REVIEW ARTICLE | OPEN ACCESS

Time to exercise: Circadian regulation of cardiac preconditioning

Graham R. McGinnis[1], John C. Quindry[2,3]

Myocardial ischemia reperfusion injury remains a significant health concern worldwide. The pursuit of therapeutic interventions to reduce the severity of ischemia reperfusion (IR) injury by preconditioning the heart has been ongoing for decades, and through preclinical studies the approach broadly includes three methodological categories; ischemic, pharmacological, and exercise preconditioning. These efforts have yielded many exciting experimental candidates, which have largely been unsuccessfully translated into clinical practice. One potential hurdle in clinical translation and efficacy of myocardial preconditioning may involve the circadian rhythm (i.e. – the ~24 hour recurring cycles in physiological processes), and the experimental or clinical timing of interventions designed to improve cardiac outcomes. Circadian rhythms are regulated by the direct influence of environmental input (light, food, activity), as well as the cell autonomous transcriptional mechanism known as the circadian clock. While circadian rhythms (and their disruption) are implicated in various cardiovascular disease states and IR-injury (with increased incidence and severity in the early morning), more recent attention has been directed toward the circadian regulation of myocardial preconditioning. Indeed, intact circadian rhythms, which are modulated by physical activity, are a cornerstone of health. As such, exercise may play an important role as a cardioprotective, and chronoprotective intervention. However, the circadian timing of interventions eliciting cardioprotection has not been explored. Thus, it is the purpose of this novel review to highlight cardioprotective mechanisms that are directly and indirectly controlled or influenced by the circadian rhythm, concluding with the perspective that preconditioning the heart may be optimally timed based on the circadian rhythm for maximal efficacy.

Keywords: cardioprotection; chronoprotection

1. Introduction

Cardiovascular disease (CVD) is, and has been, the uninterrupted leading cause of death in the United States since the middle of the 20th century (Center for Disease Control). Within the scope of CVD, ischemic heart disease (primarily manifesting as myocardial ischemia-reperfusion injury; IR-injury), represents a significant burden, comprising nearly fifty percent of CVD-related deaths. The extent of IR-injury occurs in a dose-dependent manner, where injury is greater following increasing duration of ischemia prior to reperfusion. Thus, prompt reperfusion is essential for preservation of myocardial function and survival. In the case that reperfusion therapies are successfully deployed (thrombolytic infusion, angioplasty, etc), the restoration of blood flow is accompanied by a secondary reperfusion injury, creating the cumulative insult of IR-injury. Myocardial IR-injury occurs in evolutionary fashion through three phases that accumulate in a time-dependent manner (as reviewed in Powers et al., 2007). At the onset of ischemia,

the supply-demand mismatch rapidly produces a series of potentially lethal ventricular arrhythmias (0-5 minutes) (Miller et al., 2012). In the absence of immediate reperfusion, the pathological progression devolves to left ventricular pump dysfunction and myocardial stunning (5-20 minutes) (Bolli and Marban, 1999). Finally, unremitting ischemia eventually results in myocardial infarction (MI) (>20 minutes) through a combination of apoptotic and necrotic cell death processes (Powers et al., 2008; Quindry et al., 2010; Quindry et al., 2012; McGinnis et al., 2015; Miller et al., 2015).

From a cellular perspective, the biological underpinnings of ischemic tissue death are well described and the reader is directed to several well-articulated reviews on the topic (Kloner and Jennings, 2001a, 2001b; Bolli et al., 2004; McCully et al., 2004; Gross and Auchampach, 2007; Buja and Weerasinghe, 2010; Vetterlein et al., 2003). In brief, the initiating events central to IR-injury include, but are not limited to, free-radical production/oxidative stress, calcium overload,

[1]University of Nevada, Las Vegas. Las Vegas, NV. School of Integrated Health Sciences. [2]University of Montana. Missoula, MT. School of Integrative Physiology and Athletic Training. [3]International Heart Institute, St. Patrick's Hospital. Missoula, MT.

Correspondence should be addressed to Graham R. McGinnis (graham.mcginnis@unlv.edu).

a drop in cellular pH and metabolic substrate shift towards anaerobic fuels, activation of apoptosis, and the opening of the mitochondrial permeability transition pore (mPTP). Relevant to the current review, the foundational mechanisms of IR-injury are also subject to circadian influence. With respect to the aforementioned mechanisms, links have been established for autophagy, apoptosis, and necrosis (Rabinovich-Nikitin et al., 2019).

Circadian rhythms in myocardial autophagy been appreciated since the 1980's (Pfeifer and Strauss, 1981), where autophagic vacuoles appear to peak in the resting phase. In the years since, mechanistic connections between autophagic signaling (microtubule-associated proteins 1A/1B light chain 3B (LC3), p62, etc) and flux (measured in the presence of inhibitors) to the circadian clock have been made (Ma et al., 2011), which may contribute to rhythms in IR tolerance (Rotter and Rothermel, 2012). Several studies have established circadian regulation of cardiac mammalian target of rapamycin (mTOR)/ adenosine monophosphate-activated protein kinase (AMPK) balance, which serve as the proverbial brake/gas pedal for autophagy induction (Khapre et al., 2014; McGinnis et al., 2017). Mechanistic studies in other metabolically active peripheral tissues have found that Rev-erbα is both necessary and sufficient for skeletal muscle autophagy (Woldt et al., 2013), while Period 2 (Per2) inhibits hepatic mTOR complex formation, and increases autophagy (Wu et al., 2019).

Evidence also exists for circadian regulation of apoptosis in the heart. A large scale screening of putative p53 activators identified the core clock component, brain and muscle arnt-like 1 (Bmal1) as a candidate that actively binds to transcriptional promotor sites regulating p53 (Mullenders et al., 2009), a key regulator of apoptosis signaling. Additionally, Bmal1 was recently found to control cardiomyocyte Bcl-2/adenovirus E1B 19-kD interacting protein (Bnip3), a key regulator of mitochondrial dynamics (Li et al., 2020). As such, deletion of Bmal1 was associated with reduced Bnip3 expression, leading to decreased mitochondrial fission and mitophagy, and increased apoptosis, Ca^{2+} dysregulation, and cardiac dysfunction (Li et al., 2020). This represents transcriptional circadian control of apoptosis.

Based on this collective understanding, there is a growing body of knowledge to indicate mediators of IR-mediated injury and death are under circadian control, and loss of circadian control is central to post-infarct clinical outcomes. Thus, the scientific process of uncovering novel countermeasures to IR-injury should be holistically mindful of proper circadian control. This is particularly applicable to the appropriate design of experiments taking circadian biology into consideration. For example, nocturnal rodents are active during the dark cycle, but acute exercise interventions are commonly performed during work hours (which, unless mice are housed on reverse light/ dark cycles means exercising in the middle of the sleep phase). Savvy readers of the conditioning/preconditioning literature should be aware that, more often than not, scientific reporting of the chronobiological considerations in experimental design goes completely unreported. In these instances, the reader then remains uncertain of whether circadian influences are optimized or confounding to the key dependent outcomes being examined. Further considerations of circadian control are forthcoming.

In addition to considerations of circadian control, and in the context of exercise preconditioning research, even if exercise intervention is appropriately timed, it may not be carried out under dim red light conditions or in darkness, thus imposing a bright light stimulus in the middle of the dark phase (light is an extremely potent zeitgeber, which can shift circadian rhythms) (Morin and Studholme, 2014). This technical shortcoming is of course not restricted to the field of exercise, but also extends to pharmacology studies, as a recent study reported that 50 of the top 100 prescribed drugs in the US have a target that displays a circadian rhythm in at least one tissue (Zhang et al., 2014), yet the timing of prescription is rarely, if ever, considered. Within the experimental paradigm of exercise and the cardioprotected phenotype, there is a burgeoning body of work to suggest that the now established subfield of exercise cardiac preconditioning may be influenced by circadian biology in ways that have not been understood previously. For the purposes of this review, we will briefly overview the foundational concepts of cardiac preconditioning, cellular-level circadian control, circadian links to a cardioprotected phenotype, and chrono-exercise mechanisms.

Cardiac Preconditioning – Protecting the heart against IR-injury holds great potential for alleviating the significant burden presented by IR-injury. Historic understanding of cardiac preconditioning has centered upon beneficial adaptations to cardiac anatomy and architecture such as optimizing myocardial vascularization, chamber size, and transmural wall thickness, which take place over prolonged periods of training. Important as these structural adaptations are, they don't attend to a wealth of understanding, which clearly demonstrates that the biochemistry of the myocardium can be acutely modified by a variety of stressors to produce a robustly protected phenotype (Hoshida et al., 2002).

While indirect evidence of biochemical cardioprotection extends back to the 1970s (Paffenbarger et al., 1970), the first direct evidence stems from an investigation of what is now called *ischemic preconditioning* (IPC) (Murry et al., 1986). In this now classic publication, Murry and colleagues employed a surgical model of regional ischemia (left anterior descending artery (LAD) of anesthetized dogs) to demonstrate that the myocardium could be largely spared when an experimental infarction was preempted by a series of short duration (4 x 5 minutes ischemia, separated by 5 minutes reperfusion) sub-lethal ischemic bouts (Murry et al., 1986). Importantly, no damage to the heart is induced by these preemptive short bouts of preconditioning ischemia (Reimer et al., 1986). Because the surgery to induce the short duration ischemic bouts preceded the extended duration, and clinically relevant infarct challenge 40 minutes later, it was apparent that IPC was biochemical in nature. Indeed, in the years since this foundational investigation, it has been revealed that IPC evokes acute allosteric changes and up-regulation in a concert of mediators that prevent the collective pathology of IR insults (Yellon and Downey, 2003). This protection extends to all major forms of IR-injury including reactive oxygen species (ROS), calcium (Ca^{2+}) overload, and cellular perturbations leading to cell death (Bolli, 2007; Sprick et al., 2019). Importantly, from Murry's first observation of IPC in 1986, it took only a matter of years to demonstrate that the phenomenon encompasses comprehensive protection against the core mediators of ischemic injury. From this point the race was on to identify the mechanism(s) responsible for IPC in an attempt to reverse engineer a druggable solution to MI (Bolli et al., 2004).

