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REVIEW ARTICLE | OPEN ACCESS

# Circadian Effects on Clinical Outcomes following Acute Myocardial Infarction, Cardiac Procedures, and Surgery

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Circadian rhythm is a potentially important regulator of the (patho)physiology governing gene transcription and metabolism. Data from basic science studies suggest that critical cellular processes, such as oxidative stress and regeneration after ischemia and reperfusion injury (IRI), are under the control of circadian rhythm. This has implications for patients presenting with acute myocardial infarction (AMI) given that IRI is a key determinant of clinical outcomes in this patient group. However, data interpretation in the field of circadian rhythm research has been challenging due the the presence of multiple biological and non-biological factors. Circadian rhythm is affected by non-biological factors such as healthcare workers' fatigue, limited resources, and significant delay in providing critical care at night. This review aims to evaluate current evidence of the impact of circadian rhythm on clinical outcomes in AMI patients and in patients undergoing cardiac surgery.

**Keywords:** Circadian Rhythm, Cardiac Surgery, Myocardial Infarction, Percutaneous Intervention, Coronary Artery Bypass Graft, Aortic Valve Replacement

## Introduction

Circadian rhythm is an endogenous oscillating pattern of molecular and physiological activities with a near-24-hour period that allows organisms to adapt to external stimuli and the environment (Patke et al., 2020). The circadian rhythm is regulated by circadian clocks. There is a central clock involving neurons residing in the suprachiasmatic nucleus of the hypothalamus and a peripheral clock that is present in other tissues (Crnko et al., 2019). Light transmitted from the retina to the suprachiasmatic nucleus is an important biological cue that not only regulates the central clock but also synchronizes the peripheral clock via hormones and neurotransmitters (Cajochen et al., 2003). The circadian rhythm is a potentially important regulator of cardiovascular physiology and pathogenesis (For further reading see Hausenloy and Yellon, 2017; Thosar et al., 2018; Slomski, 2019; Dong et al., 2020; Rana et al., 2020; Lecour et al., 2021) as multiple studies suggest that peripheral clock gene expression displays a circadian pattern in cardiac cells, including cardiomyocytes (Beesley et al., 2016), endothelial (Takeda et al., 2007), vascular smooth muscle (Lin et al., 2014), and stem cells (Du Pré et al., 2017). Moreover, blood pressure is under the influence of the circadian rhythm (Xu et al., 2019; Cortés-Ríos and Rodriguez-Fernandez, 2021; Zhang et al., 2021). Despite the well-documented demonstration of circadian patterns for cellular activities and gene transcription in isolated cardiovascular cells in vitro, the exact impact of circadian rhythm in major cardiac diseases and prognosis after cardiac interventions is still unclear. This controversy over the significance of the circadian rhythm is partially due to the conflicting associations of intervention time with clinical outcomes following major cardiac events and interventions, such as acute myocardial infarction (AMI), coronary artery bypass surgery (CABG), percutaneous coronary intervention (PCI), and aortic valve replacement (AVR). The unclear association stems from the presence of multiple biological and non-biological factors involved in the studies, such as the time lapse between the onset of cardiac symptoms to admission in hospital. Therefore, this review aims to summarize and discuss the association of circadian rhythm in major cardiac diseases and interventions.

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### Time of Onset of Symptoms in Myocardial Infarction and Prognosis

