,[13] a phenomenon that is being used already to optimise patient benefit in the treatment of cancer.[14] The effects (and side effects) of anaesthetic, analgesic and antibiotic drugs are time-of-day dependent, and it may be that this also contributes to differences in both anaesthetic recovery and surgical outcomes. Unfortunately, this remains a field in which virtually no data exist. From the reverse perspective, anaesthetic drugs, as well as the stress response triggered by surgical insult, and the imposed alterations in the timings of Zeitgebers (such as pre-operative fasting and inactivity) might lead to desynchronisation between the SCN and peripheral tissue clocks. At least one class of drug used in anaesthesia, benzodiazepines, has been shown to phase-shift circadian rhythms, with the effect depending on the relative time of day that the drug is administered.[15] Most of these relationships between the relative timing of perioperative events and peripheral clock synchrony are yet to be explored, but results from the studies described above hint at the progress to be made.

It important to consider that *time of day* does not only affect patients, but also substantially influences human factors relating to the surgeon, anaesthetist and other healthcare workers caring for the patients. Providing round the clock clinical care poses unique physiological challenges for healthcare workers that may impact patient outcomes. During a night shift, staff must perform tasks during the circadian phase when they are hard-wired for sleeping. This period of time coincides with the lowest levels of alertness, cognitive function, psychomotor co-ordination and mood, which reach a nadir between the hours of 3 to 5 am.[16] Performance is impaired despite increased effort, and the impairment is greater than the individual's subjective awareness of sleepiness, further increasing the risk of errors and harm. Following a night shift, the rest period is shifted to the circadian phase least conducive to sleeping, leading to sleep loss and the many documented adverse effects of fatigue.[17] Reducing the length of shifts and overall weekly number of hours worked by trainee critical care doctors increased their total sleep hours and dramatically reduced the number of attentional failures during night duties. [18] Even after a single night shift, when compared to a night of sleep, trainee anaesthetists demonstrate impaired non-technical skills in a simulated crisis management scenario. [19] In the future it would perhaps be beneficial to include recognition of fatigue into the training programmes for healthcare professionals. [20] Perhaps the ultimate clock desynchroniser is space travel, during which time there is complete loss of a natural 24-hour day. For those astronauts orbiting the earth in the international space station, a sunrise was experienced every 90 minutes. Studies from space shuttle missions concluded that the astronauts experienced circadian rhythm disturbances, diminished sleep duration, decrements in neurobehavioural performance, and alterations in rapid eye movement sleep homeostasis. [21] Simulation work looking into the effect of 520 days of isolation and loss of normal external cues that would be experienced in a mission to Mars suggested similar circadian disturbances. [22]

In the long-term, shift work may result in chronic sleep disturbance, termed "shift work sleep disorder."[23] The long-term sequelae of recurrent circadian misalignment are increasingly recognised,[24] with shift workers demonstrating increased risk for developing cancer, metabolic dysfunction and diabetes, heart disease and gastrointestinal disorders.[25] Reducing the impact of these challenges requires intervention at both an organisational and an individual level. The former will require research to determine optimum shift duration, direction and speed of shift rotation, and provision of adequate rest periods and facilities. This is the subject of an ongoing Cochrane review (protocol by Erren et al: 10.1002/14651858.CD010639), and current guidelines have been issued by the UK Health and Safety Executive (http://www.hse.gov.uk/pubns/books/hsg256.htm). Two recent Cochrane systematic reviews concluded that the evidence base for both pharmacological and non-pharmacological strategies to tackle the acute symptoms of sleep-wake inversion in shift workers is limited.[26 27] Suggested strategies to reduce night shift sleepiness included consumption of caffeine and other stimulants, short naps and bright light. Proposed interventions to improve sleep quality and quantity during the day rest period between shifts include: melatonin, hypnotic agents and a cohort of behavioural strategies to improve 'sleep hygiene' (e.g. dark quiet room, relaxation techniques). Problems with trial design and study heterogeneity have so far yielded mostly low quality evidence, and there is a need for adequately powered randomised controlled trials in a real-world setting. Sleep and performance are both complex phenomena, and it has been proposed that a multi-modal approach will provide the greatest benefit [28].

Alternatively, it has been proposed that administration of exogenous melatonin could offer a form of chemical chronotherapy, by supporting the re-entrainment of circadian rhythms to the new schedule. A trial of melatonin in medical and nursing staff working night shifts has recently completed recruitment (the MIDNIGHT trial, **ISRCTN15529655**), in which melatonin or placebo was given just before sleep time and the effects on psychomotor vigilance, gene expression and actigraphy measures of sleep were determined. The results of this trial will be available shortly. Pharmacological rehabilitation of disrupted circadian rhythms using melatonin has also been investigated as a means of reducing postoperative delirium. Perioperative melatonin administration has been shown to reduce the incidence of postoperative delirium in elderly patients undergoing elective arthroplasty,[29] although other studies have demonstrated conflicting results.[30] The timing of melatonin administration relative to the patient's circadian phase is likely to influence its effect. Although the pharmacokinetics of exogenous melatonin at different doses in healthy subjects has been reported [31], further studies are needed to determine the pharmacokinetics of this drug in different patient cohorts. [32] A randomised controlled trial comparing the antioxidant and anti-inflammatory effects of 50 mg and 100 mg of melatonin in sepsis is currently underway (DAMSEL2: ISRCTN70688534). Modafinil (a wakefulness promoting drug) has also been used in studies to treat patients with shift-work sleep disorder and found to bring about improvements in performance. [33] It has also been used by the military to improve battle readiness and performance of troops on long missions. However, use of this controversial drug outside of these situations would require careful investigation as it has significant side effects.