Is circadian biology the missing link in the translation of cardiac preconditioning research? Unfortunately, these pioneering findings in the subfield of IPC have not resulted in successful clinical translation. Indeed, although preliminary results from preclinical trials have offered promise, confirmation of these findings into humans remains problematic. The barriers to progress include a host of independent factors. While delineation of these scientific sticking points is beyond the scope of the current manuscript, there is a rationale to believe that deleterious alterations to circadian biology may be among the mitigating factors that has not been fully considered to date (Heusch, 2017; Montaigne and Staels, 2018). In contrast to
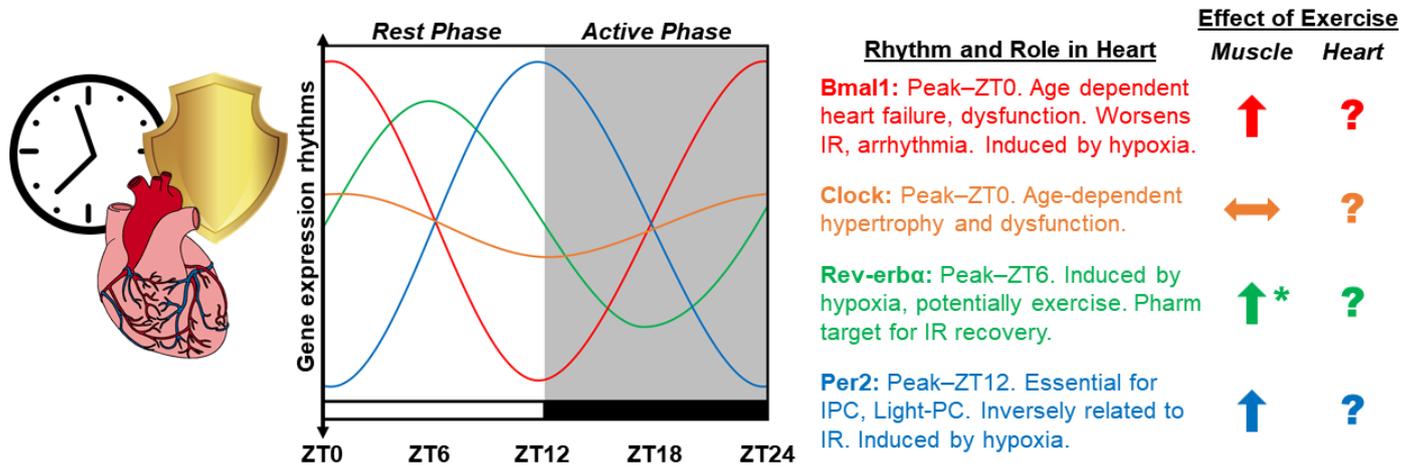
Figure 1. Diagram depicting the proposed integration of chronobiology and exercise-induced cardioprotection. Graphic representation of circadian rhythms in the mRNA expression of core clock genes *CLOCK, BMAL1, PER2, REV-ERBα*, in the mouse heart over the 24-hour light dark cycle. Established roles for clock genes in the heart based on whole body and cardiomyocyte specific deletion models, as well as extrapolation from relevant studies in skeletal muscle. Additionally, the role of exercise as a means to induce the expression of clock genes is summarized in skeletal muscle and the heart. The amplitude of animated lines is based on published observations of clock gene expression. ↑ Induced by exercise, ↔ No change, ? Unknown influence of exercise, * effects of exercise only at ZT22.

these dead ends in preconditioning research, there is a parallel rationale to believe that exercise, being cardioprotective in nature, may partially exert its effects through a restoration of, or optimization in, circadian control within the heart (i.e. – chronoprotection). In order to advance these parallel rationales, we will discuss exercise preconditioning as a prelude to a review of chronobiology related to cardioprotection against IR-injury.

Exercise preconditioning of the heart against an ischemic insult - In order to advance the foundational postulate of this review paper, that cardiac preconditioning via exercise includes the essential influence of circadian control mechanisms, it is important to reflect on the key descriptive and mechanistic observations of exercise-induced cardioprotection against an ischemic insult. Because these details are briefly addressed in this manuscript, the reader is directed to several authoritative reviews by several prominent groups (Starnes and Taylor, 2007; Quindry and Hamilton, 2013; Powers et al., 2014; Powers, 2017; Quindry and Franklin, 2018; Chowdhury et al., 2019).

The early descriptive observations indicate that exercise-induced cardioprotection, primarily examined using rodent models (rats and mice) of surgical ligation of the LAD, prevents and/or mitigates all major forms of ischemic injury. Specifically, exercise prevents the severity and frequency of several lethal forms of ventricular ectopy, during both ischemia and reperfusion (Hamilton et al., 2004; Quindry et al., 2010; Quindry et al., 2012; Frasier et al., 2013; Miller et al., 2015; Alleman et al., 2016). Just as important, ventricular pump dysfunction associated with an acute ischemic insult are also largely prevented by exercise training (note that some of these observations are derived from isolated perfused heart preparations using global ischemia, but are confirmed by LAD ligation models) (Bowles & Starnes, 1994; Taylor et al., 1999; Demirel et al., 2001; Quindry et al., 2005; French et al., 2006; Taylor et al., 2007; French et al., 2008). Finally, an exercise regimen prevents myocardial tissue death by both frank necrosis (Yamashita et al., 1999; Quindry et al., 2007; McGinnis et al., 2015; Miller et al., 2015) and apoptosis (Quindry et al., 2005; Quindry et al., 2007; Quindry et al., 2012; McGinnis et al., 2015).

Central to these observations of potent cardioprotection against all the major forms of ischemic pathology, the dose of exercise used to precondition the heart is just a few days.

Indeed, between 1-3 days of moderate intensity treadmill exercise in rats and mice underpin the cardioprotective outcomes mentioned above (Demirel et al., 2001; McGinnis et al., 2015). Relative to the question of dose, cross-study comparisons indicate that longer duration exercise programs (weeks to months) are no more protective than a few days of exercise (Demirel et al., 1998; Demirel et al., 2001; Lennon et al., 2004a). Just as interestingly, high intensity exercise (~75% VO$_2$max) is no more protective than moderate intensities (~50% VO$_2$max) (Lennon et al., 2004b), though there are indications that high intensity exercise may have added benefits (Esposito et al., 2011).

Of importance to the current discussion, the exercise-protected phenotype appears to be heavily reliant upon acute modulation of biochemical factors local to the myocardium. Once introduced, the exercise stimulus appears to evoke a cardioprotected phenotype for at least 9 days (Lennon et al., 2004a). This important observation contrasts with the less robust time frame (3-4 days) associated with non-exercise approaches to cardioprotection (Kuzuya et al., 1993; Guo et al., 1998; Yellon and Downey, 2003). While still debated, observational differences between exercise and non-exercise forms of preconditioning may infer that the various methodologies protect the heart through divergent mechanisms (Frasier et al, 2011; Quindry and Hamilton, 2013). Moreover, that moderate and high intensity exercise is equally protective suggests that from the perspective of the exercised myocardium, the stimulus is threshold-independent. Indeed, within circadian biology, the phase-shifting capacity of exercise as a zeitgeber is similarly threshold-independent, and vigorous physical activity was no more effective than moderate intensity exercise (Buxton et al., 1997).

As a final consideration of exercise preconditioning, a number of mechanisms appear to be responsible for the exercised phenotype. Early observations confirmed that exercise improves Ca^{2+} control during ischemia and reperfusion (Bowles and Starnes, 1994; French et al., 2006; Starnes et al., 2007). Accordingly, and despite the supply-demand mismatch of an ischemic challenge, bioenergetic control is better supported in the exercised heart (Bowles and Starnes, 1994; Kavazis et al., 2014; Alleman et al., 2016). Related to the above mechanisms, the mitochondrial isoform of superoxide dismutase is upregulated in the exercised heart and appears to be essential to prevent ventricular dysrhythmias and necrotic tissue death in

the exercised heart (Hamilton et al., 2004; French et al., 2008). How improvements in mitochondrial control are facilitated is not fully understood, but improvement in K_{ATP} channels on the sarcolemma and mitochondrial membranes are likely contributors (Brown et al., 2005; Chicco et al., 2007; Quindry et al., 2010; Quindry et al., 2012). Finally, several preliminary instances of receptor-mediated protection have been observed in the exercised hearts. To date, the delta opioid receptor and interleukin-6 (IL-6) mediated cardioprotection has been observed (Dickson et al., 2008; McGinnis et al., 2015; Miller et al., 2015). In summation, exercise evokes a robustly protective phenotype against ischemic injury and death. As will be discussed shortly, many of the mechanisms of exercise-induced cardioprotection also have chronobiological underpinnings. First, however, it is important to provide an overview of the foundational mechanisms of circadian rhythm as they pertain to both ischemic injury and cardioprotection.

Diurnal/Circadian Rhythms in physiology, circadian clock, and rhythms in the heart – Numerous behavioral, cellular, and metabolic processes have evolved to maximize the integration of physiology with the recurring cycles of light and dark in our environment, and compose our circadian rhythm. These rhythms are driven by extrinsic factors (i.e. - exposure to light, intake of nutrients, and activity), as well as intrinsic mechanisms (i.e. – the molecular circadian clock), and are present in almost all forms of life on earth (Roenneberg and Merrow, 2005). The molecular circadian clock, which has been identified in essentially every tissue studied to date, is composed primarily of a core heterodimer of the transcription factors circadian locomotor output cycles kaput (Clock) and Bmal1, which bind to conserved E-box domains in the promotor regions of clock-controlled genes (CCG's) (Hogenesch et al., 1998). While variability exists between tissues, it is estimated that between 10-15% of the cardiac transcriptome oscillates with a circadian rhythm (Storch et al., 2002; Martino et al., 2004), which is ameliorated by cardiomyocyte specific deletion of the Clock (Bray et al., 2008) or Bmal1 (Young et al., 2014). Among CCG's are the negative regulators of the clock mechanism, Period (Per1/2/3), Cryptochrome (Cry1/2), and Rev-erbα, which feed back to either inhibit the heterodimerization of Clock/Bmal1 or inhibit the expression of Bmal1, respectively, in effect 'turning off' the clock. Circadian rhythms in the heart have been shown to display significant control of cardiac physiology (signaling, metabolism, and function) and is reciprocally linked to pathophysiology (i.e. – circadian rhythm disruption leads to CVD, and cardiometabolic diseases disrupt cardiac circadian rhythms) (Young et al., 2001; Young et al., 2002; Kung et al., 2007; Martino and Young, 2015; Crnko et al., 2019; Zhang et al., 2019; Rana et al., 2020).