The potential importance of the circadian rhythm in cardiovascular (patho) physiology has been supported by the finding of increased AMI incidence during certain times of the day. In 1960, Master et al. (1960) described that AMI occurred with an increased frequency between 07:00 to 13:00. The increased occurrence of AMI during these times was consistently reproduced in other early studies, and it is now accepted to be an established clinical association (Pell and D'Alonzo, 1963; Muller et al., 1985; Hjalmarson et al., 1989; Willich et al., 1989). More importantly, the occurrence of AMI appears to have an oscillating pattern with a 24-hour period, also known as a circadian rhythm (Hansen et al., 1993; López Messa et al., 2004), and the mortality has been potentially associated in a circadian manner (Fournier et al., 2015). Various hypotheses have been proposed to explain the implication of the circadian rhythm in AMI and the potentially increased mortality of AMI depending on time of symptom onset. One of the plausible hypotheses is that the underlying pathological or defensive mechanisms, such as necrosis, ischemia-reperfusion injury, or cellular regeneration, are under the control of the circadian rhythm leading to a change in mortality following AMI events and subsequent reperfusion interventions (Bochaton and Ovize, 2018; Liu et al., 2021). However, another proposed explanation for the increased mortality is that non-biological factors, such as a delayed transportation to the hospital and, thus, an increased total ischemic time, can lead to worsened mortality. Indeed, patients who have AMI symptoms near midnight or early in the morning might not present to an emergency room early due to logistical issues (Khaper et al., 2018). This section of the review will focus on studies examining the possible involvement of non-biological factors on the time of onset of AMI symptoms and mortality.

A study by Hansen et al (1993) is one of the earliest papers that aimed to describe the significance of circadian rhythm on mortality following AMI. In this study, consistent with later reports, the symptoms of AMI ocurred more frequently in the morning, between 07:00 and 10:00. The time of symptom onset between 06:00 and 12:00 was associated with a greater infarct size, indicative of more severe MI. However, after adjusting for infarct size, in-hospital mortality was not associated with the time of onset of AMI symptoms. The author interpreted this result as evidence of a circadian rhythm in mortality following AMI, as infarct size is associated with oxygen demand and supply, which could be under the control of the circadian rhythm, and the statistical significance for the circadian pattern was lost after the adjustment. Although this paper was pioneering as the authors attempted to adjust the mortality with infarct size to evaluate the involvement of circadian rhythm, this interpretation is limited; the change in infarct size could be due to a significant pre-hospital delay (correlated with a prolonged total ischemic time), not just the circadian rhythm. Since there were at least two variables affecting the infarct size, total ischemic time and circadian rhythm, this study could not establish the association of time of onset of AMI symptoms with mortality. A proper statistical adjustment for total ischemic time is important to assess the impact of time of onset of AMI symptoms on mortality. In a later study performed by Holmes et al (2010), a significant pre-hospital delay in the patients with symptom onset between 00:00 and 06:00 (121 min) was observed as compared to those from 12:00 and 18:00 (70 min). After adjustment for potential confounders including the pre-hospital or total ischemic time, the mortality was not significantly associated with the onset time of AMI symptoms, suggesting that the ischemic injury, as indicated by mortality, might not have been under the influence of the circadian rhythm. Similarly, in other studies, the circadian pattern of mortality over onset time of ST-segment elevation myocardial infarction (STEMI) symptoms, was significant, but the mortality itself was not significant after adjusting for total ischemic time (Fournier et al., 2015; Albackr et al., 2019; Sager et al., 2019). Our research group previously demonstrated that the time variation over STEMI mortality is significantly observed only in the group with 120 min or a longer ischemic time and the circadian pattern was not observed in the group with a short ischemic time (Paradies et al., 2020). This result suggests that total ischemic time is a crucial component of the onset time-dependent mortality following AMI events, and thus the significance of the circadian rhythm is questionable.

In summary, it is widely accepted that there is an increased frequency of first onset of AMI symptoms in the morning. However, it is still unclear if a specific onset time of AMI symptoms is significantly associated with an altered mortality following AMI events after proper statistical adjustments, especially for total ischemic time (Table 1).

