ABSTRACT

EXAMINING THE RELATIONSHIP BETWEEN CIRCADIAN RHYTHM AND DISCONTINUATION OF MECHANICAL VENTILATION

The purpose of this research was to explore the relationship between circadian temperature rhythm and discontinuation of mechanical ventilation. Discontinuation of the ventilator can be challenging for some patients and current criteria used to predict successful discontinuation have a 31% failure rate. Therefore, additional criteria need to be identified for this population of patients. The hypothesis is that there will be a relationship between circadian rhythms and successful discontinuation of the mechanical ventilator. Data were obtained via a retrospective medical record review of patients on mechanical ventilation >96 hr. Hourly temperature was analyzed for presence of circadian rhythm. Measures of the discontinuation process and successful discontinuation were collected and compared with respect to rhythm presence or absence. The data indicate that rhythm presence, prior to extubation, correlates to successful ventilator discontinuation in 89% of patients. The data also indicate that rhythm absence correlates to success in only 73% of patients. Additional studies will validate the existence of this relationship and potentially lead to modification of the ICU environment in such a way to encourage circadian rhythm presence, and subsequent reduction in ventilator time and improved patient outcomes.

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May 2015
EXAMINING THE RELATIONSHIP BETWEEN CIRCADIAN RHYTHM AND DISCONTINUATION OF MECHANICAL VENTILATION

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A thesis
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APPROVED

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CHAPTER 1: INTRODUCTION

Every client who receives mechanical ventilation will require the weaning process and eventually discontinuation of the ventilator. However, removal of mechanical ventilation and subsequent extubation is an invasive intervention that can be extremely challenging and lead to poor outcomes if it is attempted when optimal health is not present (Drouot, Cabello, d’Ortho, & Brochard, 2008). Circadian researchers have demonstrated the relationship between circadian rhythms and health outcomes (Campo et al., 2010; Garaulet, Ordovas, & Madrid 2010; Knauth & Hornberger, 2003; Kondratov, 2007). The relationship suggests that the presence of circadian rhythms are an indicator of optimal health and the absence leads to poor outcomes (Olofsson, Alling, Lundberg, & Malmros, 2004; Valente et al., 2002). Furthermore, it has been hypothesized that the presence of circadian rhythms will allow the patient to recover from invasive interventions (Drouot et al., 2008; Hanneman, 2009). This research serves to examine the relationship between circadian rhythm presence and successful discontinuation of the mechanical ventilator.

Problem Statement

Mechanical ventilation is a frequent intervention used in intensive care settings for patients who have difficulty maintaining their airway or gas exchange processes (Boles et al., 2007). Every client who undergoes mechanical ventilation will require discontinuation of the ventilator. However, discontinuing the ventilator and extubating can often become a difficult task and lead to poor patient outcomes (Boles et al., 2007; Brochard et al., 1994). For example, if extubation is timed incorrectly and the patient is not ready, they will require reintubation. From this experience the patient may develop both cardiovascular and respiratory
adverse effects (Brochard et al., 1994; Nemer et al., 2009). The poor outcomes of
difficult extubations and subsequent reintubations include increased risk of
tracheostomy, pneumonia and even mortality (Thille, Richard, & Brochard, 2013).
It has been proposed that some of the difficulties related to its removal are
associated with prolonged use of the ventilator itself, Intensive Care Unit (ICU)
acquired weakness, sedation, psychological issues, nutrition and metabolic factors,
muscle properties of the ventilation system, and cardiovascular demands
(Brochard et al., 1994; Girard et al., 2008; MacIntyre, 2001).

Currently, one of the more common practices used to identify patient
readiness to discontinue mechanical ventilation, consists of a daily screen for
readiness of Spontaneous Breathing Trials (SBTs) (Blackwood et al., 2011; Ely,
Baker, Evans, & Haponik, 1999). If the patient is successful with the screen, it is
followed by SBTs (often misnamed ‘weaning’) until parameters are met and
discontinuation can be attempted (Blackwood et al., 2011; Hess & MacIntyre,
2011). However, while utilizing these criteria, 31.2% of patients identified to be
ready for ventilator discontinuation fail at extubation (Boles et al., 2007).
Furthermore, the literature indicates there is a population of patients who struggle
with the removal of mechanical ventilation. Researchers suggest 10-50% of
patients will experience prolonged ventilation due to difficulty with the
discontinuation process (Boles et al., 2007). A study by Ely et al., (1999) indicates
use of the screening methods can lead to patients being falsely identified as not
ready for discontinuation. Although the screening methods they refer to, in that
study, have some differences than what is currently used, additional experts have
alluded to the continued incidence of a small percent of patients falsely identified
as unable to wean (Boles et al., 2007; MacIntyre, 2001). This false identification
leads to a prolonged intubation and can contribute to poor outcomes such as
pneumonia (Ely et al., 1996; MacIntyre, 2001). Clients who have successfully self extubated are prime examples of missed opportunities for timely removal of the mechanical ventilator (Boles et al., 2007; MacIntyre, 2001). Since the outcome for patients on long term ventilation is grim, it is important to have clear parameters for healthcare providers to utilize in order to accurately assess readiness for ventilator discontinuation (Boles et al., 2007).

Sleep and circadian researchers have suggested there is a relationship to their field of study with medical interventions such as mechanical ventilation. The expressed relationship involves improved patient outcomes if invasive interventions are performed in the presence of optimal health (Drouot et al., 2008). Since the removal of mechanical ventilation can be extremely challenging and lead to poor outcomes, discontinuation should only be attempted when clients are at their optimum (Drouot et al., 2008; Hanneman, 2009). The stability of circadian rhythms would be a good indicator of the return of optimal health. The underlying assumption that rhythms function to indicate this, is that when the patients become ill they will lose endogenous rhythmic patterns as has been shown in previous studies (Frisk, Olsson, Nylen, & Hahn, 2004; Mundigler et al., 2002; Olofsson et al., 2004). However, as they adapt to the current acute condition they will regain rhythmic cycling moving toward improvement of health (Drout et al., 2008; Hanneman, 2009; Mundigler et al., 2002). This relationship is further complimented by shift work research, which has shown that asynchronous circadian rhythm results in poor health outcomes, while synchronized circadian rhythm can be used as a marker for identification of optimal health (Knauth & Hornberger, 2003). In theory, when the patient is in the healing process the body would be better equipped to tackle removal of the mechanical ventilator.
Due to the potential serious consequences of both early or delayed removal, and the frequency of this medical intervention, identifying methods that improve the criteria for identifying readiness for discontinuation warrants further investigation. Utilization of these additional fields of study could advance the practice of discontinuing mechanical ventilation. Currently, there have been no studies directly linking successful discontinuation of a ventilator to the presence of circadian rhythms. This research aims to elucidate the relationship between circadian rhythm presence and success with discontinuing the mechanical ventilator. If a relationship is found such that abnormal circadian rhythm is an influencing factor in the inability to discontinue the ventilator, then circadian rhythm presence can be used as additional criteria for the patient experiencing difficulty, in aiding to determine readiness to wean and discontinue the ventilator. To my knowledge, this relationship has not been specifically investigated for this outcome. However, it has been suggested that sleep disturbances may be a contributing factor to weaning difficulties, and researchers advise this area be further studied (Drouot et al., 2008).

**Purpose of the Study**

By utilizing circadian rhythms to indicate the presence of optimal health, this study will identify and describe any correlation between successful discontinuation of the ventilator and optimal health. The study will compare the outcomes of two groups of patients: those exhibiting circadian rhythm and those not exhibiting rhythm. The outcomes are those that describe success with discontinuation of the mechanical ventilator. Comparison of these two groups will shed light on the extent of correlation between circadian rhythm and success in the
discontinuation process. The aim of this study is to contribute to the body of knowledge regarding the process of safely removing mechanical ventilation.

Theoretical Framework

Two theories support the concept that a relationship exists between circadian rhythm and success with discontinuation of the mechanical ventilator. Among these, Roy’s model supports the underlying assumptions for this research study. Lenz’s model supports the existence of a relationship between circadian rhythm and successful discontinuation.

Roy’s Adaptation Model

The first theory supports the underlying assumption that clients in the ICU should exhibit a return of circadian rhythmicity upon adaptation. This theory of adaptation was developed by Sr. Callista Roy beginning in 1970. Roy’s adaptation model is a nursing theory that recognizes both health and illness are a part of life. The person is a complex being in constant interaction with its environment, therefore, the person must adapt to the changes presented by the environment to maintain optimal health. The overall goal of nursing is to support adaptation for the patient, who is the adaptive system. Nurses should assist with adaptation, by assessing the environment for adaptive demands, the patient’s response to those demands, and for factors that the nurse can modify. Once adaptation has been achieved, the person is then ready to respond to new and other stimuli (George, 1995; Roy & Corliss, 1993).