It is now well appreciated that the time of day and circadian rhythms has a marked effect on the incidence and severity of MI (Muller et al., 1985; Mistry et al., 2017). Several large studies, old and new, have consistently shown that there is a morning peak in MI. This pattern (Muller et al., 1985) and a review of the precipitating factors (morning surge in blood pressure, coagulation, etc.) (Muller 1989; Muller et al., 1989) was originally revealed by Muller et al (1989) in the 1980's. In the 30 plus years following, numerous prospective and retrospective observations have supported these original claims (Suarez-Barrientos et al., 2011; Mogabgab et al., 2012; Bulluck et al., 2017; Mistry et al., 2017). While many factors are involved, one key mechanism is the diurnal rhythm in plasminogen activator inhibitor 1 (PAI-1) activity, which shows increased activity in the morning hours for healthy individuals and those with a history of MI (Angleton et al., 1989), indicating increased coagulability of blood in the morning. PAI-1 expression was subsequently shown to be under direct circadian control, as its expression is induced by the binding of Clock:Bmal1 to its transcriptional promoter sites (Schoenhard et al., 2003). Thus, the body is biologically primed for clotting in the morning, creating a temporal window when thrombi are more likely to form.

The contribution of the molecular circadian clock on cardiovascular function has been elucidated mechanistically via global and cardiomyocyte specific deletion of core clock genes including clock (Bray et al., 2008; Durgan et al., 2010; Durgan et al., 2011; Podobed et al., 2014; Alibhai et al., 2017) bmal1 (Lefta et al., 2012; Kohsaka et al., 2014; Young et al., 2014; Ingle et al., 2015; He et al., 2016; McGinnis et al., 2017), and per2 (Eckle et al., 2012; Bonney et al., 2013; Virag et al., 2013; Bartman et al., 2017). The subsequent section will discuss the interplay between circadian rhythms, the molecular clock components, and myocardial IR-injury, with specific reference to the potential for preconditioning with exercise or IPC (See Figure 1).

Circadian clock and cardioprotection –

Clock: Clock is a core component of the transcriptional heterodimer in the positive arm of the molecular circadian clock, and binds with Bmal1 to induce transcription of CCG's. The amplitude of clock gene expression is not as robust as other molecular components of the clock in wild-type (WT) mice, presenting less than 2 fold oscillations in gene expression (peak ~Zeitgeber Time (ZT)-0) (Young et al., 2002; Young et al., 2014; Alibhai et al., 2017). The role of Clock in the heart has been investigated mechanistically using Clock$^{\Delta19/\Delta19}$ mice, overexpressing a loss of function mutated *clock* gene (Durgan et al., 2010; Alibhai et al., 2017; Alibhai et al., 2018). These mice display cardiac hypertrophy and alterations in metabolism, transitioning to dilation and failure with age (Bray et al., 2008; Durgan et al., 2011; Alibhai et al., 2017). Using a closed-chest model of IR, it was found that IR-injury severity displays a robust rhythm in WT mice that was absent in Clock$^{\Delta19/\Delta19}$ mice, which was similar at all times of the day, corresponding to ZT0 in WT hearts (Durgan et al., 2010). Others have shown that whole body Clock$^{\Delta19/\Delta19}$ has worsened cardiac outcomes in response to aging, as well as permanent coronary artery ligation (Alibhai et al., 2017).

The role of Clock in the heart in the context of IPC and exercise preconditioning has not been investigated. It is worth noting that in a recent study examining the time-of-day dependent regulation of gene expression in *skeletal* muscle found that moderate intensity exercise had no effect on Clock mRNA levels, whether it was performed in the early or late portion of the dark phase (Ezagouri et al., 2019). Whether the same is true in the heart is currently not known.

Bmal1: Bmal1 is a core component of the positive arm of the circadian clock, which interacts with its binding partner, Clock, as a heterodimeric transcription factor initiating transcription of CCG's. *Bmal1* mRNA expression peaks at ZT0 (lights on) in mouse hearts, displaying a high amplitude rhythm (up to >15-fold) (Schroder et al., 2013; Rotter et al., 2014; Young et al., 2014; Zhang et al., 2015; Alibhai et al., 2017). Global germline deletion of Bmal1 results in an accelerated aging phenotype with reduced lifespan, associated with reduced activity levels and cardiovascular pathology (Kondratov et al., 2006; Kondratov et al., 2009; Lefta et al., 2012), though some effects are attributable to developmental, and not recapitulated in adult deletion (Yang et al., 2016). Cardiomyocyte specific deletion of Bmal1 similarly reduces lifespan and tolerance to hypertrophic stimuli and stress (Durgan et al., 2011; Young et al., 2014; Ingle et al., 2015; McGinnis et al., 2017) and increases cardiac arrhythmias (Schroder et al., 2013). At the cellular level, Bmal1 regulates the hypoxia-induced activation of hypoxia-inducible

factor (HIF)-1α in C212 cells (Peek et al., 2017), suggesting its importance for adaptation to hypoxia/ischemia. Pathological aspects of Bmal1 loss have been rescued with antioxidants (Kondratov et al., 2009), and rapamycin supplementation (Khapre et al., 2014; McGinnis et al., 2017) (both of which are exercise mimetics), while the laudatory effects of exercise have not yet been investigated. Though exercise has been shown to have a modest impact on Bmal1 expression in skeletal muscle (Zambon et al., 2003), the effects appear to be time-of-day independent (Ezagouri et al., 2019), and the effects of exercise on the physiological and pathological cardiac-related outcomes have not been investigated in a bmal1-dependent manner.

Per2: The period proteins (Per1/2/3) are components of the negative arm of the circadian clock and feedback to prevent the heterodimerization of clock and bmal1, thereby reducing their ability to initiate transcription of clock genes. *Per2* mRNA expression oscillates with a peak in expression at ZT12 (lights off) in mouse hearts, antiphase with *bmal1* (Young et al., 2014). Several studies have shown that Per2 plays an important role in myocardial IR-injury and is necessary for IPC (Eckle et al., 2012; Bonney et al., 2013; Bartman et al., 2017; Oyama et al., 2018; Oyama et al., 2019). Per2$^{-/-}$ mice were shown to have larger infarct sizes compared to control littermates, suggesting Per2 is essential for myocardial adaptation to and recovery from ischemia. A series of elegant studies showed that in response to ischemia, myocardial adenosine signaling through the adenosine receptor 2b (Adora2b) induces a strong upregulation and stabilization of Per2 in the heart. Ischemic preconditioning activated strongly Adora2b signaling and Per2 expression, leading to a reduction of IR-injury, which was lost in Adora2b$^{-/-}$ and Per2$^{-/-}$ mice. Furthermore, treatment of mice with an Adora2b agonist (BAY 60-6583), reduced IR-injury in a Per2 dependent manner. Per2 dependent cardioprotection allowed for metabolic flexibility in the heart, increasing anaerobic glycolysis and lactate consumption during ischemia, when aerobic metabolism is limited (Eckle et al., 2012). Interestingly, consistent with Per2 being a core clock component with input from the sun/light, exposure to intense light (>10,000 lux, equivalent to sunlight) induced the expression of myocardial Per2 in a time-dependent manner (Eckle et al., 2012), which was absent in mice lacking the ability to perceive light (Oyama et al., 2019). The light-induced Per2 expression was associated with a strongly protected phenotype, which was absent in Per2$^{-/-}$ mice (Eckle et al., 2012). Additionally, intense light was shown to induce the expression of micro-RNA (miR)-21 in a Per2 dependent manner, inducing cardioprotected phenotype in mice that was abolished in miR-21$^{-/-}$ mice (Bartman et al., 2017). While numerous studies support the notion that myocardial Per2 is important for myocardial preconditioning, one contradictory study found that Per2$^{-/-}$ mice were protected against IR-injury, showing *lower rates* of cardiac apoptosis and infarction (Virag et al., 2013). This discrepancy could be the result of differing experimental models of IR or timing of surgery. Regardless of the exact combination of confounding factors, these uncertainties reinforce the underpinning premise that dynamic interplay between chronobiology to physiologic challenges have the potential to influence study outcomes in unpredictable ways. Collectively, these findings strongly implicate Per2 as a critical mediator of IPC and intense light-mediated preconditioning, with strong potential for pharmacological targeting.

While similar and divergent pathways exist between different mechanisms of preconditioning, the role of Per2 in exercise preconditioning has not been investigated. As previously described, acute exercise (1-3 days) elicits equal or greater protection against IR-injury compared to IPC and pharmacological methods. Exercise training has the capability to *shift* the circadian rhythm of Per2 expression in

several peripheral tissues, including skeletal muscle (Sasaki et al., 2016), though the heart was not investigated. A recent investigation on the time-of-day dependent effects of acute exercise in skeletal muscle found that exercise increases the expression of Per2 to a similar extent (~1.5-2 fold) regardless of when it is performed, though the levels of Per2 are still strongly effected by time-of-day independent of exercise (>10 fold) (Ezagouri et al., 2019). A thorough investigation of the acute effects of exercise on *myocardial* Per2 expression is lacking, so the contribution of Per2 to exercise-induced preconditioning is currently unknown.