### Time Variation in Percutaneous Coronary Intervention and Prognosis

Percutaneous coronary intervention (PCI) is another method of intervention for reperfusion following AMI events. The association of PCI with clinical outcomes in AMI in relation to intervention time has been studied in the context of potential sub-optimal care for patients admitted after working-hours to examine whether patients treated after-hours are more likely to have a worse prognosis. One of the very first reports on this issue was by Garot et al. (1997) who demonstrated that there was no increased mortality in the AMI patients treated with PCI after working-hours as compared to those treated between 08:00 and 20:00. Interestingly, other studies on the same research question reported a significantly increased 30-day mortality or in-hospital mortality in patients who received PCI during after-hours. PCI performed during after-hours was associated with an increased rate of failure for angioplasty (Henriques et al., 2003; Dominguez-Rodriguez et al., 2007), a significant delay in door-to-balloon time (Magid et al., 2005), advanced age of the patients (Saleem et al., 2004), and therefore suggests that the increased mortality for the PCI performed during after-hours was presumably due to resource or patient factors. Studies reporting no difference in delay of door-to-balloon time (Assali et al., 2006; Barbosa et al., 2018; Lattuca et al., 2019) or a minimal delay (Ortolani et al., 2007) demonstrated insignificant change in mortality in the patients treated with PCI following AMI during after-hours. This result is in line with the well known importance of the short door-to-balloon time for prognosis following AMI events (Rathore et al., 2009). In summary, PCI performed during after-hours is associated with a poorer prognosis in AMI patients presumably due to an increased door-to-balloon time and increased failure rate for angioplasty. When there was no significantly delay in the door-to-balloon time, PCI performance was not associated with the intervention time, working hours, or after-hours (Table 2). Therefore, these studies collectively suggest that PCI centers are required to minimize the door-to-balloon time by optimizing the infra-structure and resources especially during the after-hours.

### Time Variation in Coronary Artery Bypass Surgery and Prognosis

Coronary artery bypass graft surgery (CABG) is a surgical intervention for reperfusion following AMI events. Circadian rhythm has been proposed as a potential mechanism affecting the clinical outcome after CABG as the rhythm can affect ischemia-reperfusion injury and recovery. The influence of circadian rhythm over the outcome of patients undergoing cardiac surgery has been controversial. This controversy

**Table 1. Summary of Major Clinical Studies exploring the Association between Onset Time of AMI Symptom and Clinical Outcomes.**

| Author / Year | Exposure | Population | Outcome / Major Finding | Adjusted for Total Ischemic Time | Association with Mortality |
|---|---|---|---|---|---|
| Hansen 1993 | Symptom onset | - 10,791 AMI<br>- 1973 – 1987<br>- Single center<br>- Sweden | 1. Increased occurrence of AMI between 07:00 and 10:00<br>2. Symptom onset between 06:00 and 12:00 associated with a greater infarct<br>3. Symptom onset between 00:00 and 0600 associated with a lower risk of cardiac arrests.<br>4. No association with in-hospital mortality after adjustment (infarct size). | Adjusted for infarct size<br>(not time) | No |
| Holmes 2010 | Symptom onset | - 2,143 STEMI<br>- 2004-2008<br>- Single center<br>- USA | 1. Increased occurrence of AMI between 08:00 and 15:00<br>2. Significant prehospital delay in patients with onset from 00:00 and 06:00 (121 min) as compared to patients from 12:00 and 18:00 (70 min)<br>3. Significant delay in door-to-balloon in patients with onset from 00:00 and 06:00 (75 min) as compared to patients from 06:00 to 12:00 (60 min) | Yes | No |
| Fournier 2015 | Symptom onset | - 6,223 STEMI<br>- 1999 – 2013<br>- National Registry,<br>82 hospitals<br>- Switzerland<br>- All treated with PCI within 6 hours of onset | 1. Circadian rhythm of CK levels<br>2. CK peak at 23:00 and minimum at 11:00<br>3. Circadian rhythm of mortality with a peak at 00:00 and a minimum at 12:00 | No | The circadian pattern was significantly associated, but no calculation for the risk of mortality. |
| Sager 2019 | Symptom onset | - 1,206 STEMI<br>- 2002 – 2007<br>- Two centers<br>- Germany | 1. Significant prehospital delay in patients with onset from 00:00 and 06:00 (6.5h) as compared to patients from 06:00 and 12:00 (3.5h).<br>2. No significant association between onset time and infarct size, 5-year all-cause mortality, or recovery of left ventricular ejection fraction 6 months after STEMI. | Yes | No |
| Albackr 2019 | Symptom onset | - 2,909 STEMI<br>- Arabian Gulf Countries | 1. Significant prehospital delay in patients with onset from 00:00 and 06:00 (150 min) as compared to patients from 06:00 and 12:00 or 12:00 and 18:00 (90 min) | Yes | No. The circadian pattern was significantly associated, but mortality itself is not significantly associated. |
| Peng 2021 | Symptom onset | - 1,099 STEMI<br>- 2013 – 2019<br>- China | 1. Significant prehospital delay in patients with onset from 00:00 and 06:00 (120 min) as compared to patients from 12:00 and 18:00 (100 min).<br>2. Significant ischemic time in patients with onset from 00:00 and 06:00 (220 min) as compared to patients from 12:00 and 18:00 (190 min).<br>3. Increased incidence of long-term major adverse cardiovascular events (MACE) in patients with onset from 00:00 and 06:00 | Yes | The circadian pattern was significantly associated, but no calculation for OR or HR of mortality. |