Using this model with respect to circadian rhythms, the adaptive demands of the environment include, but are not limited to, the illness, light, noise, and feeding schedules in the ICU. The nurse can assess for adaptation to this environment by analyzing biomarkers of circadian rhythmicity. The intensive care
nurse can also assist the patient in adaptation by modifying the environment to a more natural environment such as reducing light and noise at night, exposing natural light during the day and adjusting feeding schedules to a more natural rhythm (Malik & Parthasarathy, 2014). In compliance with this theory, adaptation to the ICU environment would be considered an indicator for improved health status, suggesting the patient is reaching a point of optimal health for their condition. Studies have indicated that circadian rhythms are lost at the onset of an acute critical illness, but that they can be regained in time by adaptive processes (Fanfulla et al., 2011; Frisk et al., 2004; Hanneman, 2009; Mundigler et al., 2002; Olofsson et al., 2004). Therefore, the presence of circadian rhythms could be utilized as an indicator for adaptation to the environment and consequently achievement of optimal health.

This theory and assumption can be applied to the ICU environment and patients on a ventilator. If discontinuation is attempted too early, the patient may not be able to withstand such a demanding intervention. However, if the patient is exhibiting signs of moving in the direction of wellness, they may be better equipped to handle the demands of breathing independently when the ventilator is removed, and consequently have a positive outcome with extubation. For the ventilated patient, a sign that their underlying condition is improving and they may be ready for ventilator liberation is the return of circadian rhythms. This theory supports the utilization of circadian rhythm in the criteria for predicting successful discontinuation.

**Theory of Unpleasant Symptoms**

The second theory was created in 1995 and is called the “Theory of Unpleasant Symptoms.” This theory supports the notion that abnormal rhythm can
lead to poor outcomes. This theory is composed of physiological, psychological, and situational factors, which influence the chance of developing an unpleasant symptom. The developed symptom then goes on to affect the performance of the individual (Lenz, Suppe, Gift, Pugh, & Miligan, 1995). An additional interactive component was added to the model in 1997. It expanded the model such that the performance of the individual acts as a feedback loop on both the symptom and the three factors (physiological, psychological, and situational) influencing the system (Lenz, Pugh, Miligan, Gift, & Suppe, 1997).

Many Zeitgebers influence the circadian clock (Campbell, Minors, & Waterhouse, 1986). With application of this theory, the unpleasant symptom would be defined as an asynchronous clock. The lack of circadian rhythm is a direct reflection of suboptimal wellness. The suboptimal wellness is influenced by physiological, psychological, and situational factors. Some examples of these factors include the acute illness, lack of normal social cues, environment with constant noise and light, changes in feeding schedule, and stress of the new environment leading to changes in sleep patterns (Malik & Parthasarathy, 2014). Just as the theory describes the symptom affecting performance, an asynchronous clock influences the success with discontinuing the mechanical ventilation. To close the loop, as the theorist indicates, poor performance leads to fatigue and further distress to the system, exacerbating the symptom of an asynchronous clock. As Brochard et al. (1994) explain, attempting removal of the ventilator before the patient is ready can lead to severe deterioration in respiratory status such as poor arterial blood gases, low oxygen consumption, and increased breathing workload. All of these are indicators of poor performance from removal of the ventilator and lead to further distress, which further exacerbates the unpleasant symptom. Therefore, for some patients, particularly those considered
difficult to discontinue the ventilator, medical professionals should consider these additional stressors and optimize the time at which another SBT is attempted.

**Significance of Nursing**

Maintaining patients on mechanical ventilation is a frequent medical intervention. This intervention requires regular assessment to identify both continued need and readiness to discontinue use. Nursing, along with respiratory care providers and physicians, provide objective and subjective assessments that collaboratively leads to the decision to discontinue the ventilator. Currently, providers utilize both objective and subjective criteria for determining readiness to discontinue mechanical ventilation (Blackwood et al., 2011). Subjective criteria that have been relied upon include past experience and intuition. According to Blackwood et al., due to the consequences of both early and delayed discontinuation of the ventilator, many providers are beginning to recognize the importance of utilizing standard protocols for predicting success. However, even with the standard protocols the predictive ability is still not 100% (Blackwood et al., 2011). Because it is the obligation of all medical professionals, including nurses, to improve patient outcomes, it is important to study and improve the method for identification of readiness to discontinue mechanical ventilation.

**Definition of Terms**

**Circadian Rhythm Terms**

Circadian Rhythm: Recurring biologic cycles of approximately 24 hr period (Czeisler et al., 1986).

Desynchronous: Refers to uncoupling of the biologic clock with the environmental rhythm and deviation from the 24 hr cycle (Hanneman, 2009)
Shift work: Indicates work around the 24 hr clock managed in shifts. Often the name given for the population that works primarily at night (Knauth & Hornberger, 2003).

Zeitgebers: Factors that contribute to setting the endogenous circadian rhythm. Some examples include light and feeding patterns (Campbell et al., 1986).

**Mechanical Ventilation Terms**

**Extubation:** Turning off the mechanical ventilator and removal of the endotracheal tube (Hess & MacIntyre, 2011; MacIntyre, 2001).

**Discontinuation of Mechanical Ventilation:** Termination of the mechanical ventilator and extubation for patients deemed ready for its removal (Hess & MacIntyre, 2011; MacIntyre, 2001).

**Self-Extubation:** The patient removes the mechanical ventilator or endotracheal tube accidentally or against medical advice (Boles et al., 2007; MacIntyre, 2001).

**Successful discontinuation of mechanical ventilation:** The patient does not require the ventilator for 48 hr post extubation. (Boles et al., 2007)

**Spontaneous Breathing Trial:** An abrupt cessation of ventilator support (Blackwood et al., 2011; Brochard et al., 1994).

**Weaning from Mechanical Ventilation:** Gradually reducing the level of mechanical ventilator support as tolerated by the patient (Hess & MacIntyre, 2011).
CHAPTER 2: REVIEW OF LITERATURE

Published literature, on both circadian rhythms and mechanical ventilation, is vast. However, there are fewer studies combining these two related topics. Currently, the main focus in relating these two topics is the impact that mechanical ventilation has on the ability to sleep, thereby disturbing circadian rhythms (Drouot et al., 2008). Relatively speaking, it has recently been hypothesized that the lack of circadian rhythms may be the cause or influence on the body’s ability to recover from acute illness (Campo et al., 2010; Drouot et al., 2008). There have been several studies indicating nurses should promote good sleep in order to provide a healing environment (Bourne & Mills, 2006; Campbell et al., 1986; Dunn, Anderson, & Hill, 2010; Friese, 2008). Few researchers have ventured to propose circadian rhythms may be a cause for ventilation failure after extubation and have suggested further research be undertaken (Drouot et al., 2008). This review aims to shed light on the two fields of study, in order to clearly state the potential association between circadian rhythm presence and successful discontinuation of the mechanical ventilator.

Mechanical Ventilation

Mechanical Ventilation is frequently used in the ICU to support the patient with abnormal ventilation and gas exchange processes. These processes may be inhibited by various diseases, trauma, and drugs, including pharmacologic agents (Peñuelas et al., 2011). It has been estimated 33% of ICU patients are on a mechanical ventilator for more than 12 hr (Esteban et al., 2002). Patients on mechanical ventilation consume 37% of available ICU resources, costing $2,000 per day for mechanical ventilation alone (Boles et al., 2007).
When mechanical ventilation is initiated, it is important to consider the process of discontinuation, in regards to the individual’s circumstance, to prevent prolonged use. Prolonged mechanical ventilation increases a patient’s morbidity and mortality (Blackwood et al., 2011; Peñuelas et al., 2011). These patients have increased risks for ventilator associated pneumonia (VAP), lung injury, airway trauma, clots, difficulty weaning, and diaphragmatic atrophy (Blackwood et al., 2011; Brochard et al., 1994; Ely et al., 1996; MacIntyre, 2001; Nemer et al., 2009). On the other hand, discontinuation that occurs prematurely increases stress on the patient as is evidenced by both respiratory and cardiovascular adverse effects, and may even lead to prolonged mechanical ventilation (Brochard et al., 1994; Nemer et al., 2009). Therefore, it is still extremely important to study and expand the present criteria for evaluating ventilated patients, so as to help determine or identify the most significant and appropriate time for removal from mechanical ventilation, assuring for greater success rates post extubation.