Rev-erbα: Rev-erbα (nr1d1) is a nuclear receptor in the negative arm of the circadian clock, which serves as a transcriptional repressor, specifically inhibiting *Bmal1* expression. *Rev-erbα* mRNA expression peaks during the light phase (~ZT6) in mouse hearts (Young et al., 2014; Alibhai et al., 2017). Several studies have shown a role for Rev-erbα on myocardial IR-injury severity (Stujanna et al., 2017; Zhang et al., 2017; Reitz et al., 2019). These findings suggest that pharmacologically targeting Rev-erbα is sufficient to reduce inflammation, apoptosis, as well as dilation and heart failure following IR or transverse aortic constriction (TAC). However, these studies have all been conducted in the post-IR period. Thus, the role for Rev-erbα in cardiac preconditioning remains unknown.

Interestingly, recent clinical observations on the diurnal rhythm in subacute cardiovascular complications following surgery involving cross-clamping (inducing a predictable period of ischemia) found that morning operations were associated with greater risk/injury. Transcriptomic analysis revealed that Rev-erbα is higher in the morning (when risk was *higher*) vs evening samples, suggesting a *negative* role for Rev-erbα in the time-dependent susceptibility to ischemic stress. Mechanistic studies using *ex vivo* Langendorff perfused hearts confirmed that genetic (Rev-verbα$^{-/-}$ hearts) and pharmacologic (SR8278, a Rev-erbα antagonist) inhibition of Rev-erbα protected hearts from ischemic damage (Montaigne et al., 2018).

Several studies have also explored the role for Rev-erbα in skeletal muscle (which may be reflective of its role in the heart) (Woldt et al., 2013), as well as the immune system (Sato et al., 2014). Rev-erbα plays an important role in the regulation of skeletal muscle metabolism and autophagy (Woldt et al., 2013), as well as muscle mass (Mayeuf-Louchart et al., 2017), both of which are implicated in IR-injury and cardioprotection. Deletion of Rev-erbα in muscle leads to mitochondrial dysfunction and pronounced changes in muscle mass, morphology, reduced exercise capacity (Woldt et al., 2013; Mayeuf-Louchart et al., 2017), while overexpression or pharmacological agonism had the opposite effect (i.e. increasing exercise capacity and mitochondrial content) (Woldt et al., 2013), suggesting activation of Rev-erbα could be beneficial in the heart.

The ability for IPC or exercise to acutely induce the expression of Rev-erbα has not been conclusively shown, although a scientifically plausible rationale exists. Hypoxia (Adamovich et al., 2017) and exercise (Zambon et al., 2003; Ezagouri et al., 2019) were shown to modestly increase Rev-erbα expression in skeletal muscle, but neither has been tested in the heart, or in the context of preconditioning. Interestingly, Ezaguori et al. (2019) showed that exercise performed at ZT22 (late in the active period) increased Rev-erbα expression, while exercise at ZT14 (early in the active period) had no effect, suggesting exercise timing to induce Rev-erbα can be optimized. Pharmacological activation of Rev-erbα has been achieved with several ligands, of which SR9009 has received considerable attention. While several studies demonstrate that the benefits of SR9009 are dependent on Rev-erbα, it was recently shown that SR9009 also has Rev-erb-independent

effects (Dierickx et al., 2019). Thus, the benefits of this compound may not be dependent on the circadian rhythm. Time-dependent administration of SR9009 (to mimic the *in vivo* rhythm of Rev-erbα expression), has important implications for chronopharmacological cardioprotection.

Chrono-Exercise and mechanisms of cardioprotection – Time-of-day dependent regulation of exercise performance and adaptation is an area of increasing interest, as it holds great potential for human performance and athletics, as well as precision exercise prescription for health. While it is well appreciated that diurnal and nocturnal animals significantly consolidate their habitual activity to a single phase of their circadian rhythm, several recent excellent studies have highlighted that, within the respective active phases, there are distinct time-of-day dependent differences in both acute exercise responses and training induced adaptations (Dalbram et al., 2019; Ezagouri et al., 2019; Sato et al., 2019). A thorough appreciation of interaction between exercise physiology and the circadian rhythm may accelerate mechanistic underpinnings of the laudatory effect of exercise, and optimize exercise interventions to maximize their efficacy. This section will focus on the concept of 'chrono-exercise,' based on the tenet that exercise timing augments activation of protective pathways.

Reciprocal regulation exists between exercise and the circadian rhythm, as there are appreciable time-of-day dependent rhythms in exercise performance (peaking in the afternoon in humans), and exercise serves to synchronize or phase shift the circadian clock in peripheral tissues (Gabriel and Zierath, 2019; Wolff and Esser, 2019). Forced and voluntary exercise in the early night or late night can significantly phase shift the rhythms in cardiovascular function and clock gene expression in several peripheral tissue (Wolff and Esser, 2012; Sasaki et al., 2016), although subsequent investigation revealed that the effects in the heart were modest (Schroeder et al., 2012). These molecular insights have metabolically meaningful impact, as time-restricted exercise in the late active period prevented high fat diet induced obesity, while exercise in the early active period exercise did not (Dalbram et al., 2019).

While the topic of chrono-exercise has been relatively understudied in the cardiovascular system, two recent excellent studies sought to elucidate the mechanistic underpinnings of chrono-exercise in skeletal muscle using state-of-the-art omics approaches (Ezagouri et al., 2019; Sato et al., 2019). These studies employed a range of exercise intensities (low, moderate, high), performed in either the early-active or late active phases (Ezagouri et al., 2019), or in the early light phase and early dark phase (Sato et al., 2019). Exercise capacity was shown to be time-of-day dependent, with high intensity exercise performance being higher at the beginning of the active period (ZT14), and low-moderate intensity exercise performance being better at the end of the active period (ZT22) (time-of-day differences in performance were abolished in Per2-/- mice) (Ezagouri et al., 2019). Interestingly, among transcripts that were influenced by exercise, only 4% were common between the two different times of exercise tested, indicating strong time-of-day dependent influence of exercise (Sato et al., 2019). Robust time-of-day dependent signatures of genomic and metabolomic exercise responses were identified, profiling a critical role for critical cardioprotective pathways.

The AMPK pathway has been implicated in exercise and pharmacological approaches to cardiac preconditioning against IR-injury (Kristiansen et al., 2009; Barr et al., 2017), and is also important for exercise training-induced protection against myocardial fibrosis (Ma et al., 2015). Exercise-induced augmentation of glycolytic myocardial metabolism during reperfusion was associated with reduction in infarction, suggesting AMPK activation is critical for the metabolic response to IR (Kristiansen et al., 2009). Indeed, exercise in the late active period resulted in a comparably stronger activation of the AMPK pathway compared to exercise in the early active period, suggesting that exercise may be more protective at this time (Ezagouri et al., 2019). Interestingly, the regulation of this time-dependent response was potentially via 5-aminoimidazole-4-carboxamide ribonucleotide (ZMP). The adenosine analog and ZMP precursor 5-aminoimidazole-4carboxamide-1β-D-ribofuranoside (AICAR) also activates cardioprotection (Kristiansen et al., 2009), but these findings raise the chronopharmacological question as to if AICAR administration could be optimally timed.

Additionally, important to the chronobiological timing of exercise to induce robust cardioprotection, a significant time-of-day dependent regulation of exercise induced HIF-1α was identified (Sato et al., 2019). HIF-1α is strongly implicated in cardiac preconditioning (Ong and Hausenloy, 2012), and IR-injury is worse in HIF-1α knockout mice (Nanayakkara et al., 2015). Furthermore, there is an inextricable link between the circadian clock mechanism and hypoxia trough HIF that has been identified in multiple tissues (Adamovich et al., 2017; Peek et al., 2017; Wu et al., 2017). These recent findings suggest that exercise more strongly induces HIF-responsive glycolytic pathways in the early active period (ZT15) compared to early rest (ZT3) (Sato et al., 2019). These data agree with previous observations that exhaustive exercise induced expression of HIF-responsive genes in skeletal muscle in a time-of-day dependent manner (Peek et al., 2017). While almost all of the studies were performed in skeletal muscle, they highlight the potential for robust circadian control of exercise-induced adaptations in the heart, which may significantly impact cardioprotection.

Lastly, one integrating component in cardioprotective interventions (exercise, IPC, and remote IPC) is the contribution of muscle-derived cytokines, or myokines. Exercise elicits production and secretion of numerous myokines that have broad impact on exercise-induced adaptations in a variety of tissues, including the heart (Pedersen, 2013; Whitham and Febbraio, 2016). Previous research has shown that IL-6 is essential for both IPC (Dawn et al., 2004), and exercise-induced cardioprotection (McGinnis et al., 2015). Interestingly, it was recently found that the circadian clock regulates the production and secretion of a number of myokines in synchronized cultured human fibroblasts. Specifically, Perrin, et al. (2015) showed a circadian rhythm in IL-6 secretion into culture media, which was abolished by *in vitro* suppression of the clock. Furthermore, human studies have shown that exercise-induced IL-6 release is higher and more sustained following exercise performed in the evening (Abedelmalek et al., 2013; Kim et al., 2015). Together, these findings present a compelling rationale that time-of-day dependent exercise prescription may be a potential strategy to maximize the cardioprotective myokine response.

Conclusions and Future Directions – Chronobiology is a burgeoning field of research with health and performance at its core. To this end, it is important to recognize the magnitude of circadian rhythm regulation of the molecular and physiological responses to exercise and ischemia. It is now critical at preclinical and clinical levels that we apply the principles of chronobiology to exercise and pharmacological interventions. Accordingly, there is reason to be hopeful that exercise induced preconditioning is intrinsically linked to circadian influences, yet the definitive investigations to support or refute this notion remained untested to date. Elucidation of time-dependent regulation of exercise-induced cardioprotection has the potential to maximize the efficacy of potent preconditioning against IR-injury and increase the likelihood of clinical translation, a goal that has been elusive for over 40 years.

References

Abedelmalek S, Chtourou H, Aloui A, Aouichaoui C, Souissi N, Tabka Z (2013) Effect of time of day and partial sleep deprivation on plasma concentrations of IL-6 during a short-term maximal performance. Eur J Appl Physiol 113:241-248. doi:10.1007/s00421-012-2432-7.