is partially due to the complexity of the data interpretation confounded by non-biological factors, such as fatigue of the surgical teams, limited resources during after-hours, and also urgent surgeries being performed at night times or weekends (Khaper et al., 2018). Dhadwal et al. (2007) resolved this issue by stratifying the CABG patients not only into times (morning, afternoon, and night) but also into urgency (elective, urgent, and emergency). There was no significant difference in 30-day mortality for the elective and urgent groups in relaionship to time. Interestingly, emergency cases performed in the morning and night were associated with an increased risk of death as compared to the afternoon group. Nonetheless, given the fact that the circadian pattern was not observed in the other two types of cases and the severity of the cases in the emergency group, surgery time did not seem to be associated with a mortality change. This result was corroborated in two other studies of over 14,000 patients consisting of both elective and urgent cases (Tan et al., 2009; Nemeth et al., 2021). Furthermore, beyond mortality outcomes, other complications, such as stroke, prolonged ventilation, renal failure, wound infection, reoperation, AMI, atrial fibrillation, and readmissions were not associated with the time of surgery. Additionally, two recent studies where the influence of the urgency of surgeries was considered for statistical adjustments (Coumbe et al., 2011) or the urgent cases were excluded (Fudulu et al., 2021), demonstrated that there was no change in mortality in relation to time of surgery. In summary, the studies collectively suggest that there is no change in mortality following CABG surgery in AMI patients in relation to time of surgery (Table 3). This result suggests that circadian rhythm may not influence clinical outcomes following CABG.

**Table 2. Summary of Major Clinical Studies exploring the Association between Intervention Time for PCI and Clinical Outcomes.**