**Current Practice for Identification of Readiness to Discontinue Mechanical Ventilation**

The discontinuation process starts with identification of readiness to begin liberating the patient from the ventilator and continues to the removal of the ventilator (Hess & MacIntyre, 2011; MacIntyre, 2001). Successful discontinuation is often defined as extubation without re-intubation for 48 hr (Boles et al., 2007). For some patients, discontinuation can become a long and complicated process resulting in poor outcomes (Boles et al., 2007; Blackwood et al., 2011; Brochard et al., 1994). It is estimated that the time spent in the discontinuation process is 42% of the overall documented time of ventilator use (Esteban, Alia, Ibañez, Benito, & Tobin, 1994). Furthermore, 10% of ICU patients will have, what has
been identified as prolonged failure at attempts to discontinue the ventilator, this volume of patients consumes 50% of the ICUs financial resources (Boles et al., 2007).

Typically, the identification of readiness to begin the discontinuation process consists of both the patient’s ability to meet the criteria in the protocol and physician judgment (Blackwood et al., 2011). It is noted that providers may include subjective criteria such as past experience to determine improvement of the disease process and readiness for discontinuation (Blackwood et al., 2011; Ely et al., 1996). As a consequence to this type of subjective data it has been shown that patients are often left on mechanical ventilation longer than necessary; there is a greater tendency to underestimate success (Blackwood et al., 2011; Strickland & Hasson, 1991). More recently, physicians are getting on board with standardizing the process and utilizing tools such as screening and SBTs to determine readiness for discontinuation (Blackwood et al., 2011). However, these tools could be improved with additional studies to increase their predictive ability.

**Screening process.** The screening process consists of criteria for determining readiness to attempt to reduce ventilator support. The criteria most often utilized, and highly recommended based on evidence, was summarized by the Sixth International Consensus Conference on Intensive Care Medicine (Boles et al., 2007). The screening tool consists of the following: improved status of cause for respiratory failure, intact airway reflex (demonstrated by cough when suctioning), reduced airway secretions, no vasopressor agents in use, stable cardiovascular function (demonstrated by heart rate ≤140 beats/min, systolic blood pressure 90-160), ratio of PaO2:FiO2 ≥150, PEEP ≤8cm, respirations ≤35breaths/min, respiratory frequency to tidal volume less than 105
breaths/min/liter, no respiratory acidosis, and adequate mentation (Boles et al., 2007). Some facilities, providers, and researchers utilize a narrow version of these criteria, while others use a more comprehensive version (Boles et al., 2007, Ely et al., 1996; Peñuelas et al., 2011).

**Reducing ventilator support.** Reducing ventilator support is the next step to predicting successful discontinuation of the ventilator. There are several methods for reducing ventilator support and they range from an abrupt cessation to a gradual decrease (Blackwood et al., 2011; Brochard et al., 1994). An abrupt cessation is typically called an SBT. Utilizing this method, the ventilator is turned off and the patient is allowed to breath. A gradual decrease in ventilator support may include other methods such as synchronized intermittent mechanical ventilation, and pressure support ventilation (Blackwood et al., 2011).

Esteban et al. (2008) suggest that SBTs are utilized in 62% of patients ventilated to determine readiness for extubation. The SBT is often the standard diagnostic indicator. However, its predictability does not capture the entire ventilated population. Nemer et al. (2009) showed 18% of patients who successfully completed an SBT, failed at extubation. Another study indicated a 31.2% failure at extubation with a successful SBT (Boles et al., 2007). The variance in these studies may be due to diversity in inclusion/exclusion criteria such as age, sex, and comorbidities, or due to differences in definitions of a successful SBT. In addition to the potential for false positives, false negatives have been seen such that patients will be falsely deemed not ready for discontinuation due to unsuccessful screening and SBTs (Ely et al., 1999). Of those who self extubate, roughly 60% are successful with discontinuing the ventilator (Boles et al., 2007).
The criteria to indicate SBT failure were also outlined by the Sixth International Consensus Conference on Intensive Care Medicine (Boles et al., 2007). Failure of an SBT consists of anyone of the following: agitation or anxiety, diaphoresis, cyanosis, increased work of breathing, $\text{PaO}_2 \leq 50-60$ on $\text{FiO}_2 > 0.5$, $\text{PaCO}_2 > 50$, $\text{pH} < 7.32$, respiratory frequency to tidal volume $>105$ breaths/min/liter, respirations $>35$ breaths/min, or increased by $\geq 50\%$, heart rate $>140$ beats/min, or increased by $\geq 20\%$, systolic blood pressure $>180$ or $<90$ (Boles et al., 2007). Since there is evidence regarding the failures in predictability, it is important to utilize the SBT as a tool, rather than strict criteria, for considering discontinuation (Boles et al., 2007). Therefore, in addition to this tool, other criteria must be elucidated by future studies.

**Decision to extubate.** Overall, it is recommended by the Sixth International Consensus Conference on Intensive Care Medicine, to utilize these tools (Boles et al., 2007). Blackwood et al. found that these tools, while not perfect, have been found to assist with reducing duration of ventilation and ICU stay. However, there is still some level of discordance with the effectiveness of the protocols. It has been suggested that this is due to population differences, and that it may be necessary to develop specific protocols for specific patient populations. It may also be related to the differences in predictive criteria among different providers and facilities (Blackwood et al., 2011).

**Clarifying Weaning and Discontinuation of Mechanical Ventilation**

At this time, it is important to discuss the difference between weaning and discontinuation. Many authors utilize both terms interchangeably, complicating the process and study of discontinuing a mechanical ventilator. For example, some
studies identify ‘weaning failure’ as failure of an SBT, or reintubation within 48 hr post extubation (Boles et al., 2007; MacIntyre, 2001). Just as extubation is not weaning, an SBT is also not weaning; both are discontinuation attempts. The SBT’s purpose is to trial discontinuation for identifying readiness to turn off the ventilator; it is not slowly reducing ventilator support (Hess & MacIntyre, 2011). Due to the variable use in terminology, successful discontinuation is measured differently across studies, thereby, creating variances in statistical analyses. Additionally, Boles et al. suggest that some studies utilizing SBTs for diagnosing successful discontinuation may have different criteria for passing the SBT. Future studies should have clear standardized definitions. The following definitions have been recommended: weaning, is the process of reducing levels of ventilator support, while discontinuing a ventilator is the actual attempt at termination of the ventilator and removal of the endotracheal tube when deemed no longer needed for treatment (Hess & MacIntyre, 2011; MacIntyre, 2001).

Circadian Rhythms

Biologic rhythms are known to be present in almost every living being. Circadian rhythms are an example of such biologic rhythm and exhibit 24-hr cycling patterns. The human body exhibits rhythms in biochemical, cellular, physiological, and behavioral processes. Some of these cyclic processes include hormone secretion, sleep-wake pattern, body temperature changes, desire for food intake and even gene transcription (Appleman, Figueiro, Rea, 2013; Freedman, Gazendam, Levan, Pack, & Schwab, 2001; Kondratov, 2007). Storch et al. (2002) explain that circadian clock genes are present in all cells. Thus far it has been shown that these genes are responsible for the transcription of 10% of the genome,
therefore, rhythms are fundamental to many of our physiologic processes (Storch et al., 2002).

Circadian rhythms are influenced by the environmental cues which aid our bodies in the maintenance of 24-hr cycling. Over the past few decades it has been elucidated that the primary signal for synchronization of the body’s endogenous clock with the environment’s 24-hr rhythm, is light (Czeisler et al., 1986). Melanopsin is a protein, in retinal ganglion cells, that is responsible for perceiving light and transmitting the signal to a specific location in the brain known to be the primary circadian pacemaker: the Suprachiasmatic Nucleus (SCN) (Hatori et al., 2008). It has also been found there are peripheral clocks in other organs such as the liver, lung, and heart (Koldobskiy, Diaz-Abad, Schar, Brown, & Verceles, 2014; Kondratov, 2007; Storch et al., 2002). The primary pacemaker receives the light signal which then influences hormone production and gene transcription to ensure synchronization of all the clocks and their functions with the environment (Hatori et al., 2008; Kondratov, 2007). In addition to light, there are several other known zeitgebers, which influence endogenous circadian clocks. Among these include, but are not limited to, patterns of light-dark cycle, sleep times, mealtimes, and social schedules (Campbell et al., 1986).

Circadian Rhythm and Its Contribution to Chronic illness

Our society and way of life today has influenced our endogenous clock and has given us the opportunity to study the long term outcomes of a desynchronized clock. Specifically, many studies have come from people who have done long term shift work (Knauth & Hornberger, 2003). It has been clearly shown that shift work causes significant effects on human health. Among these effects include obesity, diabetes, sleep disturbances, hypertension and gastrointestinal problems
(Garaulet et al., 2010; Knauth & Hornberger, 2003). Maintenance of rhythmicity and clock synchronization with the environment is therefore important in the well-being of the individual, while desynchronization leads to many pathologic conditions in humans.