Adamovich Y, Ladeuix ., Golik M, Koeners MP, Asher G (2017) Rhythmic Oxygen Levels Reset Circadian Clocks through HIF1alpha. Cell Metabolism 25:93-101. doi:10.1016/j.cmet.2016.09.014

Alibhai FJ, LaMarre J, Reitz CJ, Tsimakouridze EV, Kroetsch JT, Bolz SS, Shulman A, Steinberg S, Burris TP, Oudit GY, Martin, TA (2017) Disrupting the key circadian regulator CLOCK leads to age-dependent cardiovascular disease. J Mol Cell Cardiol 105;24-37. doi:10.1016/j.yjmcc.2017.01.008

Alibhai FJ, Reitz CJ, Peppler WT, Basu P, Sheppard P, Choleris E, Bakovic M, Martino TA (2018) Female ClockDelta19/Delta19 mice are protected from the development of age-dependent cardiomyopathy. Cardiovasc Res 114:259-271. doi:10.1093/cvr/cvx185

Alleman RJ, Tsang AM, Ryan TE, Patteson DJ, McClung JM, Spangenburg EE, Shaikh SR, Neufer PD, Brown DA (2016) Exercise-induced protection against reperfusion arrhythmia involves stabilization of mitochondrial energetics. Am J Physiol Heart Circ Physiol 310:H1360-1370. doi:10.1152/ajpheart.00858.2015

Angleton P, Chandler WL, Schmer G (1989) Diurnal variation of tissue-type plasminogen activator and its rapid inhibitor (PAI-1). Circulation, 79(1), 101-106. doi:10.1161/01.cir.79.1.101

Barr LA, Lambert JP, Shimizu Y, Barouch LA, Naqvi N, Calvert JW (2017) Exercise training provides cardioprotection by activating and coupling endothelial nitric oxide synthase via a beta3-adrenergic receptor-AMP-activated protein kinase signaling pathway. Med Gas Res 7:1-8. doi:10.4103/2045-9912.202904

Bartman CM, Oyama Y, Brodsky K, Khailova L, Walker L, Koeppen M, Eckle T (2017) Intense light-elicited upregulation of miR-21 facilitates glycolysis and cardioprotection through Per2-dependent mechanisms. Plos One 12. doi:ARTN e017624310.1371/journal.pone.0176243

Bolli R (2007) Preconditioning: a paradigm shift in the biology of myocardial ischemia. Am J Physiol Heart Circ Physiol 292:H19-27. doi:10.1152/ajpheart.00712.2006

Bolli R, Becker L, Gross G, Mentzer R,Jr., Balshaw D, Lathrop DA, NHLBI Working Group on the Translation of Therapies for Protecting the Heart from Ischemia (2004) Myocardial protection at a crossroads: the need for translation into clinical therapy. Circ Res 95:125-134. doi:10.1161/01.RES.0000137171.97172.d7

Bolli R, Marban E (1999) Molecular and cellular mechanisms of myocardial stunning. Physiol Rev 79:609-634. doi:10.1152/physrev.1999.79.2.609

Bonney S, Kominsky D, Brodsky K, Eltzschig H, Walker L, Eckle T (2013) Cardiac Per2 functions as novel link between fatty acid metabolism and myocardial inflammation during ischemia and reperfusion injury of the heart. Plos One 8(8), e71493. doi:10.1371/journal.pone.0071493

Bowles DK, Starnes JW (1994) Exercise training improves metabolic response after ischemia in isolated working rat heart. J Appl Physiol 76:1608-1614. doi:10.1152/jappl.1994.76.4.1608

Bray MS, Shaw CA, Moore MW, Garcia RA, Zanquetta MM, Durgan DJ, Jeong WJ, Tsai JY, Bugger H, Zhang D, RohrwasserA, Rennison JH, Dyck JRB, Litwin SE, Hardin PE, Chow SW, Chandler MP, Abel ED, Young ME (2008) Disruption of the circadian clock within the cardiomyocyte influences myocardial contractile function, metabolism, and gene expression. Am J Physiol Heart Circ Physiol 294:H1036-1047. doi:10.1152/ajpheart.01291.2007

Brown DA, Chicco AJ, Jew KN, Johnson MS, Lynch JM, Watson PA, Moore RL(2005) Cardioprotection afforded by chronic exercise is mediated by the sarcolemmal, and not the mitochondrial, isoform of the KATP channel in the rat. J Physiol 569:913-924. doi:10.1113/jphysiol.2005.095729

Buja LM, Weerasinghe P (2010) Unresolved issues in myocardial reperfusion injury. Cardiovasc Pathol 19:29-35. doi:10.1016/j.carpath.2008.10.001

Bulluck H, Nicholas J, Crimi G, White S K, Ludman A J, Pica S, Raineri C, Cabrera-Fuentes HA, Yellon D, Rodriguez-Palomares J, Garcia-Dorado D, Hausenloy DJ (2017) Circadian variation in acute myocardial infarct size assessed by cardiovascular magnetic resonance in reperfused STEMI patients. Int J Cardiol 230:149-154. doi:10.1016/j.ijcard.2016.12.030

Buxton OM, Frank SA, L'Hermite-Baleriaux M, Leproult R, Turek FW, Van Cauter E (1997) Roles of intensity and duration of nocturnal exercise in causing phase delays of human circadian rhythms. Am J Physiol 273:E536-542. doi:10.1152/ajpendo.1997.273.3.E536

Chicco AJ, Johnson MS, Armstrong CJ, Lynch JM, Gardner RT, Fasen GS,Gillenwater CP, Moore RL (2007) Sex-specific and exercise-acquired cardioprotection is abolished by sarcolemmal KATP channel blockade in the rat heart. Am J Physiol Heart Circ Physiol, 292:H2432-2437. doi:10.1152/ajpheart.01301.2006

Chowdhury MA, Sholl HK, Sharrett MS, Haller ST, Cooper CC, Gupta R, Liu LC (2019) Exercise and Cardioprotection: A Natural Defense Against Lethal Myocardial Ischemia-Reperfusion Injury and Potential Guide to Cardiovascular Prophylaxis. J Cardiovasc Pharmacol Ther24:18-30. doi:10.1177/1074248418788575

Crnko S, Du Pre BC, Sluijter JPG, Van Laake LW (2019) Circadian rhythms and the molecular clock in cardiovascular biology and disease. Nat Rev Cardiol 16:437-447. doi:10.1038/s41569-019-0167-4

Dalbram E, Basse AL, Zierath JR, Treebak JT (2019) Voluntary wheel running in the late dark phase ameliorates diet-induced obesity in mice without altering insulin action. J Appl Physiol 126:993-1005. doi:10.1152/japplphysiol.00737.2018

Dawn B, Xuan YT, Guo Y, Rezazadeh A, Stein AB, Hunt G, Wu WJ, Tan W, Boll, R (2004). IL-6 plays an obligatory role in late preconditioning via JAK-STAT signaling and upregulation of iNOS and COX-2. Cardiovasc Res 64:61-71. doi:10.1016/j.cardiores.2004.05.011

Demirel HA, Powers SK, Caillaud C, Coombes JS, Naito H, Fletcher LA, Vrabas I, Jessup JV, Ji LL (1998) Exercise training reduces myocardial lipid peroxidation following short-term ischemia-reperfusion. Med Sci Sports Exerc 30:1211-1216. doi:10.1097/000057,68-199808000-00005

Demirel HA, Powers SK, Zergeroglu MA, Shanely RA, Hamilton K, Coombes J, Naito H (2001). Short-term exercise improves myocardial tolerance to in vivo ischemia-reperfusion in the rat. J Appl Physiol 91:2205-2212. doi:10.1152/jappl.2001.91.5.2205

Dickson EW, Hogrefe CP, Ludwig PS, Ackermann LW, Stoll LL, Denning GM (2008). Exercise enhances myocardial ischemic tolerance via an opioid receptor-dependent mechanism. Am J Physiol Heart Circ Physiol 294:H402-408. doi:10.1152/ajpheart.00280.2007

Dierickx P, Emmett MJ, Jiang C, Uehara K, Liu M, Adlanmerini M, Lazar MA (2019) SR9009 has REV-ERB-independent effects on cell proliferation and metabolism. Proc Natl Acad Sci 116:12147-12152. doi:10.1073/pnas.1904226116

Durgan DJ, Pulinilkunnil T, Villegas-Montoya C, Garvey ME, Frangogiannis NG, Michael LH, Chow CW, Dyck JR, Young ME (2010) Short communication: ischemia/reperfusion tolerance is time-of-day-dependent: mediation by the cardiomyocyte circadian clock. Circ Res 106:546-550. doi:10.1161/CIRCRESAHA.109.209346

Durgan DJ, Tsai JY, Grenett MH, Pat BM, Ratcliffe WF, Villegas-Montoya C, Garvey ME, Nagendran J, Dyck JRB, Bray MS, Gamble KL, Gimble JM, Young, ME (2011) Evidence suggesting that the cardiomyocyte circadian clock modulates responsiveness of the heart to hypertrophic stimuli in mice. Chronobiol Int, 28:187-203. doi:10.3109/07420528.2010.550406

Eckle T, Hartmann K, Bonney S, Reithel S, Mittelbronn M, Walker LA, Lowes BD, Han J, Borchers CH, Buttrick PM, Kominsky DJ, Colgan SP, Eltzschig HK (2012) Adora2b-elicited Per2 stabilization promotes a HIF-dependent metabolic switch crucial for myocardial adaptation to ischemia. Nature Medicine 18:774-U173. doi:10.1038/nm.2728

Esposito F, Ronchi R, Milano G, Margonato V, Di Tullio S, Marini M, Veicsteinas A, Samaja M (2011) Myocardial tolerance to ischemia-reperfusion injury, training intensity and cessation. Eur J Appl Physiol 111:859-868. doi:10.1007/s00421-010-1707-0