| Author / Year | Exposure | Population | Outcome | Delay in Door-to-Balloon Reported | Associated with Mortality |
|---|---|---|---|---|---|
| Garot 1997 | PCI performed during working hours (08:00 - 20:00) after-hours (20:00 – 08:00 weekdays and weekends/holidays) | - 288 PCI<br>- admitted <6 hours after onset<br>- Single center<br>- France | 1. No significant change in in-hospital mortality. | No | No |
| Henriques 2003 | PCI performed during working hours (08:00 – 18:00) after-hours (18:00 – 08:00) | - 1,702 STEMI who received PCI<br>- admitted <6 hours after onset<br>- 1994 – 2000<br>- Single center<br>- Netherlands | 1. An increase in failure rate for angioplasty between 18:00 and 08:00 (6.9% VS 3.8%)<br>2. An increase in 30-day mortality between 18:00 and 08:00 (4.2% VS 1.9%) | No<br>Maybe delayed;<br>a significant increase in failure rate for angioplasty during after-hours | Yes |
| Saleem 2004 | PCI performed during working hours (07:00 – 19:00) after-hours (19:00 – 07:00 weekdays and weekends/holidays) | - 1,050 PCI<br>- 1998 - 2002<br>- PCI within 24 hours of symptoms<br>- Single center<br>- USA | 1. Increased in-hospital mortality in patients aged 75 to 95 years (10%) as compared to aged 21 to 50 years (2.1%), 51 to 64 years (2.3%), and 65 to 74 years (4%) during the after hours | No | Yes |
| Magid 2005 | PCI performed during working hours (07:00 – 17:00) after-hours (17:00 – 07:00 weekdays and weekends/holidays) | - 33,647 STEMI who received PCI<br>- 1999 – 2002<br>- National registry<br>- USA | 1. Significant delay in door-to-balloon time during after-hours (116.1 min VS 94.8 min)<br>2. Significantly higher in-hospital mortality for after-hours upon adjustment (OR 1.07, 95% CI 1.01-1.14) | Yes<br>Significant delay | Yes |
| Assali 2006 | PCI performed during working hours (08:00 – 18:00) after-hours (18:00 – 08:00) | - 273 STEMI who received PCI<br>- 2001 – 2005<br>- Single center<br>- Israel | 1. No significant delay in door-to-balloon time during after-hours<br>2. No significant difference in one-month mortality after adjustment. | Yes<br>No delay | No |
| Dominguez 2007 | PCI performed during working hours (08:00 – 18:00) after-hours (18:00 – 08:00) | - 90 STEMI who received PCI<br>- admitted <6 hours after onset<br>- Single center<br>- Spain | 1. An increase in failure rate for angioplasty between 18:00 and 08:00 (17.9% VS 3.9%)<br>2. An increase in-hospital mortality between 18:00 and 08:00 (12.8% VS 1.9%) | No<br>Maybe delayed;<br>a significant increase in failure rate for angioplasty during after-hours | Yes |
| Ortolani 2007 | PCI performed during working hours (08:00 – 19:30) after-hours (19:30 – 08:00 weekdays and weekends/holidays) | - 985 STEMI who received PCI<br>- 2003 – 2005<br>- Single center<br>- Italy | 1. Significant delay in door-to-balloon time during after-hours (75 min VS 65 min)<br>2. No significant difference in mortality during after-hours | Yes<br>Statistically significant, but absolutely short door-to-balloon time for both groups | No |
| Graham 2010 | PCI performed during<br>- Working hours (07:00 – 18:00 on weekdays)<br>- After hours (18:00 – 07:00 weekdays and weekends/holidays) | - 1,664 PCI<br>- 1999 – 2006<br>- Multi-institutional<br>- Canada<br>- +additional meta-analysis | 1. Not significant difference in 30-day and 1-year mortality between working and after-hours.<br>2. Meta-analysis revealed RR of 1.23 (95% CI 1.00 to 1.51) for short-term outcomes | No | No |
| Barbosa 2018 | PCI performed during<br>- Working hours (07:00 – 19:00 on weekdays)<br>- After hours (19:00 – 07:00) | - 446 STEMI who received PCI<br>- 2013 – 2016<br>- Single center<br>- Brazil | 1. No significant delay in door-to-balloon time during after-hours (101 min Vs 99 min, p=0.59)<br>2. No significant delay in onset-to-balloon time (294 VS 278, p=0.32)<br>3. No significant difference in in-hospital mortality by PCI time. | Yes<br>No delay | No |
| Tokarek 2020 | PCI performed during<br>- Working hours (07:00 – 17:00 on weekdays)<br>- After hours (17:00 – 07:00 weekdays and weekends/holidays) | - 99,783 STEMI who received PCI<br>- 2014 – 2018<br>- National registry<br>- Poland | 1. Higher in-hospital mortality for PCI during after-hours (1.49% VS 1.49%, p=0.0001)<br>2. Significant delay in door-to-balloon time during after-hours (104 min VS 99 min)<br>3. Significant delay in pain-to-balloon time during after-hours (253 min VS 246 min) | Yes<br>Significant delay | Yes |