**Circadian Rhythm and Its Contribution to Acute Illness**

Less is known about the specific short term consequences of altered rhythms and the outcomes of patients in relation to acute illness. Additional studies must be done in this area to bring light to this relationship. The research that has occurred, has led to suggestions that abnormal rhythms can increase mortality, especially in the acutely critical ill population (Malik & Parthasarathy, 2014). Among the research studies demonstrating the relationship between the critically ill patient and biologic rhythm there is a correlation between poor patient outcomes and the lack of rhythm (Campo et al., 2010; Valente et al., 2002).

It has been demonstrated that post-trauma, comatose clients, who lacked normal circadian sleep rhythms had lower survival rates (Valente et al., 2002). Other studies have shown a connection between poor sleep and insulin resistance with an increase in blood sugar (Laposky, Bass, Kohsaka, & Turek, 2008; Leproult, Holmback, & Van Cauter, 2014; Reutrakul & Van Cauter, 2014). Campo et al. showed that sleep disturbances lead to ventilation failure. Furthermore, Olofsson et al. (2004) and Mundigler et al. (2002) found there was a definite link between disturbance of rhythms and presence of delirium in critically ill clients. The combination of these studies attributes validity to monitoring circadian disturbances in patients that are acutely ill. After review of studies in the critically ill population, Malik and Parthasarathy suggested that abnormal sleep rhythms may be a critical identifier of poor patient outcomes. Further study of the
critically ill population would provide more insight into the immediate or short term effects of a desynchronized circadian clock.

Circadian Disturbance in the ICU

It has previously been shown that circadian rhythms are significantly disturbed in the critically ill population (Frisk et al., 2004; Mundigler et al., 2002). Furthermore, studies have identified that ICU patients can in fact synchronize their endogenous rhythm during the healing process even if they have not re-entrained to the natural light dark cycle (Guo, Kuzumi, Charman, & Vuylsteke, 2002; Hanneman, 2009; Mundigler et al., 2002). This disturbance and subsequent re-entrainment creates a variable population to learn from.

Desynchronized rhythm. The circadian disturbances in the ICU have been studied in respect to the influences of local zeitgebers and specific illnesses. As with any environment, the zeitgebers have an effect on the endogenous clocks, and mixed environmental signals can generate even more asynchrony (Campbell et al., 1986). Both the ICU environment and the severity of the client’s illness demand around the clock care, which by nature influences the setting of the clock. Tamburri, DiBrienza, Zozula, and Redecker (2004) found on average there are 42 interactions with a patient each night in the ICU, greatly interrupting sleeping patterns. Additional zeitgebers identified in the ICU include drugs used for treatments, patterns of parenteral nutrition, lack of natural lighting, increased artificial lighting at night, and noise (Campbell et al., 1986; Dunn et al., 2010; Friese, 2008). While this environment may be necessary for the treatment of the acute illness, it is detrimental to the sleep quality and subsequent circadian rhythm that is necessary for healing. In accordance with the Theory of Unpleasant Symptoms, the physiological, psychological, and situational factors of the client,
in the ICU, cause the unpleasant symptom of circadian disturbance, which is evident in studies that found asynchrony with sleep/wake patterns, melatonin, cortisol, body temperature, heart rate, and blood pressure (Frisk, et al., 2004; Freedman et al., 2001; Mundigler et al., 2002; Olofsson et al., 2004).

**Regain rhythm.** As supported by Roy’s Adaptation model, several studies have found that some patients do exhibit a normal circadian pattern in the ICU (Guo et al., 2002, Hanneman, 2009; Mundigler et al., 2002). Furthermore, a study found adaptation and return to normal circadian pattern to occur as soon as 2 days after an invasive surgery (Guo et al., 2002). This provides evidence that adaptation to illness can occur, and it supports the notion that re-entrainment of the circadian clock in the ICU is possible.

**Identifying Circadian Rhythms in the Critical Care Setting**

Many methods can be utilized to elucidate the presence of circadian rhythms. As was previously described, circadian patterns are found in various physiological, biochemical, cellular, and behavioral processes. Given the ability to measure these processes, circadian pattern can be described.

For any given study, choosing a parameter for circadian measurement is dependent on many factors: ease of measuring the parameter, number of influential variables, and availability and validity of the tool used to measure and describe it. Many studies utilize the following to determine circadian rhythm presence: sleep analysis, vital signs such as temperature and heart rate, and metabolites such as melatonin and cortisol (Campo et al., 2010; Frisk et al., 2004; Hanneman, 2001; Olofsson et al., 2004). The ICU is a perfect location for studying circadian rhythms in acute and critically ill clients. Rhythmic patterns can
easily be assessed in these clients due to the continuous monitoring of vital signs such as core body temperature, heart rate, and blood pressure, and continuous access to blood for hormone and other metabolite sampling (Hanneman, 2001). For ICU research, circadian biomarkers include temperature, melatonin, and cortisol (Hanneman, 2001; Olofsson et al., 2004).

**Temperature rhythm.** As with most vital signs and other physiologic functions of the body, temperature exhibits circadian patterning in the healthy adult (Bourne & Mills, 2006; Jiang & Wang, 2014; Lanuza, Robinson, Marotta, & Patel, 1989). According to Hanneman (2001), utilizing temperature as a biomarker is the gold standard for identifying circadian rhythm in the ICU. It is easily measured, low cost, and least invasive, it is less likely to change with the environment, and it is an established indicator of illness.

In the healthy adult, temperature rhythm peaks in the evening and troughs in the morning (Lanuza et al., 1989; Weinert & Waterhouse, 2007). Weinert and Waterhouse hypothesized that core body temperature plays a role in regulating sleep wake cycles. They have found that as temperature begins to decrease, the person falls asleep, and sleep ends when temperature begins to rise.

Circadian research in the ICU can easily be accomplished utilizing temperature data. ICU patients are often continuously monitored and have frequent vital signs documented. Furthermore, both retrospective and prospective studies can utilize this biomarker.

**Melatonin rhythm.** Melatonin is a neurohormone that is produced by the pineal gland. It is considered a primary biomarker of circadian rhythm due to its rhythmic pattern that corresponds with sleep. This hormone functions to aid sleep. In normal healthy adults, melatonin has higher levels in the late evening (Bourne
& Mills, 2006; Frisk et al., 2004; Friese, 2008). When melanopsin retinal ganglion cells receive light, melatonin secretion is suppressed and there is consequently a sudden drop in melatonin levels, leading to awakening (Friese, 2008; Wright et al., 2013).

Melatonin can be obtained and measured directly from blood sampling, saliva, or as a metabolite in the urine (Appleman et al., 2013; Olofsson et al., 2004). It is best used as a biomarker for circadian studies when access to blood or urine is continuously available for collection, roughly every 2 hr. Frisk et al. utilized the urine metabolite and found a correlation between low levels of melatonin and patients on mechanical ventilation. This biomarker could be useful in a prospective study in the ICU. However, in this environment it has its limitations: excretion of the metabolite is affected by drugs, and it is also secreted by the gastrointestinal tract which appears to lack cyclic production (Frisk et al., 2004; Bourne & Mills, 2006).

Furthermore, it has been hypothesized that melatonin functions as an antioxidant. Due to this additional function, it is being consumed in the ICU as an adjuvant to therapy, thereby skewing the circadian appearance of its production (Bourne & Mills, 2006). Additional exogenous uses in the ICU include the prevention of delirium caused by sleep-wake disturbances (Bourne & Mills, 2006).

**Cortisol rhythm.** Cortisol is another biochemical marker of circadian rhythm. It is a hormone produced by the adrenal cortex and has many functions in metabolism and suppression of components of the immune system. Typically, the hormone level is in direct opposition to melatonin, exhibiting lower levels at night (Frisk et al., 2004; Bourne & Mills, 2006). As with melatonin, it is best used as a biomarker if continuous access to blood is available. However, accurate
measurement of its circadian production is influenced by total protein available for binding (Hamrahian, Oseni, & Arafah, 2004).

**Conclusion**

Mechanical ventilation is a common intervention in the ICU. All patients undergoing mechanical ventilation will require device discontinuation. Due to the complications of prolonged mechanical ventilation, it is important to consider discontinuation at the earliest time possible without compromising the patient’s ability to be successful in the process. Since circadian rhythms are a primary indicator of optimal health and adaptation to the environment, it seems appropriate to begin the discontinuation process when evidence of a reestablished rhythm is present (Drouot et al., 2008). This task of identifying rhythms can be performed in the ICU because vitals are continuously being monitored and there is continuous access to blood and urine such that monitoring circadian parameters could be achieved.