Ezagouri S, Zwighaft Z, Sobel J, Baillieul S, Doutreleau S, Ladeuix B, Golik M, Verges S, Asher G (2019) Physiological and Molecular Dissection of Daily Variance in Exercise Capacity. Cell Metabolism, 30:78-91 e74. doi:10.1016/j.cmet.2019.03.012

Frasier CR, Moore RL, Brown DA (2011) Exercise-induced cardiac preconditioning: how exercise protects your achy-breaky heart. J Appl Physiol 111:905-915. doi:10.1152/japplphysiol.00004.2011

Frasier CR, Moukdar F, Patel HD, Sloan RC, Stewart LM, Alleman RJ, La Favor JD, Brown DA (2013) Redox-dependent increases in glutathione reductase and exercise preconditioning: role of NADPH oxidase and mitochondria. Cardiovasc Res 98:47-55. doi:10.1093/cvr/cvt009

French JP, Hamilton KL, Quindry JC, Lee Y, Upchurch PA, Powers SK (2008) Exercise-induced protection against myocardial apoptosis and necrosis: MnSOD, calcium-handling proteins, and calpain. FASEB J 22:2862-2871. doi:10.1096/fj.07-102541

French JP, Quindry JC, Falk DJ, Staib JL, Lee Y, Wang KK, Powers SK (2006) Ischemia-reperfusion-induced calpain activation and SERCA2a degradation are attenuated by exercise training and calpain inhibition. Am J Physiol Heart Circ Physiol 290:H128-136. doi:10.1152/ajpheart.00739.2005

Gabriel BM, Zierath JR (2019) Circadian rhythms and exercise - re-setting the clock in metabolic disease. Nat Rev Endocrinol 15:197-206. doi:10.1038/s41574-018-0150-x

Gross GJ, Auchampach JA (2007) Reperfusion injury: does it exist? J Mol Cell Cardiol 42:12-18. doi:10.1016/j.yjmcc.2006.09.009

Guo Y, Wu WJ, Qiu Y, Tang XL, Yang Z, Bolli R (1998) Demonstration of an early and a late phase of ischemic preconditioning in mice. Am J Physiol 275:H1375-1387. doi:10.1152/ajpheart.1998.275.4.H1375

Hamilton KL, Quindry JC, French JP, Staib J, Hughes J, Mehta

JL, Powers SK (2004) MnSOD antisense treatment and exercise-induced protection against arrhythmias. Free Radic Biol Med 37:1360-1368. doi:10.1016/j.freeradbiomed.2004.07.025

He L, Hamm JA, Reddy A, Sams D, Peliciari-Garcia RA, McGinnis GR, Bailey SM, Chow CW, Rowe GC, Chatham JC, Young ME (2016) Biotinylation: a novel posttranslational modification linking cell autonomous circadian clocks with metabolism. Am J Physiol Heart Circ Physiol 310:H1520-1532. doi:10.1152/ajpheart.00959.2015

Heusch G (2017) Critical Issues for the Translation of Cardioprotection. Circ Res 120:1477-1486. doi:10.1161/CIRCRESAHA.117.310820

Hogenesch JB, Gu YZ, Jain S, Bradfield CA (1998) The basic-helix-loop-helix-PAS orphan MOP3 forms transcriptionally active complexes with circadian and hypoxia factors. Proc Natl Acad Sci 95:5474-5479.

Hoshida S, Yamashita N, Otsu K, Hori M (2002) Repeated physiologic stresses provide persistent cardioprotection against ischemia-reperfusion injury in rats. J Am Coll Cardiol 40:826-831. doi:10.1016/s0735-1097(02)02001-6

Ingle KA, Kain V, Goel M, Prabhu SD, Young ME, Halade GV (2015) Cardiomyocyte-specific Bmal1 deletion in mice triggers diastolic dysfunction, extracellular matrix response, and impaired resolution of inflammation. Am J Physiol Heart Circ Physiol 309:H1827-1836. doi:10.1152/ajpheart.00608.2015

Kavazis AN, Smuder AJ, Powers SK (2014) Effects of short-term endurance exercise training on acute doxorubicin-induced FoxO transcription in cardiac and skeletal muscle. J Appl Physiol 117:223-230. doi:10.1152/japplphysiol.00210.2014

Khapre RV, Kondratova AA, Patel S, Dubrovsky Y, Wrobel M, Antoch MP, Kondratov RV (2014) BMAL1-dependent regulation of the mTOR signaling pathway delays aging. Aging 6:48-57. doi:10.18632/aging.100633

Kim HK, Konishi M, Takahashi M, Tabata H, Endo N, Numao S, Lee SK, Kim YH, Suzuki K, Sakamoto, S (2015) Effects of Acute Endurance Exercise Performed in the Morning and Evening on Inflammatory Cytokine and Metabolic Hormone Responses. Plos One 10:e0137567. doi:10.1371/journal.pone.0137567

Kloner RA, Jennings RB (2001a) Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 1. Circulation 104:2981-2989. doi:10.1161/hc4801.100038

Kloner RA, Jennings RB (2001b) Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2. Circulation 104:3158-3167. doi:10.1161/hc5001.100039

Kohsaka A, Das P, Hashimoto I, Nakao T, Deguchi Y, Gouraud SS, WAki H, Muragaki Y, Maeda M (2014) The circadian clock maintains cardiac function by regulating mitochondrial metabolism in mice. Plos One 9:e112811. doi:10.1371/journal.pone.0112811

Kondratov RV, Kondratova AA, Gorbacheva VY, Vykhovanets OV, Antoch MP (2006) Early aging and age-related pathologies in mice deficient in BMAL1, the core componentof the circadian clock. Genes Dev, 20:1868-1873. doi:10.1101/gad.1432206

Kondratov RV, Vykhovanets O, Kondratova AA, Antoch MP (2009) Antioxidant N-acetyl-L-cysteine ameliorates symptoms of premature aging associated with the deficiency of the circadian protein BMAL1. Aging 1:979-987. doi:10.18632/aging.100113

Kristiansen SB, Solskov L, Jessen N, Lofgren B, Schmitz

O, Nielsen-Kudsk JE, Nielsen TT, Botker HE, Lund S (2009) 5-Aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside increases myocardial glucose uptake during reperfusion and induces late pre-conditioning: potential role of AMP-activated protein kinase. Basic Clin Pharmacol Toxicol 105:10-16. doi:10.1111/j.1742-7843.2009.00402.x

Kung TA, Egbejimi O, Cui J, Ha NP, Durgan DJ, Essop MF, Bray MS, Shaw CA, Hardin PE, Stanley WE, Young ME (2007) Rapid attenuation of circadian clock gene oscillations in the rat heart following ischemia-reperfusion. J Mol Cell Cardiol 43:744-753. doi:10.1016/j.yjmcc.2007.08.018

Kuzuya T, Hoshida S, Yamashita N, Fuji H, Oe H, Hori M, Kamada T, Tada M (1993) Delayed effects of sublethal ischemia on the acquisition of tolerance to ischemia. Circ Res 72:1293-1299. doi:10.1161/01.res.72.6.1293

Lefta M, Campbell KS, Feng HZ, Jin JP, Esser KA (2012) Development of dilated cardiomyopathy in Bmal1-deficient mice. Am J Physiol Heart Circ Physiol 303:H475-485. doi:10.1152/ajpheart.00238.2012

Lennon SL, Quindry J, Hamilton KL, French J, Staib J, Mehta JL, Powers SK (2004a) Loss of exercise-induced cardioprotection after cessation of exercise. J Appl Physiol 96:1299-1305. doi:10.1152/japplphysiol.00920.2003

Lennon SL, Quindry JC, French JP, Kim S, Mehta JL, Powers SK (2004b) Exercise and myocardial tolerance to ischaemia-reperfusion. Acta Physiol Scand 182:161-169. doi:10.1111/j.1365-201X.2004.01346.x

Li E, Li X, Huang J, Xu C, Liang Q, Ren K, Bai A, Lu C, Qian R, Su, N (2020) BMAL1 regulates mitochondrial fission and mitophagy through mitochondrial protein BNIP3 and is critical in the development of dilated cardiomyopathy. Protein Cell. doi:10.1007/s13238-020-00713-x

Ma D, Panda S, Lin JD (2011) Temporal orchestration of circadian autophagy rhythm by C/EBPbeta. EMBO J 30:4642-4651. doi:10.1038/emboj.2011.322

Ma X, Fu Y, Xiao H, Song Y, Chen R, Shen J, An X, Shen Q, Li Z, Zhang Y (2015) Cardiac Fibrosis Alleviated by Exercise Training Is AMPK-Dependent. Plos One 10:e0129971. doi:10.1371/journal.pone.0129971

Martino T, Arab S, Straume M, Belsham DD, Tata N, Cai F, Liu P, Trivieri M, Ralph M, Sole MJ (2004) Day/night rhythms in gene expression of the normal murine heart. J Mol Med 82:256-264. doi:10.1007/s00109-003-0520-1

Martino TA, Young ME (2015) Influence of the cardiomyocyte circadian clock on cardiac physiology and pathophysiology. J Biol Rhythms 30:183-205. doi:10.1177/0748730415575246

Mayeuf-Louchart A, Thorel Q, Delhaye S, Beauchamp J, Duhem C, Danckaert A, Lancel S, Pourcet B, Woldt E, Boulinquiez A, Ferri L. Zecchin M, Staels B, Sebti Y, Duez H (2017) Rev-erb-alpha regulates atrophy-related genes to control skeletal muscle mass. Sci Rep 7:14383. doi:10.1038/s41598-017-14596-2

McCully JD, Wakiyama H, Hsieh YJ, Jones M, Levitsky S (2004) Differential contribution of necrosis and apoptosis in myocardial ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 286:H1923-1935. doi:10.1152/ajpheart.00935.2003

McGinnis GR, Ballmann C, Peters B, Nanayakkara G, Roberts M, Amin R, Quindry JC (2015) Interleukin-6 mediates exercise preconditioning against myocardial ischemia reperfusion injury. Am J Physiol Heart Circ Physiol 308:H1423-1433. doi:10.1152/ajpheart.00850.2014