A further layer of circadian complexity is chronotype. This refers to an individual's innate circadian phenotype, which will lie on a spectrum from extreme 'morningness' (the lark) to extreme 'eveningness' (the owl). Chronotype determines a person's preferred waking and sleeping times, and peak physical and cognitive performance times; with performance peak occurring later in the day for those with a ‘evening’ chronotype. Chronotype is not a life-choice; it has a deep seated genetic basis through the clock gene feedback mechanism[34] and changes with age, with the peak of ‘eveningness’ occurring at 20-21 years. Timing of specific activities according to chronotype (as determined by validated questionnaires, such as the Munich Chronotype Questionnaire) has been successful in optimising athletic and educational performances.[35 36] The chronotype of the patient *and* healthcare professionals, relative to the timing of an operation, could therefore influence patient outcomes. Chronotypes have yet to be considered in studies investigating the impact of timing of surgery, but may represent a new frontier in the evolving field of personalised medicine. Chronotype must also be taken into consideration in the evaluation of any chronotherapy, such as melatonin, as its effect will be influenced by the timing of its administration with respect to chronotype and circadian phase of the patient.[29 30]

Perioperative physicians and researchers have often been early adopters of new concepts in medicine. They have driven advancements in intravenous fluid therapy, and transformed the landscape of clinical practice through the success of enhanced recovery after surgery (ERAS) programmes. It has been proposed that a rational assessment tool for ERAS would be a succinct patient related outcome measure, such as whether or not the patient is ‘DREAMing’ within 24 hours of surgery (Drinking, EAting and Mobilising);[37] a concept recently upgraded to ‘DREAMS’ [38] by the addition of ‘Sleep’. It is an interesting observation that all of these components also happen to be the most important Zeitgebers, and therefore contribute to the preservation of a healthy circadian rhythm. Perhaps ERAS programmes have inadvertently provided us with a multicomponent platform from which to launch a chronobiological approach to improving perioperative outcomes. Rapid return to normal drinking, eating, mobilising and sleeping patterns after surgery has led to improved clinical outcomes, and perhaps this is in part due to minimisation of internal clock disruption.

In summary, cellular clocks control almost every aspect of life, we can no longer ignore the fact that their circadian rhythms can influence healthcare outcomes. If we are to avoid unnecessary harm and take advantage of this inescapable clockwork we need to understand more about this phenomenal biological system and the impact it has during the perioperative period.

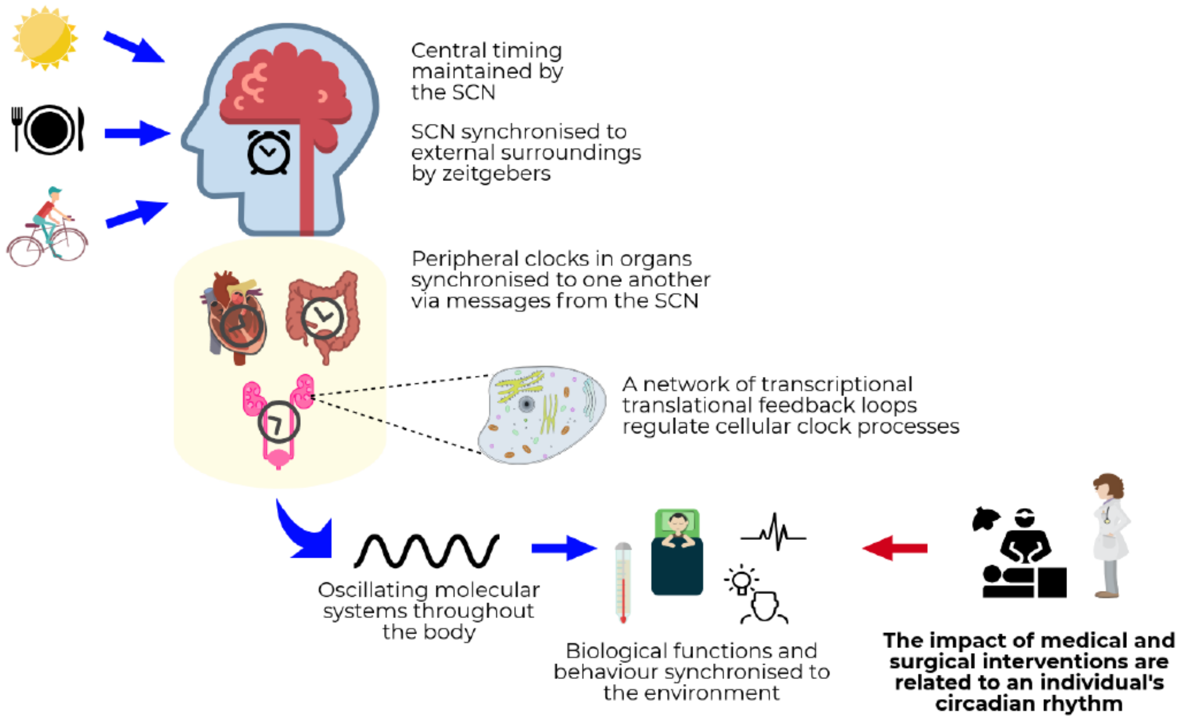

Figure 1. A schematic overview of how chronobiology affects daily life and is an essential element of healthcare delivery

SCN = suprachiasmatic nucleus.

Zeitgebers maintain timing in the 'master clock' within the SCN, which in turn provides a reference point for the multiple 'peripheral clocks' throughout our organs. The peripheral clocks maintain normal body function, with the right processes being upregulated at the right time of day. Disruption of this delicate system can lead to detrimental clinical consequences.

DM, HM and HG all conceived the idea for the article, wrote it and were directly involved with revising versions.

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