Abbreviations: CI, confidence interval; PCI, percutaneous coronary intervention; OR, odds-ratio; RR, relative risk; STEMI, ST-segment elevation myocardial infarction; USA, the United States of America

## Time Variation in Aortic Valve Replacement and Prognosis

Aortic valve replacement surgery (AVR) is another cardiac surgery where circadian rhytm has been proposed to play a role. AVR requires an aortic-cross clamping, which induces ischemic injury followed by ischemia-reperfusion injury (Rossiter et al., 1974; García-de-la-Asunción et al., 2013). Due to the potential role of circadian rhythm over the reduction and oxidation balance (redox), clinical outcomes of AVR have been studied in relation to the operation time. In a single center study performed in 2018 where 596 patients received an isolated AVR, the patients who received the surgery in the afternoon had a significantly lower incidence of major cardiac adverse events, including cardiovascular death, AMI, and acute heart failure (Montaigne et al., 2018). Moreover, the afternoon

**Table 3. Summary of Major Clinical Studies exploring the Association between Operation Time for CABG and Clinical Outcomes.**

| Author / Year | Exposure | Population | Outcome | Adjusted for Urgency | Associated with Mortality |
|---|---|---|---|---|---|
| Dhadwal 2007 | Isolated CABG<br>- AM 07:00 to 14:00<br>- AF 14:00 to 20:00<br>- NT 20:00 to 07:00<br>- Elective<br>- Urgent<br>- Emergency | - 3,140 patients<br>- 1999 – 2002<br>- Single center<br>- USA | 1. No significant difference in 30-day mortality for the elective and urgent groups.<br>2. Significantly increased risk of death in the AM and NT compared to the AF only in the emergency group. | Yes, by separating into three groups; elective, urgent, and emergency | No |
| Tan 2009 | Isolated CABG AM/PM | - 19,150 patients<br>- 1993 – 2006<br>- Single center<br>- USA | - Compound morbidity outcomes of six variables<br>1. In-hospital mortality<br>2. acute post-operative AMI<br>3. Neurologic morbidity<br>4. Sepsis<br>5. New onset of kidney failure<br>6. post-operative ventilation longer than 72h<br>- 4.8% for 30-day morbidity and 1.4% for 30-day mortality<br>- No significant difference in mortality/morbidity in relation to operation time | No | No |
| Coumbe 2011 | Isolated CABG AM/PM | - 4,714 patients<br>- 1987-2009<br>- Single center<br>- USA | 1. Operations on weekends and after 4PM associated with higher risk patients, urgency, and use of intra-aortic balloon pump for support, and post-operative complications.<br>2. Increased 30-day mortality for weekends. (OR 4.1, CI 1.6 to 10.4, p=0.003)<br>3. Increased 30-day mortality for 4PM. (OR 2.9, 95% CI 1 to 8, p=0.049)<br>4. Not significant after adjustments for the urgency and the mortality risk score. | Yes | No |