McGinnis GR, Tang Y, Brewer RA, Brahma MK, Stanley HL, Shanmugam G, Rajasekaran NS, Rowe GC, Frank SJ,

Wende AR, Abel ED, Taegtmeyer H, Litovsky S, Darley-Usmar V, Zhang J, Chatham JC, Young ME (2017) Genetic disruption of the cardiomyocyte circadian clock differentially influences insulin-mediated processes in the heart. J Mol Cell Cardiol 110:80-95. doi:10.1016/j.yjmcc.2017.07.005

Miller LE, Hosick PA, Wrieden J, Hoyt E, Quindry JC (2012) Evaluation of arrhythmia scoring systems and exercise-induced cardioprotection. Med Sci Sports Exerc 44:435-441. doi:10.1249/MSS.0b013e3182323f8b

Miller LE, McGinnis GR, Peters BA, Ballmann CG, Nanayakkara G, Amin R, Quindry JC (2015) Involvement of the delta-opioid receptor in exercise-induced cardioprotection. Exp Physiol 100:410-421. doi:10.1113/expphysiol.2014.083436

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

Mogabgab O, Giugliano RP, Sabatine MS, Cannon CP, Mohanavelu S, Wiviott SD, Antman EM, Braunwald E (2012) Circadian variation in patient characteristics and outcomes in ST-segment elevation myocardial infarction. Chronobiol Int 29:1390-1396. doi:10.3109/07420528.2012.728658

Montaigne D, et al., (2018) Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erbalpha antagonism: a single-centre propensity-matched cohort study and a randomised study. Lancet 391:59-69. doi:10.1016/S0140-6736(17)32132-3

Montaigne D, Staels B (2018) Time to Check the Clock in Cardiovascular Research and Medicine. Circ Res 123:648-650. doi:10.1161/CIRCRESAHA.118.313543

Morin LP, Studholme KM (2014) Light pulse duration differentially regulates mouse locomotor suppression and phase shifts. J Biol Rhythms, 29(5), 346-354. doi:10.1177/0748730414547111

Mullenders J, Fabius AW, Madiredjo M, Bernards R, Beijersbergen RL (2009) A large scale shRNA barcode screen identifies the circadian clock component ARNTL as putative regulator of the p53 tumor suppressor pathway. Plos One 4:e4798. doi:10.1371/journal.pone.0004798

Muller JE (1989) Morning increase of onset of myocardial infarction. Implications concerning triggering events. Cardiology 76:96-104. doi:10.1159/000174480

Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, Sobel BE, Willerson JT, Braunwald E, MILIS Study Group (1985) Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 313:1315-1322. doi:10.1056/NEJM198511213132103

Muller JE, Tofler GH, Edelman E (1989) Probable triggers of onset of acute myocardial infarction. Clin Cardiol, 12:473-475. doi:10.1002/clc.4960120814

Murry CE, Jennings RB, Reimer KA (1986) Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 74:1124-1136. doi:10.1161/01.cir.74.5.1124

Nanayakkara G, Alasmar, A, Mouli S, Eldoumani H, Quindry J, McGinnis G, Fu X, Berlin A, Peters B, Zhong J, Amin R (2015) Cardioprotective HIF-1alpha-frataxin signaling against ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 309:H867-879. doi:10.1152/ajpheart.00875.2014

Ong SG, Hausenloy DJ (2012) Hypoxia-inducible factor as a therapeutic target for cardioprotection. Pharmacol Ther 136:69-81. doi:10.1016/j.pharmthera.2012.07.005

Oyama Y, Bartman CM, Bonney S, Lee JS, Walker LA, Han

J, Borchers CH, Buttrick PM, Aherne CM, Clendenen N, Colgan SP, Eckle T (2019) Intense Light-Mediated Circadian Cardioprotection via Transcriptional Reprogramming of the Endothelium. Cell Rep, 28:1471-1484 e1411. doi:10.1016/j.celrep.2019.07.020

Oyama Y, Bartman CM, Gile J, Sehrt D, Eckle T (2018) The Circadian PER2 Enhancer Nobiletin Reverses the Deleterious Effects of Midazolam in Myocardial Ischemia and Reperfusion Injury. Curr Pharm Des, 24:3376-3383. doi:10.2174/1381612824666180924102530

Paffenbarger RS, Jr. Laughlin ME, Gima AS, Black RA (1970) Work activity of longshoremen as related to death from coronary heart disease and stroke. N Engl J Med 282:1109-1114. doi:10.1056/NEJM197005142822001

Pedersen BK (2013) Muscle as a secretory organ. Compr Physiol 3:1337-1362. doi:10.1002/cphy.c120033

Peek CB, Levine DC, Cedernaes J, Taguchi A, Kobayashi Y, Tsai SJ, Bonar NA, McNulty MR, Ramsey KM, Bass J (2017) Circadian Clock Interaction with HIF1alpha Mediates Oxygenic Metabolism and Anaerobic Glycolysis in Skeletal Muscle. Cell Metabolism 25:86-92. doi:10.1016/j.cmet.2016.09.010

Perrin L, Loizides-Mangold U, Skarupelova S, Pulimeno P, Chanon S, Robert M, Bouzakri K, Modoux C, Roux-Lombard P, Vidal H, Lefai E, Dibner C (2015) Human skeletal myotubes display a cell-autonomous circadian clock implicated in basal myokine secretion. Mol Metab 4:834-845. doi:10.1016/j.molmet.2015.07.009

Pfeifer U, Strauss P (1981) Autophagic vacuoles in heart muscle and liver. A comparative morphometric study including circadian variations in meal-fed rats. J Mol Cell Cardiol 13:37-49. doi:10.1016/0022-2828(81)90227-3

Podobed PS, Alibhai FJ, Chow CW, Martino TA (2014) Circadian regulation of myocardial sarcomeric Titin-cap (Tcap, telethonin): identification of cardiac clock-controlled genes using open access bioinformatics data. Plos One 9:e104907. doi:10.1371/journal.pone.0104907

Powers SK (2017) Exercise: Teaching myocytes new tricks. J Appl Physiol 123:460-472. doi:10.1152/japplphysiol.00418.2017

Powers SK, Murlasits Z, Wu M, Kavazis AN (2007) Ischemia-reperfusion-induced cardiac injury: a brief review. Med Sci Sports Exerc 39:1529-1536. doi:10.1249/mss.0b013e3180d099c1

Powers SK, Quindry JC, Kavazis AN (2008) Exercise-induced cardioprotection against myocardial ischemia-reperfusion injury. Free Radic Biol Med 44:193-201. doi:10.1016/j.freeradbiomed.2007.02.006

Powers SK, Smuder AJ, Kavazis AN, Quindry JC (2014) Mechanisms of exercise-induced cardioprotection. Physiology 29:27-38. doi:10.1152/physiol.00030.2013

Quindry J, French J, Hamilton K, Lee Y, Mehta JL, Powers S (2005) Exercise training provides cardioprotection against ischemia-reperfusion induced apoptosis in young and old animals. Exp Gerontol 40:416-425. doi:10.1016/j.exger.2005.03.010

Quindry JC, Franklin BA (2018) Cardioprotective Exercise and Pharmacologic Interventions as Complementary Antidotes to Cardiovascular Disease. Exerc Sport Sci Rev 46:5-17. doi:10.1249/JES.0000000000000134

Quindry JC, Hamilton KL (2013) Exercise and cardiac preconditioning against ischemia reperfusion injury. Curr Cardiol Rev 9:220-229.

Quindry JC, Hamilton KL, French JP, Lee Y, Murlasits Z, Tumer N, Powers SK (2007) Exercise-induced HSP-72 elevation and cardioprotection against infarct and apoptosis. J Appl Physiol 103:1056-1062. doi:10.1152/japplphysiol.00263.2007

Quindry,JC, Miller L, McGinnis G, Kliszczewicz B, Irwin JM, Landram M, Urbiztondo Z, Nanayakkara G, Amin R (2012) Ischemia reperfusion injury, KATP channels, and exercise-induced cardioprotection against apoptosis. J Appl Physiol 113:498-506. doi:10.1152/japplphysiol.00957.2011

Quindry JC, Schreiber L, Hosick P, Wrieden J, Irwin JM, Hoyt E (2010) Mitochondrial KATP channel inhibition blunts arrhythmia protection in ischemic exercised hearts. Am J Physiol Heart Circ Physiol 299:H175-183. doi:10.1152/ajpheart.01211.2009

Rabinovich-Nikitin I, Lieberman B, Martino TA, Kirshenbaum LA (2019) Circadian-Regulated Cell Death in Cardiovascular Diseases. Circulation 139:965-980. doi:10.1161/CIRCULATIONAHA.118.036550

Rana S, Prabhu SD, Young ME (2020) Chronobiological Influence Over Cardiovascular Function: The Good, the Bad, and the Ugly. Circ Res 126:258-279. doi:10.1161/CIRCRESAHA.119.313349

Reimer KA, Murry CE, Yamasawa I, Hill ML, Jennings RB (1986) Four brief periods of myocardial ischemia cause no cumulative ATP loss or necrosis. Am J Physiol 251:H1306-1315. doi:10.1152/ajpheart.1986.251.6.H1306

Reitz CJ, Alibhai FJ, Khatua TN, Rasouli M, Bridle BW, Burris TP, Martino TA (2019) SR9009 administered for one day after myocardial ischemia-reperfusion prevents heart failure in mice by targeting the cardiac inflammasome. Commun Biol 2:353. doi:10.1038/s42003-019-0595-z

Roenneberg T, Merrow M (2005) Circadian clocks - the fall and rise of physiology. Nat Rev Mol Cell Biol 6: 965-971. doi:10.1038/nrm1766

Rotter D, Grinsfelder DB, Parra V, Pedrozo Z, Singh S, Sachan N, Rothermel BA (2014) Calcineurin and its regulator, RCAN1, confer time-of-day changes in susceptibility of the heart to ischemia/reperfusion. J Mol Cell Cardiol 74:103-111. doi:10.1016/j.yjmcc.2014.05.004