The hypothesis is that there will be a relationship between exhibiting circadian rhythm and success with the discontinuation process. The hypothesis can be extended to a positive relationship such that clients exhibiting circadian rhythmicity will be more successful with discontinuation of the mechanical ventilator. Such a relationship will provide the basis for future studies utilizing circadian rhythms in the criteria for determining readiness to discontinue the ventilator, especially in those classified as difficult to wean. This may assist patient’s healing by reducing the stress from daily SBTs.

Future studies discussing the impact of environmental modifications that encourage the return of synchronized rhythms, will further compliment this relationship. Modification of the environment could expedite the discontinuation
process. As processes are put into place to assist in healing, patients will benefit from timely removal of the ventilator, while hospitals will save costs. Additional studies on practical modifications for the ICU environment can aid this research by elucidating techniques to encourage the body’s re-entrainment of circadian rhythms in the ICU. Such studies are already in progress and include the administration of melatonin, utilization of blue light blockers, nighttime noise and light reduction techniques, and patterning food intake according to a more normal rhythm (Bourne & Mills, 2006; Campbell et al., 1986; Drouot et al., 2008; Dunn et al., 2010; Malik & Parthasarathy, 2014). It has also been recommended to dim lights, or blindfold the patient to aid in melatonin production in the late evening (Dunn et al., 2010; Friese, 2008). If the presence of circadian rhythms shows a relationship to successful discontinuation of the mechanical ventilator, it can then be utilized as a predictive tool for discontinuation and furthermore as a modifiable target for creating a healing environment. The increased accuracy of predicting successful discontinuation can lead to reducing the time spent on mechanical ventilation, improving patient outcomes and reducing medical costs.
CHAPTER 3: METHODOLOGY

The study purpose was to examine the relationship between circadian rhythm and discontinuation of mechanical ventilation. A retrospective study of mechanically ventilated patients was used to apprehend the impact, if any, that circadian rhythm might have on the process of discontinuing the ventilator. The relationship was examined by forming two groups from the sample population: those exhibiting circadian rhythm and those without, and comparing variables that describe the discontinuation process.

Research Design

This study was a retrospective descriptive correlational study of mechanically ventilated patients that have been ventilated for greater than 96 hr at Community Regional Medical Center, from July 2012 to July 2014. After data extraction and circadian analysis, the cases were split into two groups: one with circadian rhythm and one without, and the dependent variables that define successful discontinuation were compared. For this study, body temperature measurements were utilized to identify the presence of circadian rhythms. Circadian temperature rhythm was the independent variable. The presence of a circadian temperature rhythm is defined as the peak and trough temperatures occurring at approximately the same time in consecutive 24-hr cycles. Successful discontinuation from mechanical ventilation is defined as extubation, without the need to be reintubated within 48 hr. Data collected to identify successful discontinuation included the date/time of extubation, and the date/time of reintubation if within 48 hr.

Additional data were collected to look at other parameters that describe the process of discontinuation. From this, further comparison of the process can be
done to quantify successful discontinuation. The first attempt of an SBT is the start of the discontinuation process; therefore, circadian temperature rhythm was also assessed prior to the first SBT. Parameters that describe progress with discontinuation were described and compared across two groups. One of the parameters obtained to describe progress with discontinuation included the number of hours from the first SBT to extubation. Another parameter collected was the total number of attempts at SBTs.

**Setting**

This study was completed entirely as a retrospective electronic medical record review. The descriptive correlational study was conducted at Community Regional Medical Center. The study proposal underwent an expedited review from the Institutional Review Board (IRB) at Community Regional Medical Center, and was granted approval (see Appendix A). Original request for IRB approval included only temperature data prior to the first SBT. It was later identified that temperature data should be collected prior to extubation since some patients had their first SBT several days before extubation was attempted. It did not make sense to correlate circadian temperature rhythm at the time prior to the first SBT with extubation success for some patients. Therefore, two time frames of temperature were collected. One was prior to the first SBT, and the other was prior to extubation. The correlation makes more sense concerning successful discontinuation with the temperature data obtained directly prior to extubation. The other temperature data collected just prior to the first SBT was still utilized to compare the components of the discontinuation process, such as the number of SBTs required, and total duration of time required from the first SBT to extubation. The amendment to the protocol was approved by the IRB (see
Appendix B). Written permission was also obtained from California State University, School of Nursing, to conduct research according to the California State University, Fresno, Institutional Review Board policy (see Appendix C). Data were collected from electronic medical records and stored in a secure work queue.

**Study Participants**

The study population was obtained after Institutional Review Board approval via the Health Information Management (HIM) department at Community Regional Medical Center. Figure 1 displays the process used to obtain study participants. The International Statistical Classification of Diseases and Related Health Problems (ICD-9) code 96.72 was used to obtain the sample population. The participants were acquired from July, 2012 to July, 2014 medical records. Per exclusion criteria, the HIM department further filtered the list of patients to include the age range 20-50 years old and to exclude female patients and diagnoses of neurologic trauma.

The population provided from HIM consisted of 343 patients who met the above criteria. Random Sampling Method was used. It was created by generating random codes in Excel and sorting by those random codes. All of the medical records were briefly reviewed to eliminate additional exclusion criteria including burns, home ventilator and patients with a tracheostomy. While reviewing the medical records, it was identified that several cases did not meet all inclusion/exclusion criteria, and were eliminated at that time, resulting in 71 eligible patients. The data were then collected in the order of the sorted random codes as time permitted, resulting in 31 charts thoroughly reviewed.
Exclusion and inclusion criteria were chosen to reduce the number of patients who are predicted to lack circadian rhythms based on previous research. Due to the need for a population exhibiting circadian rhythm, these populations were excluded from this study to increase the chance of a population that has evidence of adaptation with respect to circadian temperature rhythm. Neurologic trauma was excluded for two reasons. The first is that the primary circadian clock is in the brain, and if damaged, the patient may be unable to maintain a circadian rhythm (Lanuza et al., 1989; O'Neill, Gardani, Findlay, Whyte, & Cullen, 2013). Since many neurologic trauma patients end up on mechanical ventilation, it may skew the population to a large group of patients that could not exhibit a circadian rhythm. The second reason for excluding neurologic trauma is the patient may have damaged the area in the brain responsible for breathing, and/or became brain dead, and therefore would not be appropriate to compare discontinuation progress against patients with a functioning respiratory drive (MacIntyre, 2001).
Furthermore, for the brain dead patient, there is no criterion for readiness to
discontinue a ventilator, instead it is either used to maintain bodily functions or it
is simply discontinued for end of life. Therefore, it does not meet the same criteria
as the population of patients this study aims to support. To maintain consistency of
eliminating neurologic trauma, all patients admitted to the ICU for motor vehicle
accidents were excluded. Age greater than 50 was also excluded, due to
conflicting studies regarding the potential dampening of temperature amplitude in
the older adult (Kondratov, 2007; Monk, Buysse, Reynolds III, Kupfer, & Houck,
1995; Weinert & Waterhouse, 2007). The value of 50 was chosen because not all
studies define their age range criteria for older adult (Weinert & Waterhouse,
2007). Age less than 20 was excluded to capture the adult population only. Based
on time, and ability to filter through medical records, it was decided to exclude
females for this study as well. Some studies have suggested pregnancy and
menstrual cycle impact temperature amplitude (Padhe & Hanneman, 2007;
Koldobskiy et al., 2014; Jiang & Wang, 2014). Burn patients were excluded due to
the high frequency of interventions required for maintaining their body
temperature. Home ventilator patients were excluded due to the unlikely ability to
have the ventilator discontinued during the hospital stay. Long term tracheostomy
patients were excluded specifically because it did not meet the definition provided
in this study of discontinuation: turning off the ventilator and removing the
endotracheal tube. Furthermore, according to the study by Esteban et al. (2008) the
need for tracheostomy is considered weaning failure. During data collection, it
was recognized that some patients had the tracheostomy removed at the time of
ventilator discontinuation, however to maintain consistency, all patients with a
tracheostomy were excluded.
Procedures for Data Collection

Approval to conduct the study was obtained from Community Regional Medical Center Institutional Review Board and from the California State University, Fresno, School of Nursing according to their Institutional Review Board Policy. Data were collected entirely from retrospective review of electronic medical records. Each patient was assigned a study identification code to provide patient confidentiality. Coded data were entered into a spreadsheet on Excel and was stored on an encrypted password protected server at Community Regional Medical Center.

The data collected included date/time of first intubation, age, and medical diagnosis in order to identify inclusion and exclusion criteria. Temperature data for the independent variable was collected every hour for 3 days prior to discontinuation of the ventilator and 3 days prior to the first SBT. Additionally, date/time of extubation, date/time of first SBT, total hours required for the process of discontinuation (first SBT to extubation), number of SBTs, and date of re-intubation (if any) were collected to compare and describe the discontinuation process and successful discontinuation among the two groups. Other data such as temperature modifying medications and total time on mechanical ventilation were also collected to further describe the dichotomous groups.