group had a significantly lower peri-operative cardiac troponin T in their randomized controlled study. This result could be broadly due to the two factors: 1) circadian rhythm or 2) a so-called "human factor," such as allocating more challenging cases in the morning group, which is commonly done in many hospitals. The authors supported their findings by performing ex-vivo experiments where the cardiomyocytes taken from the afternoon group recovered contraction better after the hypoxia-reoxygenation injury than the morning group. However, these findings and experimental data do not necessarily rule out the potential influence of other factors. Although the authors controlled for baseline factors via propensity score matching, there could be residual confounding factors that were not accounted for. Major reports after this initial one could not reproduce the significantly better outcome in the afternoon group (Götte et al., 2020; Kenney et al., 2020; Michaud et al., 2021; Nemeth et al., 2021). In a study with only non-urgent isolated AVR cases where the study design was very similar to the original study with a greater patient number, the afternoon group did not have favorable clinical outcomes, including in-hospital mortality, death, AMI, and heart failure 500 days of follow-up (Götte et al., 2020). In fact, the afternoon group had slightly elevated troponin levels, which is contrary to the previous study. Similarly, in two other studies where the non-urgent cases of AVR with or without CABG surgery were included, there was no significant change in mortality and major adverse cardiac events between the morning and afternoon groups (Kenney et al., 2020; Michaud et al., 2021). A similar finding was reported from a study that contained both urgent and non-urgent isolated AVR cases (Nemeth et al., 2021). In summary, the initial report for AVR demonstrated that patients who received AVR surgery in the afternoon had better clinical outcomes, but multiple reports after this one could not reproduce this finding even with a similar study design and a larger cohort size (Table 4). Given the common practice of performing challenging cases of cardiac surgery in the morning group, we cannot conclude that circadian rhythm may play a pivotal role at least in AVR surgery through ischemia-

**Table 4. Summary of Major Clinical Studies exploring the Association between Operation Time for AVR and Clinical Outcomes.**

| Author / Year | Exposure | Population | Outcome | Adjusted for Urgency | Associated with Mortality |
|---|---|---|---|---|---|
| Montaigne 2018 | Isolated AVR AM/PM | - 596 patients<br>- 2009 - 2015<br>- Single center<br>- France | 1. Lower incidence of major adverse cardiac events (cardiovascular death, MI, and acute heart failure) in the afternoon group (HR 0.50, 95% CI 0.32-0.77, p=0.0021)<br><br>2. Lower peri-operative cardiac troponin T in the afternoon group (Ratio of Geometric Means = 0.79, 95% CI 0.68-0.93, p=0.0045) | No | Associated with major adverse effects |
| Gotte 2020 | Isolated AVR AM/PM (non-urgent) | - 2,720 patients<br>- 2009 – 2016<br>- Single center<br>- Germany | 1. No difference in risk of in-hospital mortality, death, MI, heart failure (up to 500 days)<br><br>2. Slight increase in post-operative troponin in the afternoon group. | Yes, including only non-urgent cases | No |
| Nemeth 2021 | Isolated AVR AM/PM | - 4,237 AVR<br>- 2008 - 2018<br>- multi-institutional<br>- USA | 1. No difference in mortality, stroke, prolonged ventilation, renal failure, deep sternal wound infection, reoperation, MI, atrial fibrillation, or readmission. | No | No |
| Kenney 2020 | AVR+/- CABG AM/PM (non-urgent) | - 7,148 patients<br>- 1999 – 2018<br>- Single center<br>- Denmark | 1. No difference in risk of 30-day mortality, MI, atrial fibrillation, CK-MB levels, and all-cause mortality up to 19 years. | Yes, by including only non-urgent cases | No |
| Michaud 2021 | AVR+/- CABG AM/PM (non-urgent) | - 538 patients<br>- 2012 - 2018<br>- Single center<br>- Canada | 1. No significant change in<br><br>death/MI/low cardiac output/stroke during the 30 days after surgery.<br><br>2. No difference in troponin T. | Yes, by including only non-urgent cases | No |

Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass graft; CK-MB, creatine kinase-MB; CI, confidence interval; HR, hazard ratio

reperfusion injury and recovery.

## Limitations and Future Directions

The major retrospective cohort studies mentioned in this review have been conducted in various countries in the world. As well documented in previous studies, circadian rhythm may affect physiological and pathological progression via multiple factors, including season, climate, diet, or microbiome (Nicolau et al., 1991; Dong et al., 2020; Mistry et al., 2020). Therefore, these factors should be considered for data interpretation (Figure 1).