Rotter D, Rothermel BA (2012) Targets, trafficking, and timing of cardiac autophagy. Pharmacol Res 66:494-504. doi:10.1016/j.phrs.2012.10.001

Sasaki H, Hattori Y, Ikeda Y, Kamagata M, Iwami S, Yasuda S, Tahara Y, Shibata S (2016) Forced rather than voluntary exercise entrains peripheral clocks via a corticosterone/noradrenaline increase in PER2::LUC mice. Sci Rep 6:27607. doi:10.1038/srep27607

Sato S, Basse AL, Schonke M, Chen S, Samad M, Altintas A, Laker RC, Dalbra E, Barres R, Baldi P, Treebak JT, Zierath JR, Sassone-Cors, . (2019) Time of Exercise Specifies the Impact on Muscle Metabolic Pathways and Systemic Energy Homeostasis. Cell Metabolism 30:92-110 e114. doi:10.1016/j.cmet.2019.03.013

Sato S, Sakurai T, Ogasawara J, Takahashi M, Izawa T, Imaizumi K, Taniguchi N, Ohno H, Kizaki T (2014) A circadian clock gene, Rev-erbalpha, modulates the inflammatory function of macrophages through the negative regulation of Ccl2 expression. J Immunol 192:407-417. doi:10.4049/jimmunol.1301982

Schoenhard JA, Smith LH, Painter CA, Eren M, Johnson CH, Vaughan DE (2003) Regulation of the PAI-1 promoter by circadian clock components: differential activation by BMAL1 and BMAL2. J Mol Cell Cardiol 35:473-481. doi:10.1016/s0022-2828(03)00051-8

Schroder EA, Lefta M, Zhang X, Bartos DC, Feng HZ, Zhao Y, Patwardhan A, Jin JP, Esser KA, Delisle BP (2013) The cardiomyocyte molecular clock, regulation of Scn5a, and arrhythmia susceptibility. Am J Physiol Cell Physiol 304:C954-965. doi:10.1152/ajpcell.00383.2012

Schroeder AM, Truong D, Loh DH, Jordan MC, Roos KP, Colwell CS (2012) Voluntary scheduled exercise alters diurnal rhythms of behaviour, physiology and gene expression in wild-type and vasoactive intestinal peptide-deficient mice. J Physiol 590:6213-6226. doi:10.1113/jphysiol.2012.233676

Sprick JD, Mallet RT, Przyklenk K, Rickards CA (2019) Ischaemic and hypoxic conditioning: potential for protection of vital organs. Exp Physiol 104:278-294. doi:10.1113/EP087122

Starnes JW, Barnes BD, Olsen ME (2007) Exercise training decreases rat heart mitochondria free radical generation but does not prevent Ca^{2+}-induced dysfunction. J Appl Physiol 102:1793-1798. doi:10.1152/japplphysiol.00849.2006

Starnes JW, Taylor RP (2007) Exercise-induced cardioprotection: endogenous mechanisms. Med Sci Sports Exerc 39:1537-1543. doi:10.1249/mss.0b013e3180d099d4

Storch KF, Lipan O, Leykin I, Viswanathan N, Davis FC, Wong WH, Weitz CJ (2002) Extensive and divergent circadian gene expression in liver and heart. Nature 417;78-83. doi:10.1038/nature744

Stujanna EN, Murakoshi N, Tajiri K, Xu D, Kimura T, Qin R, Feng D, Yonebayashi S, Ogura Y, Yamagami F, Sato A, Nogami A, Aonuma K (2017) Rev-erb agonist improves adverse cardiac remodeling and survival in myocardial infarction through an anti-inflammatory mechanism. Plos One 12:e0189330. doi:10.1371/journal.pone.0189330

Suarez-Barrientos A, Lopez-Romer, P, Vivas D, Castro-Ferreira F, Nunez-Gil I, Franco E, Ruiz-Mateos B, Garcia-Rubira JC, Fernando-Ortiz A, Macaya C, Ibanez B (2011) Circadian variations of infarct size in acute myocardial infarction. Heart, 97:970-976. doi:10.1136/hrt.2010.212621

Taylor RP, Harris MB, Starnes JW (1999) Acute exercise can improve cardioprotection without increasing heat shock protein content. Am J Physiol 276:H1098-1102. doi:10.1152/ajpheart.1999.276.3.H1098

Taylor RP, Olsen ME, Starnes JW (2007) Improved postischemic function following acute exercise is not mediated by nitric oxide synthase in the rat heart. Am J Physiol Heart Circ Physiol 292:H601-607. doi:10.1152/ajpheart.00094.2006

Vetterlein F, Schrader C, Volkmann R, Neckel M, Ochs M, Schmidt G, Hellige G (2003) Extent of damage in ischemic, nonreperfused, and reperfused myocardium of anesthetized rats. Am J Physiol Heart Circ Physiol, 285:H755-765. doi:10.1152/ajpheart.00269.2002

Virag JA, Anderson EJ, Kent SD, Blanton HD, Johnson TL, Moukdar F, DeAntonio JH, Thayne K, Ding JM, Lust RM (2013) Cardioprotection via preserved mitochondrial structure and function in the mPer2-mutant mouse myocardium. Am J Physiol Heart Circ Physiol 305:H477-483. doi:10.1152/ajpheart.00914.2012

Whitham M, Febbraio MA (2016) The ever-expanding myokinome: discovery challenges and therapeutic implications. Nat Rev Drug Discov 15:719-729. doi:10.1038/nrd.2016.153

Woldt E, Sebti Y, Solt LA, Duhem C, Lancel S, Eeckhoute J, Hesselink MK, Paquet C, Delhaye S, Shin Y, Kamenecka TM, Schaart G, Lefebvre P, Neviere R, Burris TP, Schrauwen P, Staels B, Duez, H. (2013) Rev-erb-alpha modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. Nature Medicine 19:1039-1046. doi:10.1038/nm.3213

Wolff CA, Esser KA (2019) Exercise Timing and Circadian Rhythms. Curr Opin Physiol 10:64-69. doi:10.1016/j.cophys.2019.04.020

Wolff G, Esser KA (2012) Scheduled exercise phase shifts the circadian clock in skeletal muscle. Med Sci Sports Exerc 44:1663-1670. doi:10.1249/MSS.0b013e318255cf4c

Wu R, Dang F, Li P, Wang P, Xu Q, Liu Z, Li Y, Wu Y, Chen Y, Liu Y (2019) The Circadian Protein Period2 Suppresses mTORC1 Activity via Recruiting Tsc1 to mTORC1 Complex. Cell Metabolism 29:653-667 e656. doi:10.1016/j.cmet.2018.11.006

Wu Y, Tang D, Liu N, Xiong W, Huang H, Li Y, Ma Z, Zhao H, Chen P, Qi X, Zhang EE (2017) Reciprocal Regulation between the Circadian Clock and Hypoxia Signaling at the Genome Level in Mammals. Cell Metabolism 25:73-85. doi:10.1016/j.cmet.2016.09.009

Yamashita N, Hoshida S, Otsu K, Asahi M, Kuzuya T, Hori M (1999) Exercise provides direct biphasic cardioprotection via manganese superoxide dismutase activation. J Exp Med 189:1699-1706. doi:10.1084/jem.189.11.1699

Yang G. Chen L, Grant GR, Paschos G, Song WL, Musiek ES, Lee V, McLoughlin SC, Grosser T, Cotsarelis G, FitzGerald GA (2016) Timing of expression of the core clock gene Bmal1 influences its effects on aging and survival. Sci Transl Med 8:324ra316. doi:10.1126/scitranslmed.aad3305

Yellon DM, Downey JM (2003) Preconditioning the myocardium: from cellular physiology to clinical cardiology. Physiol Rev 83:1113-1151. doi:10.1152/physrev.00009.2003

Young ME, Brewer RA, Peliciari-Garcia RA, Collins HE, He L, Birky TL, Peden BW, Thompson EG, Ammons BJ, Bray MS, Chatham JC, Wende AR, Yang Q, Chow CW, Martino TA, Gamble KL (2014) Cardiomyocyte-specific BMAL1 plays critical roles in metabolism, signaling, and maintenance of contractile function of the heart. J Biol Rhythms, 29:257-276. doi:10.1177/0748730414543141

Young ME, Razeghi P, Taegtmeyer H (2001) Clock genes in the heart: characterization and attenuation with hypertrophy. Circ Res 88:1142-1150. doi:10.1161/hh1101.091190

Young ME, Wilson CR, Razeghi P, Guthrie PH, Taegtmeyer H (2002) Alterations of the circadian clock in the heart by streptozotocin-induced diabetes. J Mol Cell Cardiol 34:223-231. doi:10.1006/jmcc.2001.1504

Zambon AC, McDearmon EL, Salomonis N, Vranizan KM, Johansen KL, Adey D, Takahashi JS, Schambelan M, Conklin BR (2003) Time- and exercise-dependent gene regulation in human skeletal muscle. Genome Biol 4:R61. doi:10.1186/gb-2003-4-10-r61

Zhang J, Chatham J, Young ME (2019) Circadian Regulation of Cardiac Physiology: Rhythms That Keep the Heart Beating. Annu Rev Physiol. doi:10.1146/annurev-physiol-020518-114349

Zhang L, Prosdocimo DA, Bai X, Fu C, Zhang R, Campbell F, Liao X, Coller J, Jain MK (2015) KLF15 Establishes the Landscape of Diurnal Expression in the Heart. Cell Rep 13:2368-2375. doi:10.1016/j.celrep.2015.11.038

Zhang L, Zhang R, Tien CL, Chan RE, Sugi K, Fu C, Griffin AC, Shen Y, Burris TP, Liao X, Jain MK (2017) REV-ERBalpha ameliorates heart failure through transcription repression. JCI Insight, 2 doi:10.1172/jci.insight.95177

Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB (2014) A circadian gene expression atlas in mammals: implications for biology and medicine. Proc Natl Acad Sci 111:16219-16224. doi:10.1073/pnas.1408886111