Instrumentation

Data were collected utilizing a research tool designed by the investigator, the Data Collection Sheet (see Appendix D). This document provided standardization for the data collected across the study population. The variables included in the research tool were those related to circadian rhythms and mechanical ventilation. Variables were defined independently by the researcher,
and were identified as attributable to the research purpose based on extensive literature review.

**Documentation.** In the ICU from which data were collected, temperature data is documented, at a minimum, every 4 hr. It may be documented more frequently especially if a Foley catheter is in place with a thermometer, or the patient’s condition requires frequent assessment. There is no protocol specifying the temperature source, therefore, data were potentially obtained from a variety of sources such as Foley catheters, temporal, oral and rectal probes. Due to the variability in frequency of temperature data documented, the data point was collected hourly if possible and as close to the hour as possible. If the documentation was not on the hour, temperature data obtained 15 min before and after the hour were collected for that nearest hour. If there was more than one data point within that timeframe of 30 min then the data point closest to the hour was collected. If temperature was charted only every 4 hr, then any temperature collected within an hour was recorded as a data point for the hour it was documented. For example, if frequency of documentation was greater than 4 hr, documentation of temperature at 0845 was recorded in data collection sheet at the 0800 hr. However if frequency of documentation was less than 4 hr, documentation of temperature at 0845 was recorded in data collection sheet at the 0900 hr. Missing temperature data were coded ‘x’ in the data collection sheet.

**Data Analysis**

Data were analyzed by the program Statistical Package for the Social Sciences (SPSS). Descriptive statistic studies were used to apprehend the relationship between circadian rhythms and discontinuation of mechanical ventilation. Each case was analyzed for rhythmicity and categorized as rhythmic
or non-rhythmic at the time of discontinuation of the ventilator. Two groups were created based on rhythm presence or rhythm absence prior to extubation, and the demographics were compared among those two groups. Again, the same cases were split into two groups based on presence or absence of rhythms prior to the first SBT, and analyzed for relationships. Temperature data collected were analyzed for rhythm over 72 hr without respect to time of day. The analysis included identification of temperature rhythm using Cosinor Analysis, a mathematical representation of percentage of rhythm (Padhe & Hanneman, 2007). An ordinary least squares regression was utilized to model sine and cosine function on temperature data (see Appendix E). Temperature rhythm was identified with a threshold of $r^2 > 0.30$, such that if $r^2$ is higher then circadian rhythm is present. Standardized t-tests were used to compare variables across the two groups. The compared variables included the need for re-intubation within 48 hr, total time on a ventilator, duration of the process of discontinuation, age, and total hospitalization.

**Ethical Considerations**

There was no more than a minimal risk to privacy to the study population. There were no psychological, physical, or economic risks associated with this study. In order to further minimize the risks, all attempts were made to protect patient confidentiality. All data were collected solely by the investigators. All investigators have completed training for the protection of human subjects in research. Cases were identified by the Director of the HIM Department at Community Regional Medical Center, according to the ICD-9 code specified. The request for a Waiver of Patient Authorization was granted, therefore no consent form was sent to the study population. The cases obtained were de-identified using
a coded system, with the key stored on an encrypted password protected server. All protected health information obtained from Epic was kept on an encrypted secure server, within a password protected file. Only combined data have been reported. At the end of the study all data collection sheets and electronic data records with protected health information were destroyed, via shredding service and software, respectively.

The potential benefits of the identification of a relationship between circadian temperature rhythm and successful discontinuation of mechanical ventilation, could lead to improved care practices, such that a temperature rhythm could be an indicator of readiness to discontinue mechanical ventilation. There were no direct potential benefits to this study population. No compensation was provided to the study population/family. However, benefits to the patient are indirect as it could lead to improved care practices in their future medical encounters.
CHAPTER 4: RESULTS

This research study was a retrospective, descriptive correlational study, of patients from July, 2012 to July, 2014 on mechanical ventilation for >96 hr at Community Regional Medical Center. The research goal was to identify a relationship between circadian rhythm and successful discontinuation of the ventilator. A total of 72 hr of temperature data were collected prior to the first SBT and prior to extubation. Additionally, the dates and times of first intubation, extubation, re-intubation and SBTs were collected, and age and medical diagnosis were included. Furthermore, the total number of SBTs, total hours required for discontinuation process (timeframe from first SBT to extubation) and total time on mechanical ventilation were gathered from that collected data. After data extraction, circadian analysis was performed utilizing Cosinor Analysis in SPSS, and the cases were split into two groups: one with circadian rhythm and one without. Descriptive statistics were used to elucidate the correlation between circadian rhythms and discontinuation of mechanical ventilation.

As shown in Figure 1 (p. 27), a total of 342 patient medical records were reviewed for inclusion into the research study. A total of 71 patients met all inclusion and exclusion criteria. Of these, random sampling was done and 31 patients were thoroughly reviewed and data collected (see Figure 1, p. 27). Of these 31 patients, 7 failed extubation as evidence by reintubation within 48 hr, while 24 were successful at extubation. Of these 31 patients, 9 exhibited a circadian temperature rhythm prior to extubation while 22 did not exhibit a temperature rhythm prior to extubation. Of these 31, only 26 patients were given an SBT and therefore only the 26 could be examined for temperature rhythm prior
to the first SBT. Five, of these 26, exhibited a circadian temperature rhythm prior to the first SBT, while 21 did not have a temperature rhythm prior to the first SBT.

**Determining Circadian Rhythm Presence**

A Cosinor Analysis was performed to determine the presence of rhythms. The value of $r^2 > 0.30$ indicates rhythmic presence. Figure 2 shows a graphical representation of temperature circadian rhythm. Temperature data collected prior to the first SBT indicate that 19% of 26 patients exhibited a rhythm at that time. While 29% of the 31 patients exhibited a temperature rhythm prior to extubation. Four of the 5 patients who exhibited a temperature rhythm prior to the first SBT, lost their rhythm before extubation. Only one maintained presence of circadian temperature rhythm prior to the first SBT and prior to extubation.

**Figure 2.** Temperature circadian rhythm
### Relationship Between Rhythm Presence and Successful Discontinuation of the Ventilator

Table 1 summarizes the presence of a temperature rhythm in relation to success with ventilator discontinuation. A total of 29% of 31 patients exhibited a rhythm prior to extubation. Of those 29% who exhibited a rhythm, 89% were successful at ventilator discontinuation. A total of 71% of 31 patients did not exhibit a rhythm. Of those 71%, only 73% were successful at ventilator discontinuation.

#### Table 1

**Outcomes of Ventilator Discontinuation Among Patients With and Without Circadian Rhythms**

<table>
<thead>
<tr>
<th>Rhythm prior to Discontinuation</th>
<th>Frequency (n)</th>
<th>Failed discontinuation (n)</th>
<th>Successful discontinuation (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rhythm</td>
<td>22</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Rhythm</td>
<td>9</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>7</td>
<td>24</td>
</tr>
</tbody>
</table>

### Relationship Between Rhythm Presence and the Discontinuation Process

It is important to note, that 5 of the 31 cases did not have a documented SBT during the time of mechanical ventilation. Therefore, there is no extracted temperature data for these patients prior to the first SBT. However, they are still included in the study for temperature data collected prior to extubation. Table 2 displays the presence of temperature rhythm in relation to the average number of SBTs and the average duration of the discontinuation process. The data in this table indicate that patients with circadian temperature rhythm prior to the first SBT, had on average a slightly greater number of SBT and an increased duration of the discontinuation process. Although not statistically significant, p>0.05, on
average the time from the first SBT to extubation is greater by 12.9 hr for those with rhythm, and the number of SBT’s is greater by 0.19.

Table 2

**Outcomes Among Patients with and without Circadian Temperature Rhythm**

<table>
<thead>
<tr>
<th>Rhythm prior to the first SBT</th>
<th>Frequency</th>
<th>Percent</th>
<th>Average Number of SBTs</th>
<th>Average Duration of discontinuation process</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rhythm</td>
<td>21</td>
<td>67.7</td>
<td>2.81</td>
<td>58.93</td>
</tr>
<tr>
<td>Rhythm</td>
<td>5</td>
<td>16.1</td>
<td>3.00</td>
<td>71.80</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>16.1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Descriptive Analysis With Respect to Rhythm Presence Prior to Ventilator Discontinuation**

Table 3 provides the data for the average of all patients. Descriptive analysis was performed comparing age, total time of hospitalization, and the total time on the mechanical ventilator. Table 4 describes the elemental differences between those with circadian temperature rhythm prior to ventilator discontinuation and those without. The contrasting groups were based on temperature rhythm presence prior to ventilator discontinuation, rather than on temperature rhythm prior to the first SBT, due to the 5 patients with incomplete data from the lack of an SBT.