The COVID-19 pandemic has worsened the pre-existing healthcare burdens in the world potentially negatively affecting the clinical outcomes in patients. The COVID-19 infection has been proposed to be a risk factor of cardiovascular diseases as 1) the COVID-19 may aggravate cardiovascular injuries in an acute phase or 2) patients may not seek medical help out of fear of infection, causing a significant delay in administration of urgent medical treatments (Bonow et al., 2020; Harrison et al., 2021). This tendency of avoidance for medical care could be more evident especially when there is a local surge for COVID-19 cases. Therefore, this factor needs to be considered when the clinical data spanning this period are utilized for circadian studies as the seasonal periodic pattern in clinical outcomes in this period may be affected by local COVID-19 cases, rather than biological circadian patterns.

## Conclusions

While there is an extensive amount of compelling data from basic science research on the impact of circadian rhythm on cardiovascular outcomes, and with multiple clinical studies suggesting that circadian patterns may be associated with clinical outcomes for certain cardiac interventions, the overall data are still inconclusive. There are both biological factors, such as circadian rhythm, and non-biological factors, such as healthcare workers' fatigue, limited resources, and significant delay in care confounding the picture. At present, there is still insufficient evidence that circadian rhythm affects patient outcomes in these situations. Further well-designed studies are needed to explore this relationship further.

## Conflict of interests

The author(s) declare no competing interests.

## Contributions

J.K. C.H.S., and D.J.H. designed the structure and contents of the review paper; J.K. and C.H.S. reviewed the literature and interpreted the data. J.K., C.H.S., and D.J.H wrote the manuscripts. D.J.H. supervised and provided critical review of the manuscript.

## Acknowledgements

We thank the colleagues and staff members of Duke-NUS Medical School, SingHealth, National Heart Centre Singapore, and National University Hospital for their tremendous help on this project.

## Sources of Funding

CHS was supported by the National University of Singapore Yong Loo Lin School of Medicine's Junior Academic Faculty Scheme.

DJH was supported by the Duke-National University of Singapore Medical School, Singapore Ministry of Health's National Medical Research Council under its Clinician Scientist-Senior Investigator scheme (NMRC/CSA-SI/0011/2017) and Collaborative Centre Grant scheme (NMRC/CGAug16C006). This article is based upon work from COST Action EU-CARDIOPROTECTION CA16225 supported by COST (European Cooperation in Science and Technology).

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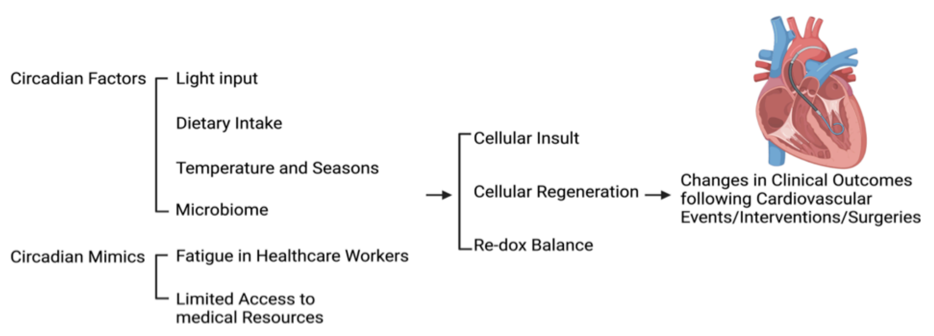


Figure 1. Potential circadian factors and mimics that affect cardiovascular clinical outcomes. Potential circadian factors and mimics, such as light input, dietary intake, temperature, microbiome, fatigue in healthcare workers, and limited access to medical resources, can affect the biological responses of the heart leading to changes in clinical outcomes following cardiac events, surgeries, and interventions.

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