Table 3

**Characteristics of All Patients**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time On Ventilator - (hr)</td>
<td>30</td>
<td>75</td>
<td>530</td>
<td>171.27</td>
<td>83.933</td>
</tr>
<tr>
<td>Age</td>
<td>31</td>
<td>21</td>
<td>52</td>
<td>40.23</td>
<td>9.051</td>
</tr>
<tr>
<td>Total Hospitalization (days)</td>
<td>31</td>
<td>5</td>
<td>144</td>
<td>28.00</td>
<td>26.065</td>
</tr>
</tbody>
</table>
### Table 4

*Characteristics Between Patients With and Without Circadian Temperature Rhythm*

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Rhythm prior to discontinuation</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time On Ventilator - (hr)</td>
<td>No Rhythm</td>
<td>21</td>
<td>155.64</td>
<td>50.429</td>
<td>11.005</td>
</tr>
<tr>
<td></td>
<td>Rhythm</td>
<td>9</td>
<td>207.72</td>
<td>130.550</td>
<td>43.517</td>
</tr>
<tr>
<td>Age</td>
<td>No Rhythm</td>
<td>22</td>
<td>41.59</td>
<td>8.279</td>
<td>1.765</td>
</tr>
<tr>
<td></td>
<td>Rhythm</td>
<td>9</td>
<td>36.89</td>
<td>10.470</td>
<td>3.490</td>
</tr>
<tr>
<td>Total Hospitalization (days)</td>
<td>No Rhythm</td>
<td>22</td>
<td>23.00</td>
<td>12.728</td>
<td>2.714</td>
</tr>
<tr>
<td></td>
<td>Rhythm</td>
<td>9</td>
<td>40.22</td>
<td>43.425</td>
<td>14.475</td>
</tr>
</tbody>
</table>

The average total time for all patients on a ventilator was 171 hr. Although not statistically significant, the average ventilator time for those with rhythm was greater than for those without by 52 hr. The average age for all patients was 40.23 years old. Again, not statistically significant, the average age for those exhibiting circadian temperature rhythm was younger than for those who did not exhibit temperature rhythm at that time, by 4.7 years. The average total hospitalization time was 28 days. The average hospital days for those with rhythm was almost two times more than for those without rhythm (not statistically significant).

**Description of Each Group from Ventilator Discontinuation Success or Failure Perspective**

In total 23% of the cases reviewed, failed at extubation. Figure 3 demonstrates the relationship to circadian presence and the elements representing the discontinuation process for each of these patients. Of those who failed ventilator discontinuation, 86% had no circadian temperature rhythm at the time of extubation. Of those who failed ventilator discontinuation, 14% had a circadian temperature rhythm at the time of extubation. Of the 86% without a rhythm, 29%
had a rhythm prior to the first SBT but had lost it prior to extubation. Of the 86% without a rhythm, 71% did not exhibit rhythm in either of the time periods collected.

Figure 3. Flowchart characterizing the seven failed extubations.
A total of 77% of patients reviewed, were successful at removal of the ventilator. Figure 4 characterizes the relationship between circadian presence and the averages of the elements representing the discontinuation process. Of those who were successful with ventilator discontinuation, 4% had a rhythm prior to the first SBT and prior to extubation; however, 29% exhibited a rhythm prior to extubation only. A total of 66% of those who were successful at extubation had no rhythm prior to extubation. However, 13% of these patients had a rhythm prior to the first SBT and lost it before extubation.

**Figure 4.** Flow chart characterizing the successful extubations
Summary

A retrospective chart review was performed, followed by data extraction of temperature and several elements regarding initiation and discontinuation of mechanical ventilation. Cosinor Analysis was performed to identify circadian temperature rhythm. Successful discontinuation was measured by discontinuation of the ventilator and extubation without the need for reintubation within 48 hr. Additional data were collected to describe the relationship between circadian presence and the discontinuation process.

The data indicate that rhythm presence prior to extubation, correlates to successful ventilator discontinuation in 89% of patients, while rhythm absence correlates to successful ventilator discontinuation in only 73% of patients. Although not statistically significant, the data also indicate that on average patients with circadian presence prior to the first SBT had an increased duration of the discontinuation process and a slightly increased number of SBTs.
CHAPTER 5: CONCLUSION

Based on the theories that circadian presence indicates optimal health, it has been proposed that early discontinuation of the ventilator could be possible for patients exhibiting a circadian rhythm (Hanneman, 2009). However, up to this point there had been no studies directly linking successful discontinuation of the ventilator to the presence of a circadian temperature rhythm in the ICU. Therefore, it was important to look for a relationship between the presence of circadian temperature rhythm and successful discontinuation of the ventilator. The existence of this relationship could enhance care for those experiencing long term ventilation, as it could lead to reducing stress otherwise caused by excessive or poorly timed SBTs. In turn, this could lead to timely removal of the mechanical ventilator. This study aimed to identify that relationship, utilizing a retrospective chart review of patients mechanically ventilated for >96 hr. The underlying assumption that made elucidating this relationship possible was based on the research that indicated patients exhibited circadian rhythms while in the ICU environment (Mundigler et al., 2002). In addition to those studies, Hanneman (2009) demonstrated that patients do in fact adapt to the ICU environment and develop a circadian rhythm within 7 days. Additional researchers have also indicated that mechanically ventilated patients can in fact exhibit a circadian rhythm (Fanfulla et al., 2011; Guo, et al., 2002; Koldobskiy et al., 2014; Mundigler et al., 2002). According to Mundigler et al., the percent of ICU patients that display a circadian rhythm is dependent on diagnosis, ranging from 6% for septic patients to 78% for non-septic patients. As was suggested by the literature, adaptation to the acute illness did occur in this study’s ICU environment as evidenced by 29% developed a circadian temperature rhythm prior to extubation.
This study was suggestive of the existence of a relationship between the presence of circadian temperature rhythm and successful discontinuation of the mechanical ventilator. For patients on a mechanical ventilator >96 hr, there was a correlation indicating that there is increased success with the removal of the ventilator in the presence of a circadian temperature rhythm. Such that there was an 89% chance at being successful when rhythm is present, while only a 73% chance of success when lacking a rhythm. It is important to note, the lack of rhythm did not indicate failure, rather only decreased chance of success. Furthermore, of those that failed extubation (23% of the total population), 86% lacked a circadian rhythm. Further analysis of the one patient who failed extubation while exhibiting a circadian temperature rhythm indicated the patient sustained a gunshot wound to the chest. This type of injury may have additional implications for failure of extubation that the rest of the study population did not have related to muscle fatigue (MacIntyre, 2001).

In contrast to the above relationship, the opposite effect was found when analyzing the temperature data prior to the first SBT with respect to the number of SBTs and total duration of the discontinuation process. Although not statistically significant, it was found that patients exhibiting a circadian temperature rhythm just prior to the first SBT, had slightly increased average attempts at SBTs and increased duration of the discontinuation process. Superficial look at this data leads to the conclusion that the presence of a rhythm does not act as an indicator of readiness to discontinue the ventilator, as patients continued to have SBTs and were in the discontinuation process longer. However, upon deeper analysis, it is important to note, that data collection did not include whether or not the patient passed the SBT. Therefore, the patient may have had several successful SBTs prior to the physician making the final decision to discontinue the ventilator. This
type of response was seen during the data collection process, however, it was not included in the data collection sheet and therefore not statistically analyzed. Additionally, some patients may have been on sedatives at the time of SBTs, and therefore may have been unsuccessful with the SBT due to heavy sedation. Documentation of a sedation scale was not reviewed at the time of medical record review. Therefore, counting SBTs and duration of discontinuation, may not be an accurate measure of readiness to discontinue the mechanical ventilator with these data.

In direct opposition to the average of those with rhythm prior to the first SBT, who showed an increase in discontinuation attempts, there was one patient who maintained circadian rhythm from the time of the first SBT to extubation, was successfully extubated and had a shorter than average duration of discontinuation attempts in comparison to the other patients in the study. Furthermore, this patient had a longer than average total time on a ventilator. In theory, it is expected that a patient on a ventilator for extended time, would potentially have increased ICU acquired weakness and therefore a more difficult time with ventilator removal. However, this patient was successful and had a shorter than average duration of discontinuation. This patient is potentially an example of the possibility that the presence of circadian temperature rhythms were a true indicator of improved health and therefore the patient had a relatively quick removal process even after such an extensive ventilation time.

Furthermore, for those who exhibited a rhythm at the time of extubation, it was noted their average hospital length of stay and duration of mechanical ventilation was increased. The relationship here may be related to the fact that the patients had more time to adapt to the environment and equipment to develop and display a circadian temperature rhythm. Therefore it is not the rhythm that caused
the increase in duration of the discontinuation process, but possibly the extended
time that allowed for circadian temperature rhythm to develop through adaptation.

**Limitations**

Due to the nature of a retrospective study, there are several limitations. To
begin, the accuracy of the data is dependent on the accuracy of charting by nursing
staff who cared for the patient. Another limitation was the variability of the
temperature source, not only across patients, but within individual patient
temperature data. The sources varied from oral, rectal, temporal, and Foley
catheters. Additionally, the reliability of the thermometer cannot be validated since
different equipment was used. According to Hanneman (2001), temperature
rhythms are demonstrated more clearly if data points are taken every min.
However, that is not possible for a retrospective study where the hospital policy is
every 4 hr. Other research completed by Tweedie et al., (1989) performed a
retrospective study and collected hourly temperature data. An hour was also the
target goal for this research. However, temperature was not consistently recorded
hourly. Attempts to standardize this variation were made as described in the
methodology section.

Data regarding medications, and interventions that may influence circadian
temperature rhythm or the ability to breathe were not collected. Such data include
anti-pyretics, sedatives, and neuromuscular blocking agents, cooling or warming
blankets, and surgeries (MacIntyre, 2001). Additionally, data regarding
implementation of spontaneous awakening trials along with the SBT were not
collected. The medical record was not conducive to a rapid review of the
medications given at the time temperature data were collected, therefore these data
were incomplete, and was not included in data analysis. Furthermore, not all
patients had documented SBTs and therefore there was no temperature data for this time frame for those patients.

**Implications for Future Research**

The relationship identified in this study, supports the claim by researchers Drouot et al. and Hanneman (2009), that invasive medical interventions should be performed in the presence of circadian rhythms. Causation cannot be inferred from this data. However, it is suggestive of a correlation between circadian presence and successful discontinuation, such that those who had circadian temperature rhythm were more successful with mechanical ventilation discontinuation. Furthermore, for those who failed ventilator discontinuation, 86% did not exhibit a circadian rhythm. Further studies are necessary to identify a causal relationship. Follow up studies could be aimed at obtaining real time data rather than a retrospective analysis. Specific patient populations can be studied with respect to circadian temperature presence and success with discontinuation of the ventilator. These populations could be based on diagnosis, length of ventilator use, and difficulty experienced with ventilator discontinuation. From this, patient specific criteria can be generated to increase predictability of readiness to discontinue the ventilator, thereby improving patient outcomes.

**Implications for Practice**

This research study, in addition to others, can change the way invasive interventions are done in the future. If a causation relationship is found, indicating that the lack of circadian rhythms are risk factors for ventilation failure, then, for the high risk patients, examination for the presence of circadian temperature rhythm may occur prior to extubation. Upon developing and sustaining rhythmic patterns, the patients risk for failure of ventilator discontinuation would decrease
and attempts at extubation could be made. In essence, when the patient adapts to their condition and their environment, they will exhibit circadian rhythms and will be displaying they are at optimum health. From which, they will be better equipped to take on invasive procedures. Furthermore, nurses and other care providers may assist the patient in the adaptation process through environmental modifications that promote circadian rhythms; potentially leading to early discontinuation of the ventilator (Hanneman, 2009; Mundigler et al., 2002).
REFERENCES
REFERENCES


MacIntyre, N.R. (2001). Evidence-based guidelines for weaning and discontinuing ventilatory support. A collective task force facilitated by the American College of Chest Physicians, the American Association for Respiratory Care, and the American College of Critical Care Medicine. *CHEST Journal, 120*(6_suppl), 375S-396S. doi: 0.1378/chest.120.6_suppl.375S


APPENDICES
APPENDIX A: IRB APPROVAL CRMC
October 10, 2014

Alice Evans, RN & Sheena Keding
Community Regional Medical Center

RE: Examining the Relationship between Circadian Rhythms and Discontinuation of Mechanical Ventilation

IRB #: 2014052

Initial Review

Study Risk Assignment: Minimal Risk
Approval Date: October 10, 2014
Expiration Date: October 9, 2015

Dear Ms. Evans & Keding:

All documents for the above-referenced study were reviewed via expedited review by the Chairman of the Community Medical Centers Institutional Review Board on October 10, 2014. The study was approved for a period of twelve months. Approval for this study will expire on October 9, 2015.

The study was reviewed via expedited review and approved in accordance with regulations found at 45CFR46.110(S). Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

Your request for a waiver of informed consent and waiver of patient authorization for the use and disclosure of protected health information was approved according to federal regulations at 45CFR46.116(a).

A list of the documents reviewed in support of this application is attached. In the future, if you wish to make subsequent changes to the study, they must be re-approved by the IRB prior to implementation of the changes.

The IRB will expect a continuing review of this protocol. You will be notified in advance when the review is expected. Please notify the board immediately of any proposed changes to the protocol, amendments, revisions, or any unanticipated problems involving risks to subjects or others in the protocol. If there are any serious or unexpected adverse events please send a written response, as to your opinion whether it was study-related and whether it is safe to continue the study.
APPENDIX B: IRB APPROVAL OF MODIFICATIONS
January 30, 2015

Alice Evans, RN & Sheena Keding
Community Regional Medical Center

RE: Examining the Relationship between Circadian Rhythms and Discontinuation of Mechanical Ventilation

IRB# 2014062

Study Modification:
- Temperature data collected to include 3 days prior to extubation and re-intubation.
- Time frame for re-intubation to include up to 48 hours.

Documents reviewed in support of this modification:
- Request for IRB Approval of Modifications dated 01/19/2015
- Updated protocol dated 01/16/2015

Dear Ms. Evans & Keding:

The above-referenced study modification was reviewed and approved via expedited review by the Chairman of the Community Medical Centers Institutional Review Board on January 30, 2015. As a reminder, approval for this study will expire on October 9, 2015.

In the future, if you wish to make subsequent changes to the study, they must be re-approved by the IRB prior to implementation of the changes.

The IRB will expect a continuing review of this protocol. You will be notified in advance when the review is expected. Please notify the board immediately of any proposed changes to the protocol, amendments, revisions, or any unanticipated problems involving risks to subjects or others in the protocol. If there are any serious or unexpected adverse events please send a written response, as to your opinion whether it was study-related and whether it is safe to continue the study.
California State University,
Fresno School of Nursing
IRB Approval

Date: November 14, 2014

RE: MSNI413 – Examining the Relationship Between Circadian Rhythms and Discontinuation of Mechanical.

Dear Sheena Keding,

As the Chair of the Department of Nursing Research Committee, serving as the Institutional Review Board for the Department of Nursing, I have reviewed and approved your review request for the above-referenced project for a period of 12 months. I have determined your study to meet the criteria for EXEMPT IRB review.

Under the Policy and Procedures for Research with Human Subjects at California State University, Fresno, your proposal meets exempt criteria according to section

3.3.2.C. Research involving the collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if these sources are routinely available to the investigator, and are recorded by the investigator in such a manner that makes identification of the subjects impossible.

The Research Committee may periodically wish to assess the adequacy of research process. If, in the course of the study, you consider making any changes in the protocol or consent form, you must forward this information to the Research Committee prior to implementation unless the change is necessary to eliminate an apparent immediate hazard to the research participant(s).

This study expires: November 14, 2015

The Research Committee is authorized to periodically assess the adequacy of the consent and research process. All problems having to do with subject safety must be reported to the Research Committee. Please maintain proper data control and confidentiality.

If you have any questions, please contact me through the CSU, Fresno School of Nursing Research Committee at teresag@csufresno.edu.

Sincerely,

Teresa Giannetta, DNP
Department of Nursing, Research Committee, Chair
APPENDIX D: DATA COLLECTION SHEET
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#### Temperature modifying medications

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APPENDIX E: COSINOR ANALYSIS
Cosinor Analysis

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<td>( f(t) = M + \beta \cdot \cos(2\pi t/72) + \beta \cdot \sin(2\pi t/72) + \varepsilon_t )</td>
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Parameters of Interest:
- \( f(t) \) = temperature score;
- \( M \) = intercept (Mesor);
- \( \beta_1 \) = amplitude of cosine \( (X_1) \)
  \( X_1 = \cos(2\pi t/T) \);
- \( \beta_2 \) = amplitude of sine \( (X_2) \)
  \( X_2 = \sin(2\pi t/T) \);
- \( \varepsilon_t \) = error term at each time

\( X_1 = \cos(2\pi t/72) \)
\( t=\) time; \( T=\) trial period (in hours) under study = 72

\( X_2 = \sin(2\pi t/72) \)
\( t=\) time; \( T=\) trial period (in hours) under study = 72

(Cornelissen, 2014)
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Sheena Racheal Keding

Type full name as it appears on submission

April 10, 2015

Date